




# Mercury interactions with selenium and sulfur and the relevance of the Se:Hg molar ratio to fish consumption advice

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## Abstract

Eating fish is often recommended as part of a healthful diet. However, fish, particularly large predatory fish, can contain significant levels of the highly toxic methylmercury (MeHg). Ocean fish in general also contain high levels of selenium (Se), which is reported to confer protection against toxicity of various metals including mercury (Hg). Se and Hg have a high mutual binding affinity, and each can reduce the toxicity of the other. This is an evolving area of extensive research and controversy with variable results in the animal and epidemiologic literature. MeHg is toxic to many organ systems through high affinity for –SH (thiol) ligands on enzymes and microtubules. Hg toxicity also causes oxidative damage particularly to neurons in the brain. Hg is a potent and apparently irreversible inhibitor of the selenoenzymes, glutathione peroxidases (GPX), and thioredoxin reductases (TXNRD) that are important antioxidants, each with a selenocysteine (SeCys) at the active site. Hg binding to the SeCys inhibits these enzymes, accounting in part for the oxidative damage that is an important manifestation of Hg toxicity, particularly if there is not a pool of excess Se to synthesize new enzymes. A molar excess of Se reflected in an Se:Hg molar ratio  $> 1$  is often invoked as evidence that the Hg content can be discounted. Some recent papers now suggest that if the Se:Hg molar ratio exceeds 1:1, the fish is safe and the mercury concentration can be ignored. Such papers suggested that the molar ratio rather than the Hg concentration should be emphasized in fish advisories. This paper examines some of the limitations of current understanding

## Highlights

1. Fish have high nutritional value, but some also have high levels of methylmercury.
2. Mercury exerts toxic effects by binding to sulfhydryl (–SH) groups which are its most abundant ligand in the fish and in the human.
3. Mercury inhibits many enzymes by reacting with thiols and also selenols.
4. Mercury inhibits microtubule formation essential for cell structure, cellular transport, and cell division, by binding to –SH sites on the tubulin protein to prevent assembly.
5. Mercury has high affinity for selenium and causes oxidative damage by inhibiting selenoenzymes (e.g., GPX, TXNRD) that are major components of cells' antioxidant defenses. Some believe that this is the major mechanism for Hg toxicity.
6. Exposure to methylmercury from fish poses a public health risk, although a great excess of Se may partially mitigate the risk by assuring an adequate supply of selenocysteine for selenoprotein replacement. However, the risk of Se toxicity should not be ignored.
7. The Se:Hg molar ratio provides information on the relative excess of Se, but people who eat fish frequently should avoid fish with high mercury content. Fish advisories should take into account the mercury concentration and not rely solely on the molar ratio.

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of the Se:Hg molar ratio in guiding fish consumption advice; Se is certainly an important part of the Hg toxicity story, but it is not the whole story. We examine how Hg toxicity relates also to thiol binding. We suggest that a 1:1 molar ratio cannot be relied on because not all of the Se in fish or in the fish eater is available to interact with Hg. Moreover, in some fish, Se levels are sufficiently high to warrant concern about Se toxicity.

**Keywords** Methylmercury · Selenium · Fish consumption · Tubulin · Microtubules · Selenocysteine · Oxidative stress · Enzyme inhibition · Selenoproteins · Thioredoxin reductase · Glutathione peroxidase · Se:Hg molar ratio

## Introduction

Fish are often recommended as part of a healthful diet. However, some fish have high levels of methylmercury (MeHg). This requires careful consideration of risks and benefits (Budtz-Jorgensen et al. 2007). All forms of mercury (Hg) are toxic to all forms of life. No organism needs or benefits from Hg, yet humans have exploited its physical and toxic properties in various ways including its use as an antiseptics, pesticide, fungicide, diuretic, and vaccine stabilizer (IARC 1993). Selenium (Se) in the form of the amino acid selenocysteine (SeCys) is a critical component of selenoenzymes such as glutathione peroxidases (GPX) and thioredoxin reductases (TXNRD). These enzymes defend cells against oxidative damage (Lubos et al. 2011; Benhar 2018). Se compounds are also toxic (Vinceti et al. 2001; ATSDR 2003; Hamilton 2004), with only a narrow margin between essentiality and toxicity (Spallholz 1993; Surai 2006). Hg and Se have a high mutual affinity and binding constant (Sugiura et al. 1978; Dyrssen and Wedborg 1991), and each can confer protection against the toxicity of the other (El-Begearmi et al. 1977; Farina et al. 2003; Raymond and Ralston 2004; Dauplais et al. 2013). That Se can mitigate mercury toxicity in some situations has been known since the 1960s (Parížek and Ostádalová 1967; Ganther et al. 1972; Ganther and Sunde 1974) and has been subject to periodic reviews at approximately decade intervals (Skerfving 1978; Magos and Webb 1980; Cuvin-Aralar and Furness 1991; Watanabe 2002; Yang et al. 2008; Ralston and Raymond (2018). However, protection is not universal, and synergism (Penglase et al. 2014) or enhancement of Hg toxicity has been reported (Brandão et al. 2011; Polevoy et al. 2020). Experiments on the interactions of He and Se using different compounds, protocols, administration sequence, or endpoints may yield different results (Penglase et al. 2014), and this is still an active research area (e.g., Baldissera et al. 2020; Carvalho et al. 2019).

The toxicokinetics of MeHg is complex with various individual factors influencing the biological half-life (Rand and Caito 2019). Most MeHg in fish is complexed with Cys, but some is already bound to Se, mainly selenomethionine (Cabañero et al. 2005). A fraction of the ingested MeHg may be demethylated by gut microflora (Liu et al. 2019), but most, about 90–95% of the MeHg ingested, is absorbed from the gastrointestinal tract (Gad 2014). Much of the absorbed

Hg enters red blood cells where it binds to hemoglobin (Gad 2014). Other Hg remains in the blood transported partly bound to the SeCys of selenoprotein P (Liu et al. 2018) or to the Cys of albumin, metallothionein, or other proteins.

