Review

Mercury's neurotoxicity is characterized by its disruption of selenium biochemistry

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ABSTRACT

Background: Methylmercury (CH_3Hg^+) toxicity is characterized by challenging conundrums: 1) "selenium (Se)-protective" effects, 2) undefined biochemical mechanism/s of toxicity, 3) brain-specific oxidative damage, 4) fetal vulnerability, and 5) its latency effect. The "protective effects of Se" against CH_3Hg^+ toxicity were first recognized > 50 years ago, but awareness of Se's vital functions in the brain has transformed understanding of CH_3Hg^+ biochemical mechanisms. Mercury's affinity for Se is ~1 million times greater than its affinity for sulfur, revealing it as the primary target of CH_3Hg^+ toxicity.
Scope of review: This focused review examined research literature regarding distinctive characteristics of CH_3Hg^+ toxicity to identify Se-dependent aspects of its biochemical mechanisms and effects.
Conclusions: Research indicates that CH_3Hg^+ irreversibly inhibits the selenoenzymes that normally prevent/reverse oxidative damage in the brain. Unless supplemental Se is provided, consequences increase as CH_3Hg^+ approaches/exceeds equimolar stoichiometries with Se, thus forming HgSe and inducing a conditioned Se deficiency. As the biochemical target of CH_3Hg^+ toxicity, Se-physiology provides perspectives on the brain specificity of its oxidative damage, accentuated fetal vulnerability, and latency. This review reconsiders the concept that Se is a "tonic" that protects against CH_3Hg^+ toxicity and recognizes Se's role as Hg's molecular "target". As the most potent intracellular nucleophile, the selenoenzyme inhibition paradigm has broad implications in toxicology, including resolution of conundrums of CH_3Hg^+ toxicity.
General significance: Mercury-dependent sequestration of selenium and the irreversible inhibition of selenoenzymes, especially those required to prevent and reverse oxidative damage in the brain, are primarily responsible for the characteristic effects of mercury toxicity.

1. Introduction

Mercury (Hg) occurs in elemental (Hg^0), oxidized (Hg^+, Hg^{2+}), and organic forms such as methylmercury (CH_3Hg^+) and dimethylmercury (CH_3HgCH_3). Each form is distinguished by differences in sources, tissue distributions, and risks of neurotoxicity [1,2]. Since ~75% of inhaled Hg^0 is absorbed [2], this can be a significant source of Hg exposure in locations where ambient concentrations of this volatile form are high. Once incorporated, Hg^0 passes into tissues where it can either be exhaled or become oxidized to form Hg^+ or Hg^{2+} with the assistance of catalase [3, 144]. Anthropogenic and natural sources release 6500–8200 Mg yr^{-1} of Hg^0 into the global atmospheric pool that remain airborne until it becomes oxidized to form water-soluble $Hg^{+/2+}$ that can be deposited with rain [4]. These inorganic forms are poorly absorbed by vertebrates, however anaerobic bacteria can methylate $Hg^{+/2+}$ into CH_3Hg^+, a neurotoxicant which bioaccumulates and biomagnifies in marine and freshwater food webs. Thus, ocean and freshwater fish are the dominant sources of dietary CH_3Hg^+ exposures [126]. The addition of a second methyl group to CH_3Hg^+ creates the CH_3HgCH_3 form consistently observed in deep ocean waters, but not in freshwater systems [146]. Although chemically unreactive, CH_3HgCH_3 is readily absorbed and becomes distributed throughout vertebrate tissues [147]. However, only the minor fraction which has been demethylated to CH_3Hg^+ is retained, whereas the majority of

incorporated CH_3HgCH_3 is exhaled in the first 48 h [147]. Low level exposures to Hg^0 or CH_3Hg^+ are ubiquitous and without adverse consequences, but high exposures are neurotoxic because they can readily cross the blood-brain barrier and preferentially bind with nucleophilic chalcogens such as sulfur or selenium (Se).

Cysteine (Cys) is abundant in tissues, and its thiol is capable of binding with CH_3Hg^+ to form CH_3Hg-Cys [5], an adduct with a molecular structure resembling methionine (Met) and other uncharged amino acids [6]. As a molecular mimic of these amino acids [7] CH_3Hg-Cys is transported into cells by the large neutral amino acid transporter (LAT1). Biota in aquatic ecosystems acquire CH_3Hg-Cys in place of Met and retain it in their tissue proteins. Predators absorb the majority of the CH_3Hg-Cys present in their prey, thus bioaccumulating increasing amounts at each trophic level, resulting in the highest quantities in oldest, largest, and most voracious fish of marine and freshwater food webs as well as in piscivorous mammals. Fish consumption is the primary source of human exposures to CH_3Hg^+ and are of concern in relation to the potential risks that maternal exposures might have on fetal neurodevelopment. High CH_3Hg^+ exposures following catastrophic poisoning incidents resulted in a well characterized syndrome of motor and sensory deficits associated with extensive oxidative damage to brain, with the fetal brain being particularly vulnerable to harm [1,125]. However, the potential for risks being associated with lower CH_3Hg^+ exposures, such as those associated with fish consumption, have remained controversial. This is largely due to uncertainties regarding its molecular mechanism/s and the vulnerability of population subgroups [126].

The mistaken idea that CH_3Hg^+ localizes in association with lipids persists in some current literature. This originated from observations in protein free suspensions [8,9], but is not true in tissues [5,10], where it is predominantly bound to thiols. The sulfhydryl (RSH) or thiol group has a high affinity for Hg compounds ($K_a = 10^{39}$) [11] and for this reason, thiomolecules are often referred to as mercaptans (from the Latin; *mercurium captāns* - meaning mercury capturing) [12]. Mercury's affinity for thiols suggested this could be related to the mechanism of its toxicity. However, intracellular thiol concentrations are in the mM range, ~10,000 times greater than the 1–2.5 μM blood Hg level associated with toxicity, so defining the stoichiometry of its reaction mechanism was elusive. Interactions between Hg and thiols are bimolecular, but because thiol concentrations are saturating, their reactions follow pseudo-first order kinetics proportional to the amount of Hg present. However, interactions with thiols fail to provide compelling rationales for Hg's brain specificity, the reactions responsible for their damage, why fetal brains are more vulnerable than their mother's [1], nor the prolonged silent latency between toxic exposures and the onset of effects [13]. However, CH_3Hg-dependent interruptions of Se-metabolism provide a coherent rationale that is consistent with these consequences.

Although Se's "protective effect" against Hg toxicity was first noted by Pařízek and Oštádalová [14] over 50 years ago, the pivotal importance of this finding remained overlooked or widely misunderstood [120122,130]. The protective effect was thought to involve Se binding to Hg, thus acting as a "tonic" that sequestered Hg in a form that no longer harmed important biomolecules, but instead of acting as a "tonic" that dilutes Hg's effects, Se is the biochemical "target" of CH_3Hg^+ toxicity [134,135]. Methylmercury binding to thiols is kinetically labile, readily exchanging between thermodynamically equivalent partners [15]. However, Hg compounds have an affinity for Se ($K_a = 10^{45}$) that is ~1 million-fold higher than for sulfur [11]. Based on their high binding affinities, one might expect that Hg should be predominantly bound to selenomolecules. Due to mass action effects, > 95% of cellular Hg is associated with thiols [5]. This would have minimal influence on sulfur metabolism since intracellular thiols are 10,000 times more abundant than toxic levels of Hg. In contrast, tissue Se ranges are between 1 and 2 μM, concentrations which are stoichiometrically consistent with the ranges associated with CH_3Hg^+ toxicity

[145]. Thiomolecules function as vehicles that conduct CH_3Hg^+ into metabolic pathways where it can disrupt or interrupt normal Se-metabolism.

This focused review discusses the biochemistry of CH_3Hg^+ and Se in relation to distinctive characteristics of CH_3Hg^+ toxicity: 1) the mechanism/s of the "Se-protective" effect, 2) the biochemical mechanisms responsible for its pathology, 3) the oxidative damage specific to the brain, 4) the accentuated vulnerability of fetal brain, and 5) the biochemical basis for the latency effect. These aspects are sequentially considered from the perspective of the past 50 years of research that reveal Se as a primary target of CH_3Hg^+ toxicity and the importance of dietary Se in relation to CH_3Hg^+ exposure risks.

2. The "selenium-protective" effect

The biological functions of Se arise through the activities of Sec in 25 proteins expressed by the human proteome [16,17]. The majority of the selenoproteins are enzymes in which Sec is the primary catalytic actor in the active site. Selenoproteins are expressed in all vertebrates, and are especially important in the brain for prevention and reversal of oxidative damage that might otherwise occur due to its high metabolic activities. Therefore, the tissue [145] occurrence and distributions of these unique selenoproteins (see Table 1) are tightly controlled and preferentially preserved in brain and neuroendocrine tissues [20–22,148,149]. To understand how Se "protects" against Hg toxicity, it is necessary to understand Se physiology.