Hg enters cells exploiting various transporters, for example, Hg-Cys via an amino acid transporter (Bridges and Zalups 2010). In the cell, the Hg may encounter and bind to a SeCys perhaps inactivating an antioxidant enzyme or may bind to GSH, or interact with Cys on enzymes or tubulin molecules. Some MeHg may enter the brain or kidney where demethylation and oxidative damage may occur (Gad 2014). MeHg in the liver may be secreted in the bile, enter the intestine where most of it is demethylated (Liu et al. 2019), and then excreted. A large portion of each ingested dose will eventually be excreted mainly in the feces amounting to 95% of elimination for organomercurials (Caito et al. 2018). Published half-lives for MeHg in the body vary greatly with most estimates in the 40–70-day range but up to 130 days (Rand and Caito 2019). A carefully controlled human exposure study showed that the broad range represents true individual variability in toxicokinetics, including demethylation rate and is not a methodologic artifact (Caito et al. 2018).

Individuals who experience a long half-life for MeHg and eat fish frequently are at risk of bioaccumulating Hg in tissues, taking in more than they excrete, meal after meal (Caito et al. 2018). In this paper, we explore the benefits and risks of eating fish with respect to the Hg and Se content of fish tissue. We focus on the reliability of the Se:Hg molar ratio that is one metric of the risk of eating a lot of high mercury fish and on whether reference to a “1:1” molar ratio or “> 1:1” ratio is reliable and protective in risk communication. The benefits of fish consumption are widely publicized, tempered with warnings focused on “contaminants” including methylmercury (MeHg) and polychlorinated biphenyls (EPA 2020). In the best case, the benefits of eating fish would be maximized at a consumption level before a toxic threshold is reached (Gochfeld and Burger 2005). Most at risk are pregnant women and children as well as “people who eat a lot of fish” (EPA 2020). We refer to the latter as “high-end fish consumers”, people who eat more than 2–3 fish meals per week (Gochfeld and Burger 2005).

How much Se in fish is needed to protect against Hg toxicity is uncertain (Ralston and Raymond 2018; Spiller 2018; Gerson et al. 2020). Much of the Se-protection discussion has focused on the safety of consuming fish, including large

quantities of predatory marine fish (Ralston et al. 2016). Most of the mercury in fish, about 80–95%, is methylmercury (MeHg) (Cappon and Smith 1982; Bloom 1992), and fish is the main source of exposure to MeHg for most fish eaters (Schartup et al. 2019), although rice grown in mercury-contaminated mining areas can be a major source of Hg exposure (Feng et al. 2007).

## Fish consumption advisories

The health benefits of eating fish are due in part to beneficial nutrients such as polyunsaturated fatty acids and Se. The benefits may be offset by the high intake of MeHg (Roman et al. 2012) in people who eat high-mercury fish frequently. Many states and countries have fish advisories based on the Hg or polychlorinated biphenyl (PCB) content (EPA 2011). Mercury warnings typically target pregnant women and children or people who eat a lot of fish such as recreational and subsistence anglers. Health effects are mainly neurodevelopmental, but MeHg is also neurotoxic in adults and also increases cardiovascular disease in adults (Roman et al. 2012). Most advisories also provide guidance on the health benefits of eating fish. In the past 15 years, as our understanding of Se biochemistry and protectiveness against Hg has evolved, there has been a tendency for official advisories to discount the Hg concentration, and emphasize the benefits (EPA 2020), as long as fish contain a molar excess of Se (Spiller 2018). Most fish species do have Se:Hg > 1, although there is great inter- and intra-specific variability (Burger 2012; Burger and Gochfeld 2013; Cusack et al. 2017). The Se “protectiveness” against Hg toxicity has engendered numerous recent studies (see Spiller 2018) and contributed greatly to our understanding of Hg toxicity. It has become common to mention that as long as Se is present in at least a 1:1 molar ratio with Hg, it will protect against Hg toxicity (e.g., Azad et al. 2019). There is little empirical evidence and limited population-based validation of what ratio would connote safety, but see Lemire et al. (2011).

The question of how much molar excess of Se is protective remains unresolved. In our view, confidence in a 1:1 ratio ignores the following: (1) there are abundant endogenous metals such as Cu and Zn as well as other xenobiotic metals that bind Se, and (2) there are far more –SH (thiol) ligands that bind Hg and also Se. Hence, at any point in time, not all the Se would be available to react with or sequester Hg. By this reasoning a 1:1 molar ratio in fish is not sufficiently protective, but the relationship between ratio and risk has not been worked out. The molar ratio has come to play a controversial role in risk communication about eating fish. Ralston et al. (2016) emphasize the strong supporting evidence for relying on the molar ratio, while Gerson et al. (2020) have emphasized that the supporting evidence is “limited and ambiguous.”

Ralston et al. (2008) explained that Hg poisoning occurs by creating a deficiency of Se needed for activity and synthesis of critical selenoenzymes. Hg causes essentially irreversible inhibition of selenoenzymes, especially those required to prevent and reverse oxidative damage in the brain (GPX, TXNDR), and this is considered as primarily responsible for the characteristic oxidative damage of Hg neurotoxicity (Spiller 2018; Ralston and Raymond 2018). Their depiction of this mechanism for mercury toxicity is compelling. Se is clearly a major player in Hg toxicity. Their important work has stimulated many subsequent studies including our own (Burger 2009, Burger and Gochfeld 2011, 2012, 2013, 2020) to examine the molar relationship of Se and Hg in a variety of organisms. It is an important story, but we point out here that it is not the whole story, and that sulfur (S) and sulfhydryl groups (thiols, –SH) are an abundant target for Hg with toxic consequences (Ajsuvakova et al. 2020).