2.1. Selenocysteine synthesis and selenoprotein activities

Selenium was identified as an element in 1817 by Jöns Jakob Berzelius. The chalcogens of group 16, oxygen (O), sulfur (S), and Se are chemically similar and form analogous compounds. With six valence electrons, two of them unpaired ($[Ar] 3d^{10}4s^24p^4$), Se can form six covalent bonds due to 4d orbitals. In association with oxygen, its oxidation state is +6 in selenium trioxide (SeO_3), +4 in selenates (SeO_4^{2-}), and +2 in selenites (SeO_3^{2-}). In combination with other elements, it forms binary compounds with an oxidation state of −2, e.g., in selenide (HSe^-), hydrogen selenide (H_2Se), and organic selenides.

Sulfur and Se are chemically similar and indistinguishable to the plants or bacteria that incorporate them into various molecules including the amino acids methionine (Met) and selenomethionine (SeMet) (see Fig. 1). The SeMet and Met are incorporated into proteins nonspecifically from one another in plants and in the cells of animals that consume them [132,143]. However, an important distinction between these two amino acids is the release of inorganic selenide ($HSe^−$) following degradation of SeMet. Since Se^{2-} is the required precursor for Se-biochemistry in animals, this is the crucial first step of Se-physiology.

The synthesis, reactivities, and functions of the chalcogen amino acids; serine (Ser), Cys, and selenocysteine (Sec), the 21st proteinogenic amino acid, are vastly different (see Fig. 2). With a pKa of ~13, the hydroxyl proton of Ser is stable and unreactive. However, with displacement of its hydroxyl, Ser can serve as the precursor for biosynthesis of Sec, Cys and glycine [23; 129]. In contrast to the hydroxyl of Ser, the thiol of Cys is a nucleophile in enzymes that adjust its pKa from 8.3 to nearly neutral. The Cys thiol is easily oxidized to form the disulfides that contribute to folding and confer structural stability to proteins. Disulfide formation is an important aspect of Cys participation in reactions, such as those that help preserve intracellular reducing conditions. Incorporation of Ser and Cys into proteins involves specific ligases to form a L-seryl-tRNA^{Ser} and L-cysteinyl-tRNA^{Cys} to designate insertion into nascent polypeptides during synthesis. Like other amino acids, Ser and Cys can be repeatedly used in continuous cycles of protein synthesis, activity, and degradation. In contrast, Sec cannot be reused, and must be degraded to inorganic Se^{2-} by a Sec-specific lyase

Table 1
Mammalian selenoproteins.[a]

Gene name	Functions and/or comments regarding tissue and/or subcellular localization.
GPX1	Detoxifies peroxides in aqueous compartment of mitochondria and cytosol
GPX2	Expressed in cytosol of liver and tissues of the digestive system
GPX3	Primarily synthesized in kidney; active in plasma Se transport to other tissues
GPX4	Prevents and reverses oxidative damage to lipids in brain, testis and other tissues
GPX6	Expressed in embryos and olfactory epithelium, catalyzes reduction of peroxides
TXNRD1	Cytosolic form, reduces multiple antioxidant substrates, regulates metabolic pathways
TXNRD2	Mitochondrial form, reduces multiple antioxidant substrates, controls redox pathways
TXNRD3	Reduces both glutathione disulfide and oxidized Trx, highest expression in testis
SELENOF	Oxidoreductase that may assist in disulfide formation and protein folding
SELENOH	Oxidoreductase, protects neurons against apoptosis, promotes mitochondrial biogenesis
SELENOI	Ethanolamine-phosphotransferase 1 that synthesizes phosphatidylethanolamine
SELENOK	Participates in detoxification in endoplasmic reticulum, involved in calcium regulation
SELENOM	Perinuclear, highly expressed in brain, may be involved in calcium metabolism
SELENON	Protect against oxidative stress, regulates redox-related calcium homeostasis
SELENOO	Mitochondrial, largest mammalian selenoprotein, potentially active in redox control
SELENOP	Transports Se (10 Sec/molecule in humans) to brain, endocrine tissues, and placenta.
SELENOS	Participates in detoxification in the endoplasmic reticulum, may control inflammation
SELENOT	Thioredoxin-like protein expressed during development, and in adult endocrine tissues
SELENOV	Possesses GPX and TXNRD activities, expressed specifically in testis, may be redox active
SELENOW	Highly expressed in skeletal muscle, heart, and brain neurons, appears to be an oxidoreductase
DIO1	Activates thyroid hormone, converts T_4 into T_3 (thyroxine) predominant in liver, kidney
DIO2	Activates thyroid hormone, converts T_4 into T_3 thyroid, placenta, pituitary and brain
DIO3	Deactivates thyroid hormone in brain, placenta, and pregnant uterus, important in fetus
SEPHS2	Catalyzes formation of Se-phosphates required for synthesis of Sec to all selenoproteins
MSRB1	Repairs oxidatively damaged Met-R-sulfoxides back into native reduced Met conformation

[a] Information presented in this table was compiled from [18] using the newly approved names for the selenoproteins National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/; [19]).

[24] so that it can be used to synthesize a new Sec, which is created as it becomes incorporated in nascent selenoproteins [25].

In response to UGA (normally a stop codon) acting in concert with a specific stem-loop structure in the 3′ untranslated region, the Sec Insertion Sequence (SECIS) initiates de novo synthesis of Sec as it is co-translationally inserted into the protein sequence. Mammalian Sec synthase (SecS), a pyridoxal phosphate-containing protein, functions together with selenophosphate synthetase-2 (SEPHS2-which is itself a Sec-dependent enzyme) to form selenophosphate ($SePO_3^{3-}$), a high energy molecule that displaces the hydroxyl of the Ser moiety of O-phosphoseryl-tRNA[Ser]Sec to be replaced with a Se atom [26,27], thus generating the selenocysteyl-tRNA[Ser]Sec for incorporation of Sec in the polypeptide chain [28,29,127].

The importance of Se-metabolism is evident through the significant functions of its proteins (Table 1). For example, selenoenzymes such as glutathione peroxidase (GPX1, 2, 4, and 6) intercept and detoxify hydroxyl radicals while thioredoxin reductase (TXNRD1–3) restores vital cellular redox molecules (thioredoxin, ascorbate, and numerous others) that have become oxidized, such as vitamin C, vitamin E, ubiquinol, and polyphenols, back into their functional (reduced) forms in cytosol (TXNRD1) and within mitochondria (TXNRD2) for the prevention of oxidative damage in the cell (see Fig. 2). Selenoprotein M (SELENOM), selenoprotein N (SELENON), and selenoprotein W (SELENOW) appear to have similarly significant intracellular antioxidant functions while still other selenoenzymes restore oxidized Met (methionine sulfoxide reductase B1; MSRB1) and long chain fatty acids of phospholipids (GPX4) back to their reduced forms, using glutathione (GSH) as a cofactor. Selenoprotein P (SELENOP), the most common selenoprotein in the plasma, possesses 10 Sec residues which are preferentially delivered to the brain, placenta and endocrine tissues to supply their Se requirements [30,31]. The deiodinases (DIO1–3) regulate thyroid hormone metabolism [123,124]. DIO1 cleaves the iodine-carbon bond of T_4 (thyroxine) to activate thyroid hormone (T_3) in tissues other than brain, while DIO2 is responsible for > 75% of T_3 production in the brain, and is also active in pituitary/thyroid glands, skeletal/heart muscle, and placenta. The brain, placenta, and pregnant uterus express higher amounts of DIO3 and may protect the fetal central nervous system from disproportionately high levels of T_4 and T_3 [32,33]. Selenoprotein K (SELENOK) and selenoprotein T (SELENOT) are located on the membrane of the endoplasmic reticulum and are involved with calcium release and maintaining intracellular calcium homeostasis [34,35,142]. For comprehensive reviews of selenoproteins and their functions see Reeves and Hoffmann [18], Whanger [22], Rayman [36], Köhrle et al. [32], Köhrle and Gartner [33], and Kühbacher et al. [37].

The names of the 25 selenoprotein genes expressed in the human proteome reflect the recognized activities of the functionally characterized selenoenzymes while the nomenclature of the rest are standardized to employ the root symbol SELENO followed by a letter designating the individual gene [19]. For convenience and clarity, the gene names are used as the short name for the proteins throughout this article.
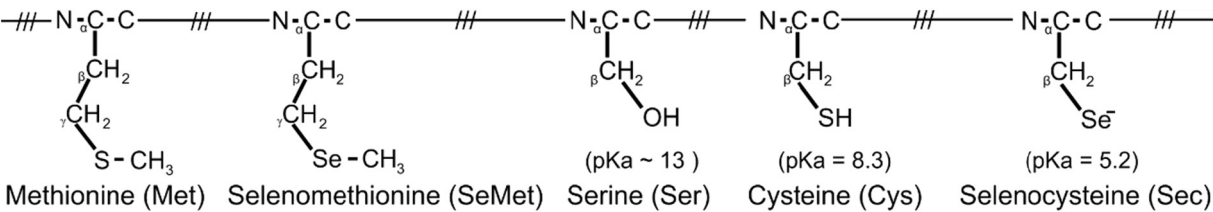

Fig. 1. The structural analogues of biologically significant chalcogen amino acids and their pKa's.
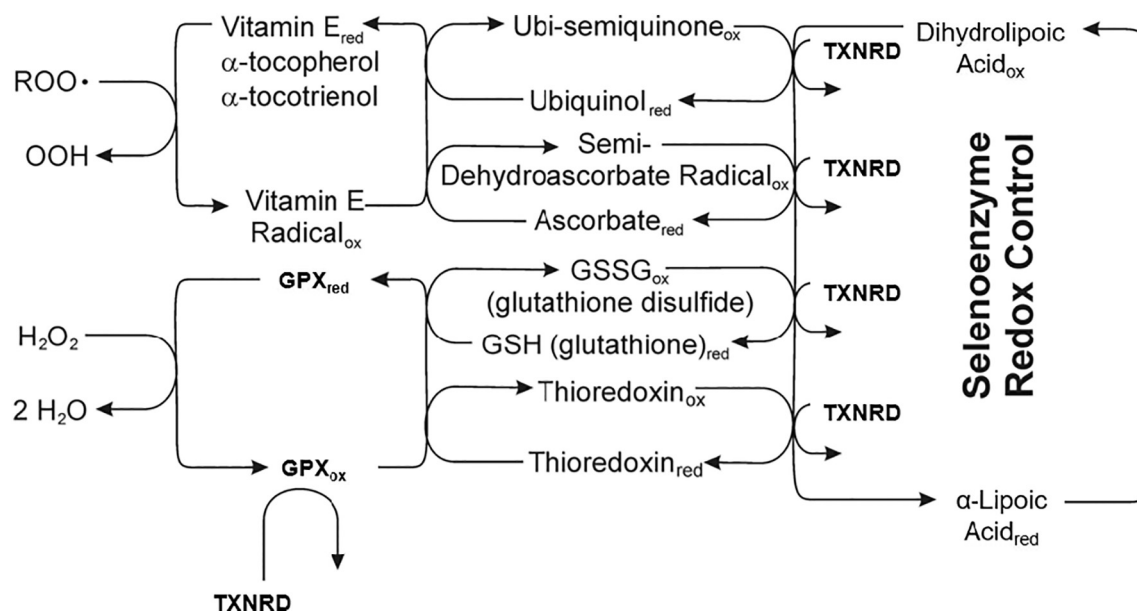
Fig. 2. Schematic of thioredoxin reductase (TXNRD) and glutathione peroxidase (GPX) activities in concert with some of the most important agents they interact with to restore oxidized (ox) forms back to their functional reduced (red) states as they cooperate in preventing and reversing oxidative damage.

2.2. Studies of mercury-selenium interactions

The role of selenoenzyme dependent prevention and reversal of oxidative damage in the brain was generally overlooked in earlier studies of Hg toxicity. Unaware that supplemental Se offset losses due to Hg sequestration, thus preventing interruption of the activities of selenoenzymes necessary to prevent oxidative damage to the brain and perform other vital functions, early investigators described Se as having a "protective effect" against Hg toxicity, − terminology which is convenient, but unacceptably imprecise. However, since Hg has greater affinity for Se than sulfur, readily exchanging association with a thiolate ligand for selenolate ligand in aqueous medium [11,38,39,150], that results in formation of HgSe within cells [40–42,131], this misapprehension is understandable. In silico calculations of quantum chemical interactions studies confirm CH_3Hg^+ complexes with Sec are thermodynamically favored (ΔG of formation from model reactants) in comparison to Cys [43]. These findings are consistent with qualitative predictions based on the Hard-Soft Acid Base concept [44], an approach which is useful for inferring interactions between electrophilic Hg and nucleophilic chalcogens. Mercury affinities would be predicted to follow the order: $O \ll S < Se$, reflecting their relative reactivities consistent with results shown in Fig. 3. Mercury continually exchanges association between thermodynamically equivalent binding partners such as thiols, but will readily exchange a bond with sulfur to form a new, higher affinity bond with Se.

2.3. Dietary selenium counteracting mercury toxicity

Selenium-containing molecules must first be degraded into inorganic Se before it can be used for de novo synthesis of Sec, regardless of whether it is obtained from the diet or originates from the breakdown of endogenous intracellular molecules. The major metabolic difference between inorganic and organic sources of Se is their rate of selenide formation. Selenite is quickly transformed into selenide once it enters the reducing environment of the cell [45] and Sec lyase degrades Sec to form selenide almost as rapidly, therefore, both promptly provide Se for Sec synthesis. Since SeMet becomes incorporated into proteins nonspecifically from Met and can engage in many cycles of protein synthesis before it is eventually degraded, the eventual release of its Se can be substantially delayed.

Numerous studies have shown Se counteracts Hg toxicity. Pařízek and Oštádalová [14] reported that lethal toxicity of mercuric chloride was alleviated by sodium selenite simultaneously administered to rats. Work by Ganther et al. (1972) showed that inorganic Se diminished the toxicity of CH_3Hg^+, reducing mortality and restoring weight gain in quail. Friedman et al. studied the protective effect of Se present in freeze-dried swordfish against CH_3Hg^+, toxicity in rats [46]. Rats fed CH_3Hg^+ containing diets that were not supplemented with Se from fish exhibited symptoms of neurotoxicity, but rats that were fed CH_3Hg^+ in a diet enriched with Se from swordfish showed no signs of toxicity. The molar concentrations of Se in the swordfish were approximately 5 times higher than their Hg concentrations. In a similar study, Japanese quail that were given 20 ppm CH_3Hg^+ in diets containing Se supplied by addition of 17% (by weight) tuna survived longer than quail given the same concentration of CH_3Hg^+ in a corn–soya diet. Methylmercury toxicity was also reduced when inorganic Se was added to the corn–-soya diets at concentrations equivalent to the tuna diets [47]. In both these studies, the authors suggested that the additional dietary Se protected against the negative consequences that otherwise accompanied the high levels of dietary CH_3Hg^+ that were administered. It has also been shown that maternal exposure to CH_3Hg^+ decreased Se concentration and impaired GPX and DIO activities in the brain of neonatal mice [48]. Watanabe et al. reported that CH_3Hg^+ exposure of Se-deficient perinatal mice resulted in retarded neurobehavioral development and persistent learning disabilities. Prenatal CH_3Hg^+ exposure affected several fetal mouse neurobehavioral and biochemical end points when their mothers were fed various amounts of dietary Se and all toxicity effects were exacerbated by perinatal Se deficiency. To determine whether CH_3Hg^+ exposure induces local Se deficiency in the fetal brain, Se concentrations and the activity of GPX were measured in the neonatal brain and other organs. Although the dietary level of Se did not affect brain Hg concentrations, the Se concentration and the activity of GPX were severely depressed by CH_3Hg^+ in fetal, but not maternal neural tissue [48], demonstrating that CH_3Hg^+ affects Se metabolism more severely in the fetal than adult brain.

Recently, dietary Se was used to successfully treat a previously healthy and athletic 70 kg (154 pound) 15-year-old patient that had been exposed to large amounts of Hg^0 vapor over a period of several weeks [49]. The patient had developed hypertension, muscular, testicular, and abdominal pain, insomnia, delusions, hallucinations,
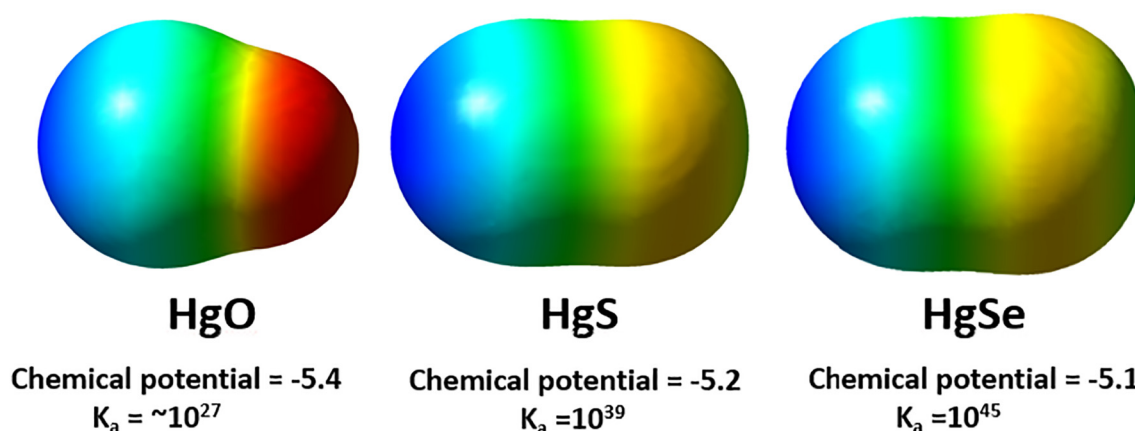
Fig. 3. Depictions of electrostatic potential surfaces of mercury in covalent association with the biologically significant chalcogens, their chemical potentials, and binding affinity constants. The electron cloud depicted in blue indicates a lower e$^-$ abundance and a more positive charge, while yellow shading to red indicates increasingly negative charge. The balance of the HgSe charges stabilizes the molecule, contributing to their remarkably high binding affinities. Images were generated using GaussView software, courtesy of Dr. Alexander Azenkeng, UND.