## Mercury poisoning is not the same as selenium deficiency

Some authors (Ralston and Raymond 2018) have suggested that mercury toxicity occurs mainly through creating a selenium deficiency, jeopardizing its antioxidant role by inhibiting GPX and TXNDR. We compare the features of MeHg poisoning and Se deficiency to show they are not congruent. Serious MeHg poisoning events have occurred from both contaminated fish (e.g., Japan) and grain (e.g., Iraq), with a syndrome progressing from paresthesias to ataxia, dysarthria, tunnel vision, hearing loss, coma, and death (Grandjean et al. 2010). Based on our clinical experience at the Environmental and Occupational Health Sciences Institute (Rutgers University, New Jersey, USA), a typical story of mild MeHg poisoning is a patient with paresthesias and visual changes who reports “I ate a can of tuna every day for years” (Gochfeld 2003; Grandjean et al. 2010). Even ingesting only “light tuna” averaging 0.1 µg/g at 140 g/day would exceed the EPA reference dose of 0.1 µg/kg-day, explaining the toxicity our patients have described.

Se deficiency is widespread where crops are grown on Se-poor soil (Shreenath et al. 2020). Mild to moderate Se deficiency is associated with infertility and neurologic effects including fatigue, muscle weakness, and brain fog. Severe deficiency syndromes include Kashin-Beck disease (deformities of bones and joints) and Keshan disease (muscle pain and weakness) (Rayman 2012; Shreenath et al., 2020). These are not prominent features of mercury toxicity. We conclude that the syndromes of Hg poisoning and Se deficiency are not congruent. Antunes dos Santos et al. (2016) said it well: “No single process can explain the multitude of effects observed in MeHg-induced neurotoxicity.” The roles of Se and S or selenols and thiols cannot be completely separated in a dynamic system.

The high affinity of Hg for Se has suggested that co-sequestration occurs as one of the major interactions. This is a suicidal relationship whereby Se binds Hg irreversibly but at the expense of inactivating crucial enzymes and tying up SeCys needed for synthesis of new enzyme as proposed by Ralston and Raymond (2018). In support of sequestration, Korbas et al. (2010) were able to identify nanoparticle HgSe precipitate in the brain.

The brain and also the kidney (Zalups and Lash 1996) are major sites for demethylation of MeHg. After chronic oral dosing with MeHg, monkeys accumulated Hg<sup>2+</sup> in most brain regions (Vahter et al. 1995). Selenite and glutathione enhanced the demethylation of MeHg (Komsta-Szumaska et al. 1983). Liu et al. (2019) reported that MeHg altered gut flora, while Se protected gut flora that enhanced the decomposition of MeHg in the GI tract.

Hg compounds have a high affinity for thiols (Clarkson 1972; Ajsuvakova et al. 2020) and an even higher affinity for selenols (Sugiura et al. 1978). Therefore, selenols and thiols play important roles in the toxicokinetics and toxicodynamics of Hg (Spiller 2018; Ajsuvakova et al. 2020). The relationship and protectiveness between Hg and Se are complicated by the several forms of Hg (elemental, inorganic, organic) and of Se (selenite, selenate, selenide, organic) that have been used in the laboratory or found in fish (Skerfving 1978; Dang and Wang 2011). For Se, the essentiality or toxicity differs among the compounds (García-Barrera et al. 2019). Ralston et al. (2007) pointed out the importance of Se sequestering Hg as an insoluble Hg-selenide but subsequently (Ralston and Raymond 2018) emphasized sequestering of SeCys by Hg as the critical mechanism.

Kaneko and Ralston (2007) are often cited as the authority for using molar ratios in risk communication about fish consumption; however, they carefully do not identify 1:1 as a critical value for the ratio. Since then, the molar ratio has gained much attention as a way of emphasizing the benefits of eating fish. Many authors have mentioned or emphasized the 1:1 molar ratio as if it were a “bright line” (our term) between Hg toxicity and safety (Polak-Juszczak 2015; Cusack et al. 2017; Azad et al. 2019; Reyes-Avila et al. 2019; Ulusoy et al. 2019 to name a few). This assumes that most of the ingested Hg molecule has encountered Se, either in the fish or in the consumer, before exerting a toxic effect. We concur that a molar excess of Se is highly beneficial, but how much of an excess is needed remains uncertain and controversial (Gerson et al. 2020). Does a 2:1 ratio provide adequate protection or is a 5:1 or even 10:1 ratio assurance of safety? A definitive answer is elusive given our current state of knowledge.

Reliance on the Se:Hg molar ratio measured in fish treats the numbers as static for a given species. However, the ratios vary greatly within as well as among fish species (Burger and Gochfeld 2013; Cusack et al. 2017), and they vary by geography and ecology (Azad et al. 2019). The interactions of Hg

and Se are very complex, and research has demonstrated that for each, the behavior in the environment, the toxicokinetics (uptake, distribution, elimination), and toxicodynamics differ among the chemical species. This accounts, in part, for the variety of results and interpretations. As Ralston and Raymond (2018) assert, “selenium toxicology is a rapidly evolving field which continually disproves dogma.”

## Mercury and selenium

Experiments showing that under some conditions Se compounds protected animals from Hg toxicity began in the 1960s, even before the amino acid SeCys was identified.