tachycardia, palmar desquamation, diaphoresis, tremor, loss of 17 kg (38 pounds), and increasingly severe ataxia leading to hospitalization. Examination revealed an elevated blood Hg level of 23 μg/L (~0.11 μM) that was below the concentration range associated with CH_3Hg^+ toxicity. Chelation with 2,3-Dimercaptosuccinic acid (DMSA) was initiated, but the patient's health continued to deteriorate. Dietary Se supplementation with 500 μg Se (~0.1 μMol/kg BW) along with 50 mg of *N*-acetylcysteine per day was initiated to support SELENOP and GSH synthesis. Within 3 days, the patient showed noticeable improvement, and by day 11, delusions, delirium, tachycardia, and abdominal pain had resolved and since he was once again ambulatory and eating normally, he was released from the hospital but maintained on the Se and NAC supplement. After 3 months, all symptoms had resolved except hypertension and after an additional 2 months, he regained 35 pounds, his hypertension resolved, and he returned to athletic activities, returning to his position on the football team soon after. Selenium supplementation was continued for 8 months, but did not result in elevated serum Se levels. The treating physician indicated this may suggest a systemic Se deficit and/or continued Se sequestration as HgSe.

3. The biochemical mechanisms of mercury toxicity

Pařízek and Oštádalová [14] were the first to report that rats treated with otherwise lethal doses of HgCl were protected when provided supplemental Se. Since then, the ability of Se compounds to decrease the toxicity of various forms of Hg has been established in all investigated species of mammals, birds, and fish [46,50–52] and described in comprehensive reviews by Cuvin-Aralar and Furness [53], Gailer [54], Bjørklund et al. [55] and Spiller et al. [106].

The toxic effects of CH_3Hg^+ (see Fig. 4) involve a sequence of biochemical reactions referred to as the "SOS" Mechanisms [56]. The consequences of these metabolic disruptions become increasingly apparent as CH_3Hg^+ concentrations approach, and especially as they exceed, equimolar stoichiometries with brain Se.

3.1. Synthesis of suicide-substrates (SOS-1)

The placental and blood brain barriers do not prevent passage of CH_3Hg-Cys, which is taken up by the LAT1 transporter and carried across cell membranes. Protein synthesis demands require higher importation of Met and other large nonpolar amino acids, explaining the higher concentrations of fetal CH_3Hg-Cys accumulation relative to maternal blood. Once across placental and blood brain barriers, CH_3Hg promiscuously exchanges binding partners among Cys residues of other

molecules. As Fig. 2 illustrates, the binding sites of the three forms of TXNRD interact with thioredoxin and a broad variety of other thiomolecule substrates [57] to reduce their oxidized disulfides. The GPX enzymes employ 2 GSH molecules as reducing agent co-substrates to reduce cellular peroxides. In these and other thioreactive selenoenzymes, the Cys residue of the substrate enters into close proximity with the active site Sec that catalyzes the proton exchange. Formation of CH_3Hg-bound thiomolecules during SOS 1 is the precipitating first step towards toxicity. If the various thiomolecules were not specific substrates for selenoenzymes, SOS-2 and all the subsequent consequences of CH_3Hg^+ toxicity would not occur. However, because SOS-1 results in CH_3Hg^+ binding to the Cys residues of these thiomolecules, they become "suicide substrates" that subsequently deliver the bound Hg to the selenoenzyme's active site.

3.2. Silencing of selenoenzymes (SOS-2)

The high vulnerability of selenoenzymes to CH_3Hg^+ exposures was proposed by Ganther et al. [47], and demonstrated by Prohaska and Ganther [10]. The development of oxidative damage as a result of Hg-dependent inhibition of selenoenzymes was described by Seppanen et al. [62]. With an IC_{50} of ~19.7 nM, TXNRD activities are especially prone to inhibition by CH_3Hg^+ [58,21,121] and numerous in vitro and in vivo studies have examined time and dose dependent effects [56,58–61,121]. Mercury dependent inhibition of GPX is well documented ([10,48,56,62,151,152] and supplemental Se has been shown to prevent interruption of these selenoenzyme activities in the brains of laboratory animals ([48]; [56; 152]).

Upon binding with the CH_3Hg-Cys adduct formed via SOS 1, the CH_3Hg^+ exchanges its covalent association from the substrate Cys to the activated Sec of the enzyme's active site (see Fig. 4) resulting in formation of an extremely stable CH_3Hg-Sec inhibitor-enzyme complex. Unlike Cys, the partnership of CH_3Hg with Sec is permanent due to the high binding affinity between Hg and Se. Therefore, the enzyme can no longer perform its essential functions because its catalytic Sec is blocked by CH_3Hg^+. Thus, by biochemical definition, CH_3Hg^+ is a highly selective irreversible inhibitor of selenoenzymes. In addition to coinciding with observations of increased oxidative damage, inhibition of SELENOT results in increased cellular free calcium and increased catecholamine release [34,63,64]. This could arise through direct binding to the active site Sec of SELENOT or as a result of depletion of biologically available Se. Since increases in catecholamine release appear to occur between > 1 and 10 mmol of Hg [65], this mechanism may explain the tachycardia and hypertension observed in acrodynia as well as in the Hg^0 exposed patient described in Section 2.3.
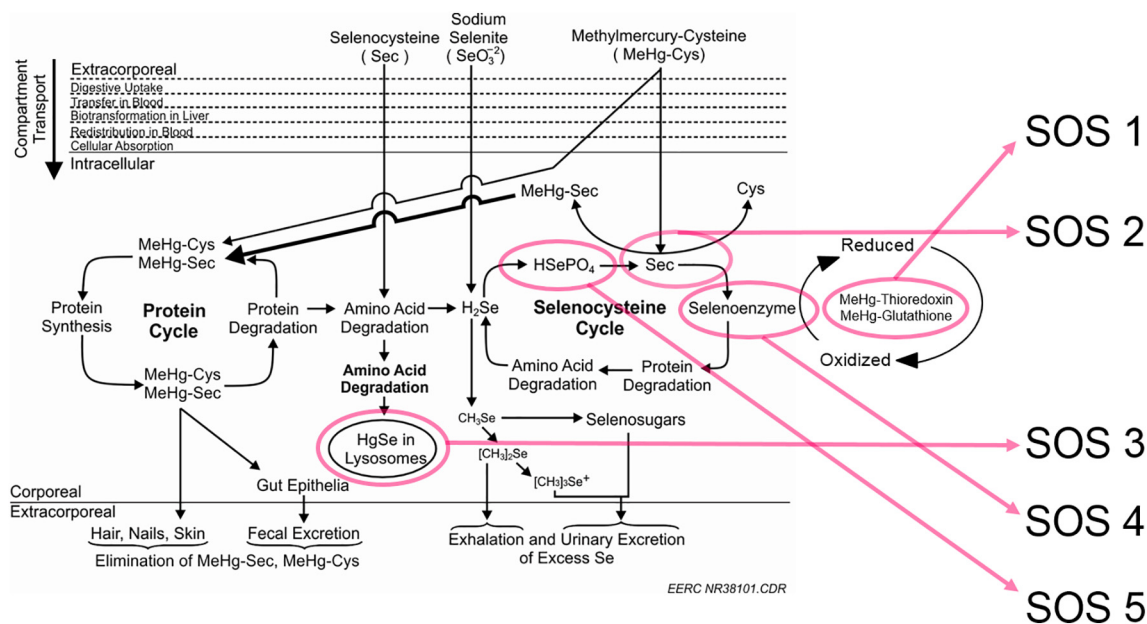
Fig. 4. Schematic of the "SOS Mechanisms" of Mercury Toxicity. Disruptions of the biochemical pathways of selenoenzyme activities, synthesis and related physiological outcomes, are indicated in the sequence in which they are expected to occur.

3.3. Sequestration of selenium (SOS-3)

Loss of selenoenzyme activities due to irreversible inhibition is augmented by CH₃Hg's uniquely insidious ability to induce a conditioned Se-deficiency in the brain. Methylmercury is the only environmental insult has been shown to diminish brain Se below the otherwise impenetrable minimum threshold of ~60% of normal [66]. Sequestration of Hg together with Se as the result of CH₃Hg⁺ binding to the Sec of TXNRD is particularly evident in kidney and liver [67]. Following catastrophically high CH₃Hg exposures, there is an ongoing attrition of Se in somatic and brain [42] tissues due to the continual formation biologically unavailable mercury selenide (HgSe). This complex is resistant to decomposition by acids other than aqua regia or by heating in excess 300 °C. Therefore, lysosomal HgSe accumulates in equimolar precipitates that exhibit long-term retention [68,69]. It is important to recognize that high Hg accumulations of Hg (e.g., 10–100 μM) in brain and endocrine tissues appear to be without toxicological consequences [69], provided at least ~1 μM of "free Se" remains available for selenoenzyme synthesis, thus ensuring their activities can proceed without interruption.