Mercury poisoning (primarily from elemental Hg<sup>0</sup>) was recognized in antiquity (Hunter 1978), and knowledge of inorganic Hg poisoning grew with the industrial and pharmacologic introduction of mercurials in the nineteenth century. Although organic mercurials came into use as pesticides and diuretics in the early 1900s, we generally point to 1960 as a turning point when MeHg was identified as the cause of the mysterious epidemic of poisoning from fish around Minamata Bay, Japan (Kurland et al. 1960; Hachiya 2006). This was a landmark event for environmental toxicology. Ironically, prior to 1960, Se was a suspected cause of the Minamata epidemic due to its high concentration in Minamata Bay fish (McAlpine and Araki 1958). In the late 1960s, ecotoxicologists demonstrated the biomethylation of Hg by bacteria in sediment (Jensen and Jernelöv 1969), which led to appreciation of the bioamplification of MeHg in the food chain (New Jersey Mercury Task Force 2001).

By contrast, our understanding of Se and the function of selenoenzymes is much newer with important questions about metabolism (Burk and Hill 2015), health effects (Rayman 2012), and interactions (Ralston and Raymond 2018; Gerson et al. 2020) to be clarified. Surai (2006:pp. xix) opens his monumental (974 pp) monograph “Among many minerals Se has a special place being the most controversial trace element.” Until the mid-1900s, Se was known only as a toxic metalloid (Hill 1975), and research on fish deformities caused by Se continues today (Johnson et al. 2020). Se was recognized as essential in mammals in 1958, and glutathione peroxidase (GPX) was identified as a selenoprotein in 1973 (Surai 2006). It is a cytoplasmic enzyme that reduces the reactive H<sub>2</sub>O<sub>2</sub> to water. In the 1980s, selenocysteine (SeCys) was recognized as the 21st amino acid.

The active site of the GPX enzymes includes a SeCys identified as primary targets of Hg, accounting for the oxidative stress attributed to it (Ralston and Raymond 2018; Spiller 2018). However, these proteins also contain Cys sites which can also be targets of Hg (Picaud and Desbois 2006; Carvalho et al. 2008). Hg blocks the active site of the selenoenzymes and also creates deficits of Se preventing synthesis of new

SeCys necessary to replenish the inactivated enzymes, thereby reducing antioxidant defense (reviewed in Surai 2006, ch 2).

Many papers have reviewed the protectiveness of Se against Hg toxicity. Ralston and Raymond (2018) suggest a different approach that Hg toxicity is due to its affinity for Se, resulting in the inactivation of selenoenzymes, a major antioxidant defense. Oxidative damage does the rest in many systems (Ralston and Raymond 2018). An excess of Se is then necessary to replace the damaged enzymes, which uniquely, in the case of SeCys, has to be synthesized anew. The Hg-SeCys cannot be reused (Papp et al. 2007). This has been a valuable observation, changing the way we think of Hg and Se interactions. However, there is more to Hg poisoning than solely tying up Se. Conversely Se supplementation may not block all Hg toxicity (Branco et al. 2012a).

In animals (including humans), mercury toxicity has usually been ascribed to its high affinity for sulfur (S) (Poopal et al. 2013) and thiols (–SH, Ajsuvakova et al. 2020), which in the form of the amino acid cysteine (Cys) is responsible for forming disulfide (–S–S) bridges in protein chains, holding proteins in various folded configurations essential for their function as enzymes. Mercury is capable of blocking thiols, thereby inhibiting the enzymes. Emphasizing the affinity of Hg for –SH, Ajsuvakova et al. (2020) provide alternative explanations for the mechanisms of Hg toxicity and oxidative stress.

## Mercury and oxidative stress

Since the early 1990s, oxidative stress has evolved as a major phenomenon in redox biology, pathogenesis, and toxicology (Sies 2015). Oxidative stress is recognized as playing significant roles in metal toxicology, particularly for mercury. Before oxidative stress was a familiar term, Ganther and Sunde (1974) had proposed that Hg poisoning involved free radicals, particularly the methyl radical (CH<sub>3</sub><sup>\*</sup>). However, oxidative stress did not figure prominently in understanding Hg toxicology until the 1990s (Miller and Woods 1993), by which time the selenoenzyme role was being recognized. Chang's compendium on *Toxicology of Metals* published in 1997 has a chapter on oxidative stress that mentions many metals, but mercury is notably absent (Kasprzak 1997).

Using PUBMED and the rubric “mercury and oxidative stress,” we found that the first few entries are from 1992, and the literature does not begin to increase rapidly until 2005. Zhang et al. (2020) provide a current review of the selenoenzymes as antioxidants with SeCys at the active site of GPX and TXNRD. These enzymes each with a single SeCys amino acid are targets for Hg (Branco et al. 2012a; Spiller 2018). However, Carvalho et al. (2011) note that the active site of TXNRDC has both a Cys(497) and SeCys(498), and Hg links these with high affinity inhibiting the enzyme.

However, in vitro some –SH rich chelating agents can remove the Hg, restoring activity and selenite is even more effective at rescue (Carvalho et al. 2011). But while Hg is inhibiting GPX, it is also tying up other Se molecules that could be used by the cell to replace the depleted enzyme. If the Se content of brain cells, for example, falls below 60% according to Ralston and Raymond (2018), the antioxidant protection fails, and brain cells including neurons die. Branco et al. (2012a) noted that Se has “limited capacity to prevent mercury effects in the brain and kidney,” particularly with regard to GPX. Indeed Se alone at high levels can promote oxidative stress (Hoffman and Heinz 1998).

Inhibition of GPX and particularly TXNRD (Branco et al. 2012a) accounts in part for oxidative stress caused by Hg and by other cations, such as Cd (Hurta et al. 1997) that also have a high affinity for Se. Branco et al. (2012b) suggest that Hg inhibition of TXNRD is a potential biomarker of Hg toxicity. GPX and TXNRD are important parts of antioxidant defense that includes the tripeptide glutathione (GSH) (Nesci et al. 2016; Farina and Aschner 2019). Markers of oxidative stress and lipid peroxidation, including malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARs), increase in the kidney as MeHg is converted to Hg<sup>2+</sup> (Carneiro et al. 2014).

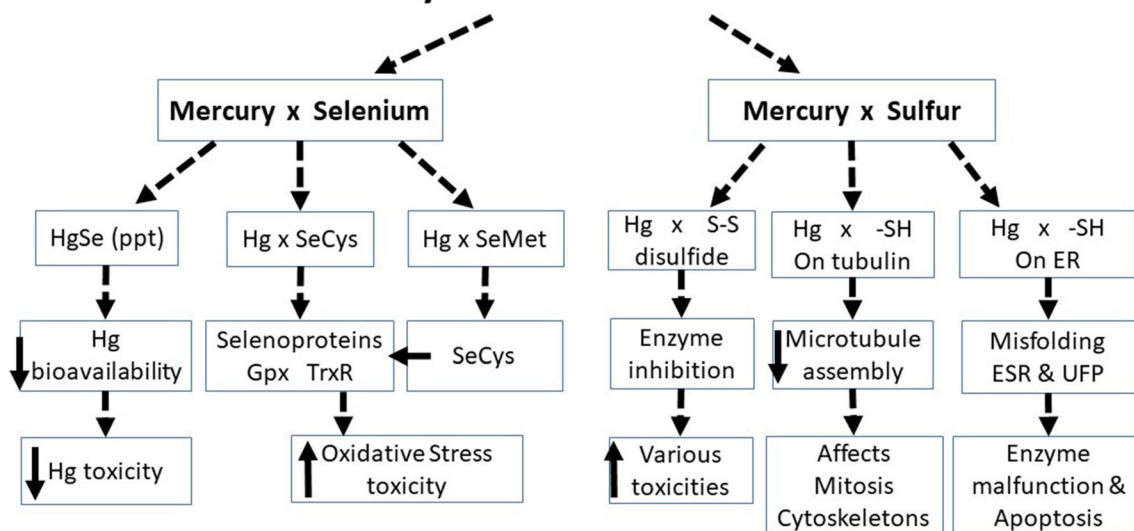
Oxidative stress from mercury is not solely due to Se affinity. Hg has a high affinity for the thiols of superoxide dismutase (Ajsuvakova et al. 2020) and for the –SH of GSH as demonstrated by Fuhr and Rabenstein (1973). GSH is part of the antioxidant chain interacting with GPX as it undergoes redox cycling from –G–S–S–G to –GSH– (Rubino 2015). Woods and Ellis (1995) showed that Hg<sup>2+</sup> increased the synthesis of GSH, which in turn lowered the MDA and TBARs markers consistent with its known role in oxidative defenses. The selenoenzymes TXNRD and GPX each have one SeCys, but several Cys which could be targets. Carvalho et al. (2011) reported that the active site of TXNRD involves Hg reacting with both Cys497 and SeCys498. Picaud and Desbois (2006) identified Hg inactivating GPX at the Cys45 and Cys50 sites. Hg also binds to Cys on manganese superoxide dismutase (Ajsuvakova et al. 2020) thereby inhibiting another antioxidant defense.

Below we discuss key issues in Hg interactions and toxicity, including interaction with S resulting in enzyme inhibition and microtubule disruption. Figure 1 presents our conceptualization of the interactions and consequences of Hg interacting with Se and S as discussed in this paper.

## Mercury and sulfur

Sulfur (S) is one of the most common minerals in the body, occurring mostly as amino acids cysteine (Cys) and methionine (Met) in proteins, with smaller quantities present as GSH

# Mercury and its Interactions



**Fig. 1** Mercury and its interactions and effects with Se or selenols (left side) and with S or thiols (right side)

and as homocysteine and taurine. Ajsuvakova et al. (2020) provide an extensive review of sulfur containing ligands for Hg. There is more than a million times more S atoms than Se atoms in the body (IOM 2006) counter balancing the apparently much greater Hg affinity for Se vs S. Raymond and Ralston (2004) emphasized that selenium's higher affinity (Sugiura et al. 1978) results in Hg binding preferentially to Se or Se disrupting Hg–S bonds. The extent to which, and the circumstances under which, Se can displace Hg from other ligands is not completely known. More importantly, by mass action, an Hg molecule has a much higher probability of encountering a thiol than a selenol (IOM 2006).

Clarkson (1972), writing at a time when the protective role of Se was barely known, emphasized the affinity of Hg for SH groups on proteins, noting that the abundance of this ligand was sufficient to bind all Hg (inorganic or organic) administered even at lethal doses.

Other proteins involved in Hg kinetics involving S binding are metallothioneins and hemoglobin. Metallothioneins are low molecular weight proteins rich in Cys that serve as reservoirs or transporters for metals, particularly Cu and Zn, but also xenobiotics such as Cd, Pb, and Hg. Hg is an efficient inducer of metallothionein in the liver which is often mentioned as a detoxification or elimination mechanism (Palacios and Capdevila 2013). Sørmo et al. (2011) demonstrated that metallothionein level could be a biomarker of a Se:Hg ratio below 1:1. Hemoglobin is also an important ligand for Hg in red cells due to –SH binding (Weed et al. 1962). A study of dolphins identified that hemoglobin (specifically Cys residues in the beta-chain) is a major ligand for MeHg (Zayas et al. 2014). Less well-defined are sulfur-containing compounds such as the amino acid taurine, which can reduce hepatotoxicity (Jagadeesan and Sankarsami Pillai

2007). Zalups and Lash (1997) describe a Hg–Cys conjugate as a vehicle leading to binding of Hg to renal luminal membranes. These exemplify the diverse roles of thiol binding influencing Hg toxicity.