3.4. Suicide of selenium-deprived cells (SOS-4)

Following Hg-sequestration of cellular Se, insufficient bioavailable Se may produce truncated molecules that lack the terminal Sec residue [70]. Truncated forms of TXNRD, known as GRIM-12; are potent apoptosis (cell suicide) initiators. Sequestration of cellular Se by CH₃Hg⁺ may not only deprive cells of the selenoenzymes they need to prevent and reverse oxidative damage, but may also transform of TXNRD into a potent apoptosis initiator. Observations of phosphorylation of apoptosis signaling kinase 1 (ASK1), caspase-3 activity, and the increase apoptotic cells following high CH₃Hg⁺ exposures are supportive of this mechanism [59], although further work is clearly needed to establish its validity. The consequences of GRIM12-dependent and other mechanisms that contribute to neuronal apoptosis could be especially damaging during fetal brain development, and might also be a contributing factor in adult CH₃Hg⁺ poisoning. Furthermore, impairment of the thioredoxin and glutaredoxin systems results in proliferation of reactive oxygen and nitrogen species in cytosol and mitochondria which lead to mitochondrial injury/loss, lipid peroxidation,

calcium dyshomeostasis, impairment of protein repair, and apoptosis [71–73].

3.5. Sustained oblivion of Sec synthesis (SOS-5)

Selenophosphate synthetase (SEPHS2), the enzyme that makes the SePO₃³⁻ required for Sec production, is itself a selenoenzyme. If SEPHS2 activities are abolished, production of Sec may never be restored in that cell since there is no way to create the Sec required in its own active site. Although this mechanism remains hypothetical, once SEPHS2 has been abolished by high CH₃Hg⁺ exposures in a cell, this biochemical "catch-22" could permanently prevent restoration of Sec synthesis. [152], found that high CH₃Hg⁺ exposures during fetal growth had a sustained effect on brain selenoenzyme activities. If confirmed, it appears that the damaging effects of CH₃Hg⁺ toxicity are not only extensive, they are likely to endure.

4. The brain specificity of mercury-dependent oxidative damage

Oxygen consumption in the brain is ~10 fold higher than in other tissues, placing the brain at an increased risk of oxidative damage due to formation of reactive oxygen and nitrogen species. This risk is accentuated by the brain's limited antioxidant enzyme pathways that are abundantly available in other tissues; its high iron contents could potentiate oxidative damage via the Fenton reaction; and the brains increased abundance of long chain polyunsaturated fatty acids, which are vulnerable to lipid oxidation [20,21]. These factors emphasize the importance of selenoenzymes that prevent as well as reverse oxidative damage in the brain. To ensure these essential functions are not interrupted, brain Se concentrations are homeostatically controlled to maintain Se availability for selenoenzyme synthesis and activities [74,75]. During extended periods of dietary Se deficiency in laboratory animals ([10,66], the Se contents of somatic tissues such as liver, muscle, and blood, diminish to < 2% of their normal contents. Selenium-transport molecules redistribute Se from somatic tissues to preferentially supply brain and endocrine tissues. When Se-deficient rats were provided radiolabeled ⁷⁵SeO₃²⁻, brain was preferentially labelled before other tissues [76]. Brain reserves in the form of cellular SELENOP serve as accessible reservoirs since Sec lyase rapidly degrades Sec to supply inorganic Se for utilization in each cycle of de novo

synthesis of new Sec molecules. These sources will maintain brain Se concentrations at a minimum plateau level of 60% of normal [66], while retaining essential selenoenzyme activities at near-normal levels. This pattern has been shown to continue in offspring, even after many generations of continual Se-deficiency.

Homeostatic regulation of selenoenzyme expression and activities in the brain varies by tissue, cell layer, and cell type ([77]. Although all selenoprotein mRNAs are expressed in brain, GPX4, SELENOK, SE-LENOM, SELENOW, and SELENOF are exceptionally rich in neurons of the olfactory bulb, hippocampus, cerebral cortex, and cerebellar cortex. The preferential expression of certain selenoproteins in the brain suggests a hierarchy of need for brain activities [78]. Because the distal compartments of dendrites and axons are remote from the soma of the neuron, it is difficult for the cell to repair damage to cellular components in the highly active regions of their synapses. Therefore, selenoenzyme-dependent maintenance of reduced ascorbate and other antioxidant molecules are essential for the prevention and reversal of oxidative damage in the synaptic interface, and homeostatic mechanisms have evolved to ensure their expression and activities proceed without interruption [66]. The only environmental insult known to severely impair brain selenoenzyme activities is high CH_3Hg^+ exposure ([10,48]; [56]; [152]). As examples of discrete tissue-dependent differences in mRNA transcription and translation in brain, the distributions of two selenoproteins, SELENOM and SELENOW, are shown in Fig. 5.

Using synchrotron X-Ray absorption spectroscopy (XAS), Korbas et al. [42] found high concentrations of HgSe in brains of individuals that had been poisoned with high CH_3Hg^+. During CH_3Hg^+ poisoning, availability of free Se in the brain declines and brain selenoenzyme activities diminish, resulting in extensive damage to the most active neurons. These neurons are destroyed as a result of SOS 1–3 and/or apoptosis as a result of SOS 4. Meanwhile, the less vulnerable cells survive the crisis because they have maintained sufficient Se for selenoenzyme activities. The severity of the pathology will be proportional to neuronal cell damage and death, even though the brain cells that

survive may gradually recover to normal levels of selenoenzyme activity, as was observed by Korbas et al.

Postmortem examination of the brains of victims of CH_3Hg^+ poisoning show varying degrees of neuronal cell loss, especially in the sensory regions of the cortex, cerebellar granular cells, primary motor cortex [79], and peripheral nerves [80], a pattern also seen in laboratory animals [81]. The loss of coordination (ataxia) that occurs during severe CH_3Hg^+ poisoning is due to cerebellar damage to small granule cells being destroyed, but Purkinje cells and other neighboring cells from the same region remain mostly unaffected. Similarly, loss of neurons from the visual cortex is responsible for the constriction of visual fields. The reasons for different sensitivities of neurons from different brain regions are currently unknown. However, distinctions in neuron sensitivity to high CH_3Hg^+ exposures are likely to be due to variances in the turnover rates of essential selenoenzymes, different efficiencies of ApoER2-mediated uptake of SELENOP from plasma by certain brain cell types, and discrepancies in relative abilities of each cell type to preserve their internal Se reservoirs.

5. Accentuated fetal vulnerability to mercury exposures

The fetus is without significant tissue Se reserves, so loss of maternal Se imports to the rapidly growing brain can result in impaired selenoenzyme activities and damage. The three main families of selenoenzymes (iodothyronine deiodinases, thioredoxin reductases, and glutathione peroxidases) have critical roles in fetal brain development, growth, thyroid and calcium metabolism, protein folding, and prevention/reversal of oxidative damage, particularly in neuroendocrine tissues (see Table 1 and reviews mentioned above). The SELENOP molecule, the most abundant form of Se in plasma, is the primary carrier of Se to the placenta where it is taken up by the SELENOP specific receptor: ApoER2 [31,82]. Approximately 25% of the body's total Se is cycled through SELENOP daily [30], and since SELENOP appears to be a Hg carrier (139,140), it may also be a vehicle for Hg transport into the brain Mice that have been genetically modified to delete SELENOP or
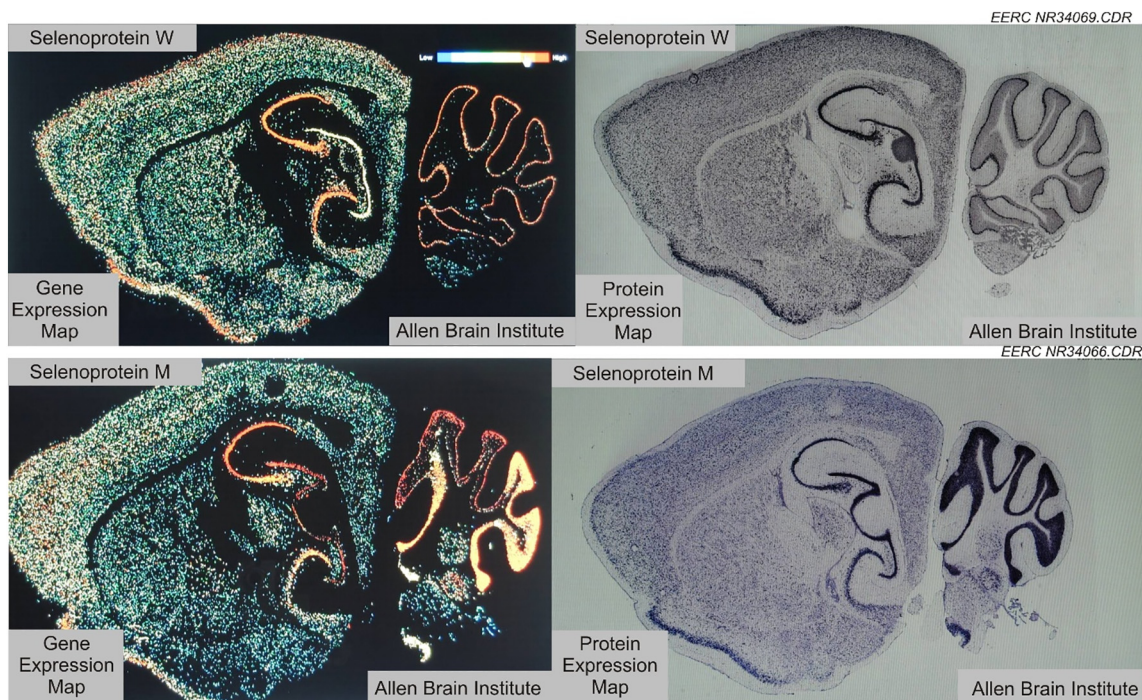