## Mercury and enzyme inhibition

Enzyme inhibition by mercury is recognized as an important part of mercury toxicity (Stratton et al. 2017). Mercury inhibition of selenoenzymes has been discussed above, but Hg compounds inhibit many non-selenoenzymes and induce others. The varied manifestations of Hg toxicity result in part from the variety of enzyme reactions or receptors inhibited (Spulber et al. 2018). In some cases, inhibition is due to binding exposed thiols. This binding by Hg can be reversible or not or can result in denaturation or protein aggregation (Frasco et al. 2007). Enzymes inhibited by Hg include acetylcholinesterase (Frasco et al. 2007), catalase (Chen et al. 2015), amylase, lipase, lactase and glucose-6-phosphatase (Temel and Taysi 2019), delta-aminolevulinic acid dehydratase (Rocha et al. 1995), and Na/K ATPase (Kade 2012). Chymotrypsin lacks available Cys, but Hg inactivates it by binding to histidine residues (Stratton et al. 2017). Of particular interest is inhibition of  $\delta$ -aminolevulinic acid dehydratase (ALA-D) that catalyzes a rate-limiting step in hemoglobin synthesis, resulting in hypochromic anemia. Both lead and Hg compounds (Rocha et al. 1995), as well as Se compounds (Barbosa et al. 1998) inhibit this enzyme experimentally.  $\text{Hg}^{2+}$  and selenite both inhibit the ALA-D with some evidence of synergism, due to binding an –SH group and displacing zinc at the active site (Farina et al. 2003).

Na/K ATPase, a ubiquitous membrane pump enzyme that maintains membrane potential, cell volume, and active transport, is inhibited by MeHg blocking thiols, specifically a Cys113 (Wang and Horisberger 1996), but this can be reversed by organoselenium or by GSH or Cys (Kade 2012). Recently, Baldissera et al. (2020) reported that pre-treatment of fish with diphenyl selenide confers some protection against MeHg inhibition of Na/K ATPase activity. They invoked the Se protection as evidence that the enzyme inhibition was due indirectly to oxidative stress rather than directly to –SH binding of the enzyme (Poopal et al. 2013).

MeHg exposure also results in a complex pattern of protein up- and downregulation at the genome level, some changes manifesting toxicity and others apparently as adaptive defenses. (Jenko et al. 2012). That is beyond the scope of the present paper.

## Mercury and microtubules

Microtubules are elongated hollow fibers that play critical roles in the cytoskeleton of cells and in cell cycling, for example, in mitosis. They are polymers of the tubulin protein. They are characterized by “dynamic instability” and by the suddenness of “catastrophic disassembly” and of polymerization or “rescue” (Gardner et al. 2013). A significant manifestation of Hg toxicity involves disruption of microtubules (Graff and Reuhl 1996). The microtubules arise from centromeres to form the mitotic spindle that separates sister chromatids during mitosis. In the 1960s studies of onion root and fruit flies exposed to MeHg, revealed a potent disruption of mitosis in metaphase arrest (Ramel 1969; Ramel and Magnusson 1969), similar to that caused by colchicine (Eigsti et al. 1949). They attributed the disruption to breaking of disulfide bonds (–S–S–), thereby disrupting enzyme functions and halting the function of the mitotic spindle. Subsequent cell culture studies showed the methylmercury disrupted microtubules, depressing the polymerization of tubulin (Imura et al. 1980) essential for mitotic spindle formation.

Microtubules form from the assembly of tubulin subunits. Tubulin, a heterodimer protein, was first discovered in the 1950s, but its structure was not elucidated until 1998 (Yarris 1998). The tubulin protein polymerizes into the filaments that form the tubules. This is a very dynamic, rapidly reversible, phenomenon as microtubule structure has to constantly change, for example, during mitosis or in the regulation of intracellular transport. Abe et al. (1975) reported that MeHg caused depolymerization of microtubules.

Sager et al. (1983) showed that MeHg disrupted microtubules of cultured fibroblasts in a dose-dependent manner. Stoiber et al. (2004) reported a dose-dependent inhibition of tubulin assembly (NOEL 1  $\mu$ M) and microtubule motility

(NOEL 0.05  $\mu$ M). Wasteneys et al. (1988) showed that MeHg caused a dose-dependent disassembly of the mitotic spindle in cultured fibroblast cell, which was reversed by washout of the MeHg. Vogel et al. (1989) studied MeHg effects on microtubules in vitro, finding inhibition of polymerization as well as depolymerization. MeHg bound to 15 “high affinity sites” (–SH) on the surface of the tubulin dimer, and binding to only 2 of the sites inhibited polymerization (Vogel et al. 1989). Microtubule function is complex requiring both the structure of the tubulin polymer and the ordered motility of the associated kinesin motor (Goshima and Vale 2003). Bonacker et al. (2004) showed that Hg inhibited both the microtubule function as well as assembly in a dose-dependent manner.

## Selenium-mercury interaction

The Parížek and Ostádalová (1967) paper is generally recognized as the first report of Se mitigating Hg toxicity. Na-selenite injected a few hours after an  $\text{HgCl}_2$  dose in rats reduced toxicity. However, reversal of the sequence resulted in increased toxicity (Parížek et al. 1971). Ganther et al. (1972) brought this into the fish consumption risk domain by feeding Japanese quail MeHg in a diet containing tuna vs corn-fed controls. The tuna-fed chicks survived, and an experiment using Se equivalent to that found in the tuna diet “confirmed” the protectiveness of Se against MeHg. Rats fed a diet containing 0.5 ppm of Se survived MeHg in drinking water whereas most of those on a Se-deficient diet died by week 6 (Ganther et al. 1972).

In Amazonian Brazil where indigenous people are exposed to Hg from gold mining directly and through fish consumption, high dietary Se protects motor function (Lemire et al. 2011). Many papers have confirmed that Se confers protection, while others found little or no protection or even synergism (Penglase et al. 2014; Heinz et al. 2012). Some authors report that Se sequesters Hg, and others (Ralston and Raymond 2018) suggested that Hg sequesters Se as the primary toxic affect, leading to oxidative damage if Se is inadequate. Se also has a high affinity for –SH groups (Mykkanen and Wasserman 1990) and may inhibit enzymes by binding to Cys. Excess Se has been implicated in lipid peroxidation (Hoffman 2002).

Not all Se and Hg interactions are protective. Se-methionine (Se-met) and MeHg were injected into bird eggs separately and together. Se-met caused more defects and hatching failure than MeHg, and injected together the hatching rate went up but paradoxically the deformity rate also went up (Heinz et al. 2012), and the effects were greater than similar concentrations conveyed to the egg from the female.

## Is a 1:1 molar ratio protective?

Now we return to the question of whether a 1:1 or even > 1:1 Se:Hg assures protection. There seems to be agreement that where the Se:Hg molar ratio is below 1:1, Hg toxicity is likely to occur. A great excess of Se is likely to confer protection until the Se itself is at a toxic level. Few people address the latter. However, the designation of “1:1” as a bright line (our term), although convenient, is misleading. Ralston et al. (2019) have proposed a new equation called the *Selenium Health Benefit Value* to incorporate the benefits of Se as well as its Hg protectiveness. This is beginning to be used in some papers (Vega-Sánchez et al. 2020). Ralston et al. (2019) report “The HBV criterion provides a reliable basis for differentiating seafoods whose intake should be limited during pregnancy from those that should be consumed to obtain health benefits.”

Although Ralston et al. (2007) emphasized the importance of the molar ratio and Se excess in evaluating Hg risk to humans from eating fish, they carefully do not identify a 1:1 molar ratio as a divide between toxicity and safety. However, the 1:1 ratio has taken on a life of its own. It is attractive to visualize a system in which every MeHg molecule meets a Se molecule, binds, and co-precipitates as insoluble HgSe. But there are many more sulfur targets in the body, and Hg molecules are much more likely to encounter sulfur, for example, in enzymes and tubulin molecules, where the toxicity may be manifest, before Se comes to the rescue.

Some examples of the emphasis on a 1:1 ratio include the following:

1. “Since Se is present in molar excess of Hg, Hg exposures from eating these fish is not a public health concern” (Ulusoy et al. 2019 from Turkey).
2. “The mean Se/Hg ratios were greater than one in all fish species indicating that Se antidotal effect in counteracting Hg occurred.” (Barone et al. 2017 from Italy).
3. “The mean molar ratios for each species were all above 1:1.” (Cusack et al. 2017, from USA).
4. “Selenium binds to organic mercury at a molar ratio of 1:1 Se/Hg to inhibit the toxic effects of Hg” (Donald 2016 from Canada).
5. “When the molar ratios of Se to Hg in fish exceed 1.0 ingestion of the fish is unlikely to deplete Se reserves” (Reyes-Avila et al. 2019 from USA).
6. “A tissue Se:Hg molar ratio greater than 1 is suggested as a threshold for the protecting action of Se against Hg toxicity”(Mulder et al. 2012 from Norway).

In addition to thiol-mediated toxicity, another reason to question the protectiveness of Se at a 1:1 ratio or any ratio close to 1:1 for human fish consumption advice is that Se has many other ligands including other cations that are present either naturally or not. Se itself binds extensively to –SH

groups on proteins. And there are specific Se-binding proteins such as selenium-binding protein 1 (SBP1) that participates in cellular motility, redox modulation, protein degradation, and other important functions including sulfur metabolism (Elhodaky and Diamond 2018). Taken together we conclude that despite high affinity for Hg, not all Se molecules are available to interact with Hg.

In general, as Hg concentration increases, the Se:Hg ratio declines. Hg generally increases with fish size, while Se which is homeostatically regulated does not (Burger and Gochfeld 2011). Therefore, it is predictable that Wang et al. (2018) and others (Burger 2009; Gochfeld et al. 2012; Santos and Silva 2017) reported a decrease in Se:Hg with increasing fish size within species and at higher trophic level in the food web (Polak-Juszczak 2015; Squadrone et al. 2015). This is not a universal observation, however. Many studies reported that Hg and Se levels in fish tissue tend to be correlated suggesting they are already complexed in the fish tissue. Although this may reduce the toxicity of the Hg to the first consumer, it is also a mechanism for enhancing the bioamplification of Hg in the food chain (Beijer and Jernelöv 1978).

We examined molar ratios in a variety of fish species and found them too variable within species to be useful in risk communication (Burger and Gochfeld 2012) and urged that Hg concentration itself not be ignored in developing fish consumption advisories (Burger and Gochfeld 2020; Gochfeld et al. 2012). We acknowledge that a substantial excess of Se over Hg confers protection, but how much of an excess is needed requires more study and whether excess Se can completely protect against high dose of MeHg is uncertain (Cusack et al. 2017; Gerson et al. 2020).

## Significance of variations in Se:Hg molar ratios

We assembled data from several of our papers on Hg and Se concentrations and molar ratios in freshwater and marine fish (Burger and Gochfeld 2013). Table 1 shows that among 53 marine fish species, 13 had some individuals with total Hg (THg) > 0.75 ppm. Among predators 72% of Swordfish (*Xiphias gladius*) and 94% of Mako Shark (*Isurus oxyrinchus*) had Hg > 0.75 ppm. Mako averaged 1.96 ppm THg ( $n = 51$ ). Only Mako Shark had a mean Se:Hg ratio below 1. However, 24 species had mean Se:Hg ratios below 5:1. Among 16 freshwater species 67% of Bowfin (*Amia calva*) had Hg > 0.75 ppm. Among freshwater species, 11 (68%) had a mean ratio below 5:1. At present we do not have a good estimate of whether even a 5:1 molar excess is adequate for protection, and there is no reason to believe that the degree of protectiveness bears a linear relationship to the ratio in edible portions of a fish or whether the same ratio is protective across species.