Fig. 5. Images from the Allen Brain Atlas depicting in situ hybridization of mRNA (left side) and protein distributions (right side) for SELENOW and SELENOM observed in sagittal sections of mouse brain cerebrum and cerebellum. High levels of mRNA expression are in red, moderate levels in yellow, low levels in green, while where mRNA below detection limits are black. Distinctive patterns of expression are evident in discrete cell layers with mRNA expression correlated with high protein concentrations. Image credit: Allen Institute [158].

ApoER2 (the cell surface receptor that captures and internalizes SE-LENOP) suffer severe neurodegeneration in brain regions that are associated with auditory and motor functions [82,83]. SELENOP knockout models demonstrate ataxia and Se-deficient diets result in lethality [84]. Additional studies indicate that high CH_3Hg^+ exposures diminish maternal Se distribution to the fetus by ~70% [85]. The combination of high Hg and low dietary Se was shown to diminish fetal brain Se to ~23% of normal, with a portion of that sequestered as HgSe, and brain GPX activities diminishing to ~14% of normal [48].

Fetal vulnerability was first observed in association with catastrophic poisoning events in Minamata Japan where 75–150 tons of Hg were dumped into the local bay of the Yatsushiro Sea, a shallow semi-enclosed inland sea separating the island of Kyūshū from the Amakusa Islands. The contaminated fish that were consumed attained CH_3Hg^+ concentrations as high as 50 mg/kg [86], or ~250 μM, a quantity 25–50-fold greater than their Se contents. Umbilical cords saved from births were found to contain ~40 times more Se than Hg prior to the poisoning events (1927–1937). However, during the poisoning event (1939–1959) [118], the umbilical cords of children with high Hg-exposures contained ~3 times more Hg than Se [118].

In addition to the poisoning events in Japan [86] and Iraq [153], epidemiological studies in New Zealand [87], which is a Se deficient region, and the Faroe Islands ([88,89] [90,91]) reported associations of CH_3Hg^+ exposures with slight, concentration-dependent adverse effects on fetal development. These studies involved mothers eating seafoods during pregnancy with high Hg:Se ratios such as great white shark and pilot whale (~5:1) respectively. Although Se-rich cod fish was consumed in greater quantities, > 95% of total CH_3Hg^+ exposure in the Faroe Islands originated from pilot whale consumption. The authors of this study later concluded that the cod fish offered substantial benefits that offset the otherwise expected neurodevelopmental damage from pilot whale consumption. Due to their high Hg content, advisories against pilot whale consumption have since been evoked and its meats removed from consumer markets [92].

Conversely, epidemiological studies have consistently found that increasing CH_3Hg-Cys exposures from maternal consumption of typical varieties of ocean fish result in neurological benefits rather than deficits in their children [93–100]. These studies report beneficial associations with neurological development, motor development, verbal intelligence quotient, perception, social behavior, and reduced inattention and hyperactivity. A partial attenuation of these positive associations was noted in the highest seafood intake category [93], but it is uncertain whether CH_3Hg-Cys was actually responsible for the slight decrease in the net beneficial effects, or if higher exposures to other persistent bioaccumulative toxicants were responsible.

In the Seychelles study, mean prenatal CH_3Hg^+ exposure was higher than in the Faroe Islands study, but no adverse associations were found between CH_3Hg^+ and 21 endpoints [94]. Instead, increasing prenatal CH_3Hg^+ was associated with improved scores on four neurological endpoints, as well as fewer reports of substance abuse and incidents of problematic behaviors in school. Furthermore, increasing maternal seafood consumption was shown to be associated with up to 5 points of child IQ benefits in the United Kingdom [96] and nearly 10 points in the United States [101], even though MeHg exposures were greatest among mothers with the highest seafood intakes. Children of mothers who avoided fish consumption during pregnancy displayed developmental impairments of a magnitude ~60 times greater than the worst-case effects associated with the highest pilot whale consumption (thus the highest CH_3Hg^+ exposures) in the Faroes [96]. Additionally, the children of mothers who complied with the 2004 U.S. Environmental Protection Agency reference dose (RfD) for CH_3Hg^+ exposure from fish consumption had an increased risk of scoring in the lowest quartile for verbal IQ, compared to children of mothers exceeding the recommended fish intake. Maternal compliance with diminished fish consumption also increased children's risks for pathological scores in fine motor, communication, and social skills.

The findings of these studies suggest that CH_3Hg^+ exposure from ocean fish which contain Se in excess of CH_3Hg^+ (a characteristic shared by nearly all commercial marine fish species) [109] does not result in developmental harm, but diminished maternal consumption of ocean fish during pregnancy is associated with significant risks. Ocean fish are a significant source of Se and other important nutrients required for the health and development of children and avoiding ocean fish consumption during pregnancy is associated with the loss of these benefits.

6. The biochemical basis for the latency effect in mercury toxicity

Mercury toxicity is characterized by (an unexplained) silent latency; a prolonged delay between ingestion of a harmful or lethal dose and the onset of symptoms, which in some cases may take months to develop [13,102,103,154–156]. The onset of clinical symptoms following high CH_3Hg^+ exposures display a similar sequence: paresthesia (a tingling sensation in lips and extremities) is the first symptom to arise followed by ataxia (loss of motor coordination gradually intensifying to severe disruption of functions), dysarthria (difficulty in pronouncing words), vision constriction, deafness, and if the dose is overwhelming, ultimately death. However, CH_3Hg^+ has a physiological half-life of ~74-days [2] and symptoms often don't arise until much of the ingested dose has left the body [13,102]. The severity of Hg-associated brain damage is directly related to the magnitude of the dose, but the latency period is not [13]. For example, a researcher that died following an accidental laboratory exposure to CH_3HgCH_3 (which is rapidly demethylated to CH_3Hg^+) showed no symptoms for ~150 days [102], whereas among Iraqis exposed to similar amounts of CH_3Hg^+ the latency period was only 16–38 days [155]. The influence of Se status on latency of CH_3Hg^+ effects are apparent in animal studies where laboratory rats fed low-Se diets rapidly show physiological, biochemical, and neurofunctional defects while those fed normal-Se diets show these effects later and to a lesser degree [128], and those fed rich-Se diets showed no consequences during the course of the 9 or 18 week study [104,105].

If CH_3Hg^+ occurred through pseudo-first order reactions, the latency period should be uniformly brief, inversely related to dose, and comparable among those exposed to similar doses. It would also be only marginally affected by supplementation with Se in quantities that are considerably smaller than the CH_3Hg^+ dose. Likewise, latency would be inversely related to the received dose if the mechanism involved gradual accumulation of toxic metabolites to some threshold level causing the damage, e.g., demethylation of CH_3Hg^+ to form inorganic $Hg^{+/2+}$. However, the latency period which characterizes CH_3Hg^+ poisoning is strong evidence in support of the concept that Hg's effects arise primarily if not exclusively from inhibition of Se-metabolism. Provided Se is available to support essential brain selenoenzyme activities, the adverse consequences of toxic levels of CH_3Hg^+ will not develop. However, CH_3Hg^+ in stoichiometric excess of the exposed individual's total Se reserves are likely to eventually overwhelm their ability to offset systemic losses of Se-sequestration as HgSe. Differences in individual Se status will influence the duration of latency since the effects of biomolecular reactions are proportional to tissue concentrations of both CH_3Hg^+ and Se. Continual attrition of Se reservoirs will gradually diminish availability of mobilized Se for the brain to maintain enzymatic function in the neurons. As the availability of selenoenzyme activities that prevent and reverse oxidative damage diminishes below a critical threshold, the damage to cellular lipids, proteins, and other important biomolecules will become increasingly evident, resulting in the symptoms which characterize Hg toxicity [106]. The extent of the delay in onset of these damaging effects are predicted to be directly proportional to the Se-reserves of the exposed individual, while the severity of the effects will be proportional to the molar ratio of CH_3Hg^+ dose in relation to total Se.