**Table 1** Comparison of high mercury levels and Se:Hg ratios less than 1.0 among 54 salt water species and 16 freshwater species (from Burger and Gochfeld 2013)

	Species with individuals having total Hg >0.75 ppm	Species with mean Se:Hg ratio less than 1:1	Species with mean Se:Hg ratio less than 5:1	Species with mean Se:Hg ratio greater than 5:1
58 salt water species	13 species 22%	1 species 2%	23 species 40%	35 species 60%
16 freshwater species	7 species 44%	1 species 6%	11 species 69%	5 species 31%

Recently, Gerson et al. (2020), relying on different information also concluded there is not a “strong scientific basis for modifying current fish consumption advisories on the basis of Se:Hg ratios.”

As an example from another source, a study of 7 fish species from Louisiana (Reyes-Avila et al. 2019) found two species with Se:Hg ratios < 1 and three species with ratios between 1:1 and 3:1, which we consider a gray area of only slight Se excess.

## Discussion

Research indicates that MeHg irreversibly inhibits the selenoenzymes that normally prevent or/reverse oxidative damage in the brain and other tissues. Unless excess Se is available or supplemental Se is provided, consequences increase as Se:Hg declines towards unity (Ralston et al. 2016). How much of a Se excess is needed for protection? This would be amenable to laboratory studies, but relevant human studies would be very difficult to conduct. Choi et al. (2008) used cord blood Hg and Se concentrations, to analyze the Faroe Island prospective cohort neurobehavioral outcome data. They reported “no evidence was found that Se was an important protective factor against MeHg neurotoxicity,” despite the 10:1 molar excess of Se in cord blood measured years earlier. Due to the long time lag between exposure and outcome, this should be interpreted with caution.

The relative abundance of thiols vs selenols suggests that any Hg molecule in fish, is probably already bound to a Cys in protein by chance alone. Once absorbed, the Hg-Cys may dissociate as other S or Se ligands are encountered, and an Hg-Cys may indeed survive without ever encountering a Se ligand. Important missing information is whether a Se bound for selenoprotein P or already incorporated in SeIP will attract or break an HgSe bond and form an HgSe bond that renders the Se, irreversibly unavailable. Protection against Hg toxicity comes at a significant cost.

Nothing in this paper should be construed as arguing against eating fish or even occasional large predatory fish that may have high concentrations of MeHg. Nor do we

underestimate the importance of Se. We believe there is abundant evidence that people who eat fish rarely, will attain some health benefits from eating fish more frequently (Rimm et al. 2018). Bernstein et al. (2019) and Domingo (2016), for example, share our cautious recommendations. People who eat fish more frequently (> 2× week) or large meals (> 200 g) should pay attention to Hg content, avoiding high Hg fish and favoring those with Hg < 0.1 ppm. There is no benefit other than preference from choosing high Hg fish, and our experience with clinical cases suggests, not surprisingly, that a predilection for predatory fish is a risk factor for Hg poisoning. Likewise, we are confident that Se does confer some protection when present in molar excess but probably substantial molar excess. We recommend that the utility of the *Selenium Health Benefit Value* (Ralston et al. 2019) continues to be evaluated in future studies. We have found (Burger and Gochfeld 2013) that Se:Hg ratios mainly reflect the Hg in the denominator and that Hg concentration is a more direct and reliable indicator of health risk than the molar ratio.

## Conclusions

Hg and Se have a high mutual affinity, and each can counteract the toxic potential of the other. A primary manifestation of Hg toxicity is oxidative stress, mainly mediated by Hg irreversibly binding SeCys on GPX and TXNRD. Hg that encounters Se can form an insoluble HgSe precipitate, or a complex, rendering Se unavailable for synthesis of SeCys and replacement of the inactivated enzymes. Hg has other oxidative stress effects through targeting SOD and catalase. Although Hg can cause a relative Se deficiency, the symptoms of Hg poisoning are not the same as the symptoms of Se deficiency. Much of the toxicity of Hg is mediated through its high affinity for sulfur, including its ability to inhibit enzymes by reacting with thiols and to interfere with microtubule assembly by binding the high affinity –SH groups on the tubulin molecule. Although this paper argues that a 1:1 Se:Hg molar ratio is not sufficient to prevent Hg toxicity, we do not attempt to estimate a molar excess that assures safety from MeHg. Indeed, at a very

high concentration of Se present in some fish, it may be Hg that protects against Se toxicity. Future laboratory and epidemiologic research may give us at least a range for a protective molar ratio. Reuhl (1988) wrote “The multiplicity of MeHg actions upon biochemical pathways and organelles makes it improbable that a single mechanism or biochemical target adequately explains MeHg’s cytotoxic effects.” We agree with Gerson et al. (2020) that significantly more information is needed to provide a strong scientific basis for modifying current fish consumption advisories on the basis of Se:Hg ratios.

## Implications

Considering the many other ligands available for Hg and the many other metals that avidly bind Se, a substantial molar excess of Se in fish tissue is necessary to mitigate Hg toxicity. The molar ratio may be an important biochemical and toxicological aspect of Hg toxicokinetics and toxicodynamics, but it is confusing for risk communication. The degree of protectiveness or conversely of risk may not be a linear function of the Se:Hg molar ratio. We believe that at the present state of knowledge, Hg concentrations in fish are more informative for risk communication to pregnant women or to people who consume fish very frequently.

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**Data availability** Data sharing is not applicable to this paper because no data sets were generated or analyzed during the study. All references used are listed in the reference section. All are available through PUBMED or at the URLs provided (updated 10 December 2020).

## Compliance with ethical standards

**Competing interests** The authors declare that they have no competing interests.

**Ethical approval** The paper is a conceptualization and analysis of the published literature on the topic. No human subjects or animals were used in this paper.

**Consent to participate** Not applicable.

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