Because Americans typically consume Se rich foods, Se reserves tend to be more extensive. The tissue Se reserves and daily dietary Se

intakes of the American researcher were apparently sufficient to preserve her brain's seleneoenzyme activities for 5 months before the consequences of the onetime toxic dose became evident. But because the diets consumed by the Iraqi population are not as Se rich as those of Americans, it is likely their Se reserves were overwhelmed more quickly by their CH_3Hg^+ exposures, resulting in more rapid onset of symptoms. These possibilities are being evaluated by a Physiologically Oriented Interactions of Nutrients and Toxicants (POINT) model. This computational method incorporates dietary Se intakes, CH_3Hg^+ exposures, and their relative rates of retention/excretion, tissue distributions and complex formation to assess Se-attrition as a result of Hg sequestration in comparison to Se-redistribution through the homeostatic mechanisms which preferentially supply Se to brain and endocrine tissues.

7. Discussion

Recognition of the biochemical interactions between CH_3Hg^+ and seleneoenzymes provides a consistent basis for understanding the distinctive aspects of Hg toxicity and previous discrepancies between results of various studies.

The consequences of the SOS mechanisms appear sufficient to account for the adverse effects that have been reported in association with toxic CH_3Hg^+ exposures. The possibility of additional mechanisms should not be excluded; however, care must be applied to distinguish potentially Se-independent consequences from those that may occur secondary to loss of seleneoenzyme activities.

Failing to adhere to laboratory study designs that properly reflect the normal physiological ranges of dietary CH_3Hg^+ exposures and Se intakes have contributed to misunderstandings of the effects that are expected to accompany Hg-Se interactions in human exposures. Prior to recognition of Se's metabolic functions, Se was only known as a toxicant, so its protective mechanism was attributed to mutual detoxification of two poisonous elements. Early attempts to examine effects of supplemental Se in protecting against Hg toxicity have sometimes used equivalent mass quantities (e.g., 10 mg/kg) of Hg and Se, rather than physiologically appropriate molar concentrations. Although 10 mg Hg/kg is ~50 µmol Hg/kg, 10 mg Se/kg (~126 µmol Se/kg), is in tremendous excess of the normal ~1 µmol Se/kg in laboratory animal diets, and ~5 times Se's toxic threshold. Such unfortunate oversights were common in early experimental studies. Later research studies have employed physiologically appropriate amounts of Se (e.g., 10 µmol Se/kg, – approximating the average Se concentration in ocean fish) and found it effective in eliminating the otherwise toxic effects of 50 µmol Hg/kg on the development and neurological functions of growing rats [104,105].

Throughout this review, our focus has been on the loss of cellular redox control that arises as a result of CH_3Hg-dependent inhibition of seleneoenzymes that prevent and reverse oxidative damage. However, intracellular Se-deficiencies due to Hg-dependent Se-sequestration seem likely to impair other Se-dependent metabolic pathways, including some which could greatly exacerbate oxidative damage [106]. Loss of SELENOK results in calcium release from the endoplasmic reticulum [35,142], coinciding with effects noted in cell culture experiments [107,108]. SELENOM, SELENON, SELENOT also have been linked to calcium homeostasis, further supporting that concept (see Table 1; [34]).

As the biochemical target of CH_3Hg^+ toxicity, Se-physiology provides perspective on the brain specificity of its oxidative damage, accentuated fetal vulnerability, and latency. However, current seafood risk assessments are based solely on the CH_3Hg^+ levels in the fish, but actual risks increase in direct relation to Hg:Se molar ratios [56,105]. Ocean fish are among the richest sources of Se in the U.S. diet, and although their CH_3Hg^+ concentrations vary in relation to their trophic level, their tissue Se concentrations generally remain constant regardless of size [109]. Conversely, MeHg is nonspecifically bioaccumulated in fish as a molecular mimic of methionine, so the amount they

bioaccumulate increases as they grow older and larger. Fish at the top of the food web can harbor tissue mercury concentrations $> 10^6$-fold higher than that of the water in which they live [110].

Similar to all other vertebrates, fish homeostatically regulate their tissue concentrations of Sec, so their brain and endocrine tissues are well protected against decrements due to poor Se intakes. Selenium is abundant in the marine food web, so regional differences in tissue Se are unlikely to be observed in pelagic fish. However, fish that inhabit estuaries of rivers whose watershed have poor soil Se availability are likely to have diminished Se in their fillets. The abundance of Se available in aquatic ecosystems is directly related to the abundance of Se in surrounding soils, but it is also dependent on pH of their soil-water environment. Even when Se is present in soil, its availability for uptake by plants becomes compromised in regions with low pH in soil or water. Waterbodies with low Se have accentuated MeHg accumulation and retention in the fish inhabiting these areas [111–115,157]. Therefore, the CH_3Hg^+ and Se levels in freshwater fish can differ considerably, possibly exacerbating Hg exposure risks.

Enhanced CH_3Hg^+ bioaccumulation in fish from Se-poor watersheds has the potential for an adverse synergy of increasing CH_3Hg^+ exposures while simultaneously increasing the risks associated with those exposures since the fish fail to provide adequate Se to offset losses due to Se-sequestration by Hg. Subsistence consumers of fresh water fish are at particular risk of toxic effects from such high exposures. For example, in a subsistence freshwater fish consuming population in the Amazon, motor function abilities were inversely related to blood Hg concentrations, but directly related to Se status [116]. Because locally grown foods in Se-deficient regions fail to provide background dietary sources of Se, the effect of other soft metallic or organic (e.g., [117]) electrophiles will accentuate risks associated with CH_3Hg^+ exposures. Risk assessments that simply assess CH_3Hg^+ exposures cannot adequately address these other important considerations.

7.1. Conclusions

Toxicology is a rapidly evolving field which continually disproves dogma, overcomes mistaken assumptions, and steadily improves understanding of biochemical mechanisms of toxicity. The five conundrums of CH_3Hg^+ toxicity: 1) the basis for the "selenium (Se)-protective" effect, 2) the absence of a clear biochemical mechanism for Hg's effects, 3) the tissue specificity of its effects, 4) the enhanced vulnerability of the fetal brain, and 5) the extended latency betweeen exposure and toxic consequences, arose from misunderstandings of Hg-Se interactions and lack of familiarity with Se physiology. This review, compiled from over 50 years of research progress, indicates that the distinctive characteristics of CH_3Hg^+ toxicity are consistent with its unique ability to impair brain seleneoenzyme activities, thus resolving these conundrums. The SOS mechanisms result in seleneoenzyme inhibition in brain tissues, thus providing a consilient perspective of the commonalities between predicted and observed reaction stoichiometries, biochemical products, tissue sensitivities, and the pathological effects that arise as a result of CH_3Hg^+ dependent impairments.

These findings have clear implications for risk assessment research, policy, and regulations. Predatory whales, certain varieties of shark, large specimens of swordfish, halibut, or any other types of fish that contain more Hg than Se should not be consumed by children or pregnant women. However, nearly all other seafoods and ocean or freshwater fish provide far more Se than CH_3Hg^+ to consumers and will therefore improve, rather than diminish, maternal and fetal Se status while providing nutritional benefits for health and development. To enhance the reliability of CH_3Hg^+ risk assessments, dietary Se intakes must be considered in relation to CH_3Hg^+ exposures.

Transparency document

The Transparency document associated with this article can be

found, in online version.

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References

[1] T.W. Clarkson, L. Magos, The toxicology of mercury and its chemical compounds, Critical Rev. Toxicol. 36 (2006) 608–662.

[2] T. Syversen, P. Kaur, The toxicology of mercury and its compounds, J. Trace Elem. Med. Biol. 26 (4) (2012) 215–226, http://dx.doi.org/10.1016/j.jtemb.2012.02.004.

[3] S. Halbach, T.W. Clarkson, Enzymatic oxidation of mercury vapor by erythrocytes, Biochim. Biophys. Acta 523 (2) (1978) 522–531.

[4] C.T. Driscoll, R.P. Mason, H.M. Chan, D.J. Jacob, N. Pirrone, Mercury as a global pollutant: sources, pathways, and effects, Environ. Sci. Technol. 47 (10) (2013) 4967–4983.

[5] H.H. Harris, I.J. Pickering, G.N. George, The chemical form of mercury in fish, Science 301 (5637) (2003) 1203, http://dx.doi.org/10.1126/science.1085941 12947190.

[6] R.E. Hoffmeyer, S.P. Singh, C.J. Doonan, A.R.S. Ross, R.J. Hughes, I.J. Pickering, G.N. George, Molecular mimicry in mercury toxicology, Chem. Res. Toxicol. 19 (6) (2006) 753–759.

[7] C.C. Bridges, R.K. Zalups, Molecular and ionic mimicry and the transport of toxic metals, Toxicol. Appl. Pharmacol. 204 (2005) 274–308.

[8] L. Giraultab, A. Boudoub, E.J. Dufourca, Methylmercury interactions with phospholipid membranes as reported by fluorescence, ^{31}P and ^{199}Hg NMR, Biochim. Biophys. Acta Biomembr. 1325 (2) (1997) 250–262.

[9] S. Nakada, K. Inoue, S. Nojima, N. Imura, Change in permeability of liposomes caused by methylmercury and inorganic mercury, Chem. Biol. Interact. 22 (1) (1978) 15–23.

[10] J.R. Prohaska, H.E. Ganther, Interactions between selenium and methylmercury in rat brain, Chem. Biol. Interact. 16 (2) (1977) 155–167.

[11] D. Dyrssen, M. Wedborg, The sulfur-mercury(II) system in natural waters, Water Air Soil Pollut. 56 (1991) 507–519.

[12] R.J. Cremlyn, An Introduction to Organosulfur Chemistry, John Wiley and Sons, Chichester, 1996.

[13] B. Weiss, T.W. Clarkson, W. Simon, Silent latency periods in methylmercury poisoning and in neurodegenerative disease, Env. Health. Persp. 110 (5) (2002) 851–854.

[14] J. Pařízek, I. Oštádalová, The protective effect of small amounts of selenite in sublimate intoxication, Experiential. 23 (2) (1967) 142–143.

[15] I. Erni, G. Geier, Kinetics of extremely fast ligand exchange reactions with methylmercury(II)-complexes of 1-methylpyridine-2-thione and 1-methyl-quinaldine-4-thione: rate-equilibria correlations, Helvetica Chimica Acta. 62 (1979) 1007–1015, http://dx.doi.org/10.1002/hlca.19790620411.

[16] V.N. Gladyshev, G.V. Kryukov, D.E. Fomenko, D.L. Hatfield, Identification of trace element-containing proteins in genomic databases, Annu. Rev. Nutr. 24 (2004) 579–596.

[17] G.V. Kryukov, V.N. Gladyshev, The prokaryotic selenoproteome, EMBO Rep. 5 (5) (2004) 538–543.

[18] M.A. Reeves, P.R. Hoffmann, The human selenoproteome: recent insights into functions and regulation, Cell. Mol. Life Sci. 66 (15) (2009) 2457–2478, http://dx.doi.org/10.1007/s00018-009-0032-4.

[19] V.N. Gladyshev, E.S. Arnér, M.J. Berry, R. Brigelius-Flohé, E.A. Bruford, R.F. Burk, B.A. Carlson, S. Castellano, L. Chavatte, M. Conrad, P.R. Copeland, A.M. Diamond, D.M. Driscoll, A. Ferreiro, L. Flohé, F.R. Green, R. Guigó, D.E. Handy, D.L. Hatfield, J. Hesketh, P.R. Hoffmann, A. Holmgren, R.J. Hondal, M.T. Howard, K. Huang, H.Y. Kim, I.Y. Kim, J. Köhrle, A. Krol, G.V. Kryukov, B.J. Lee, B.C. Lee, X.G. Lei, Q. Liu, A. Lescure, A.V. Lobanov, J. Loscalzo, M. Maiorino, M. Mariotti, K. Sandeep Prabhu, M.P. Rayman, S. Rozovsky, G. Salinas, E.E. Schmidt, L. Schomburg, U. Schweizer, M. Simonović, R.A. Sunde, P.A. Tsuji, S. Tweedie, F. Ursini, P.D. Whanger, Y. Zhang, Selenoprotein gene nomenclature, J. Biol. Chem. 291 (46) (2016) 24036–24040.

[20] U. Schweizer, A.U. Bräuer, J. Köhrle, R. Nitsch, N.E. Savaskan, Selenium and brain function: a poorly recognized liaison, Brain Res. Rev. 45 (2004) 164–178.

[21] U. Schweizer, L. Schomburg, N.E. Savaskan, The neurobiology of selenium: lessons from transgenic mice, J. Nutr. 134 (2004) 707–710.

[22] P.D. Whanger, Selenium and the brain: a review, Nutr. Neurosci. 4 (2) (2001) 81–97.

[23] H.E. Umbarger, Amino acid biosynthesis and its regulation, Annu. Rev. Biochem. 47 (1978) 533–606, http://dx.doi.org/10.1146/annurev.bi.47.070178.002533 (PMID 354503).

[24] A.V. Raman, M.W. Pitts, A. Seyedali, A.C. Hashimoto, L.A. Seale, F.P. Bellinger, M.J. Berry, Absence of selenoprotein P but not selenocysteine lyase results in severe neurological dysfunction, Genes Brain Behav. 11 (5) (2012) 601–613, http://dx.doi.org/10.1111/j.1471-4159.1976.tb02619.x.

[25] D.L. Hatfield, V.N. Gladyshev, How selenium has altered our understanding of the genetic code, Mol. Cell. Biol. 22 (11) (2002) 3565–3576, http://dx.doi.org/10.1128/MCB.22.11.3565-3576.2002.

[26] L.V. Papp, J. Lu, A. Holmgren, K.K. Khanna, From selenium to selenoproteins: synthesis, identity, and their role in human health, Antioxid. Redox Signal. 9 (7) (2007) 775–806, http://dx.doi.org/10.1089/ars.2007.1528.

[27] A.A. Turanov, A.V. Lobanov, D.L. Hatfield, V.N. Gladyshev, UGA codon position-dependent incorporation of selenocysteine into mammalian selenoproteins, Nucleic Acids Res. 41 (14) (2013) 6952–6959, http://dx.doi.org/10.1093/nar/gkt409.

[28] M.J. Berry, R.M. Tujebajeva, P.R. Copeland, X.M. Xu, B.A. Carlson, G.W. Martin III, S.C. Low, J.B. Mansell, E. Grundner-Culemann, J.W. Harney, D.M. Driscoll, D.L. Hatfield, Selenocysteine incorporation directed from the 3′UTR: characterization of eukaryotic EFsec and mechanistic implications, Biofactors 14 (1–4) (2001) 17–24, http://dx.doi.org/10.1002/biof.5520140104.

[29] X.M. Xu, B.A. Carlson, H. Mix, Y. Zhang, K. Saira, R.S. Glass, M.J. Berry, V.N. Gladyshev, D.L. Hatfield, Biosynthesis of selenocysteine on its tRNA in eukaryotes, PLoS Biol. 5 (1) (2006) e4 https://doi.org/10.1371/journal.pbio.0050004.

[30] R.F. Burk, K.E. Hill, Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis, Annu. Rev. Nutr. 25 (2005) 215–235, http://dx.doi.org/10.1146/annurev.nutr.24.012003.132120 (PMID 16011466).

[31] R.F. Burk, G.E. Olson, K.E. Hill, V.P. Winfrey, A.K. Motley, S. Kurokawa, Maternal-fetal transfer of selenium in the mouse, FASEB J. 27 (8) (2013) 3249–3256, http://dx.doi.org/10.1096/fj.13-231852 (2013 Aug).

[32] J. Köhrle, R. Brigelius-Flohe, A. Bock, R. Gartner, O. Meyer, L. Flohe, Selenium in biology: facts and medical perspectives, Biol. Chem. 381 (9–10) (2000) 849–864.

[33] J. Köhrle, R. Gartner, Selenium and thyroid, Best Pract. Res. Clin. Endocrinol. Metab. 23 (2009) 815–827.

[34] L. Grumolato, H. Ghzili, M. Montero-Hadjadje, S. Gasman, J. Lesage, Y. Tanguy, L. Galas, D. Ait-Ali, J. Leprince, N.C. Guérineau, A.G. Elkahloun, A. Fournier, D. Vieau, H. Vaudry, Y. Anouar, Selenoprotein T is a PACAP-regulated gene involved in intracellualr Ca + 2 mobilization and neuroendocrine secretion, FASEB J. 22 (2008) 1756–1768.

[35] C. Wang, R. Li, Y. Huang, F. Yang, D. Huang, C. Wu, Y. Li, Y. Tang, R. Zhang, J. Cheng, Selenoprotein K modulate intracellular free Ca2þ by regulating expression of calcium homoeostasis endoplasmic reticulum protein, Biochem. Biophys. Res. Commun. 484 (2017) 734–739.

[36] M. Rayman, The importance of selenium to human health, Lancet 356 (2000) 233–241.

[37] M. Kühbacher, J. Bartel, B. Hoppe, D. Alber, G. Bukalis, A.U. Bräuer, D. Behne, A. Kyriakopoulos, The brain selenoproteome: priorities in the hierarchy and different levels of selenium homeostasis in the brain of selenium-deficient rats, J. Neurochem. 110 (1) (2009) 133–142, http://dx.doi.org/10.1111/j.1471-4159.2009.06109.x.

[38] M.A.K. Khan, F. Wang, Mercury-selenium compounds and their toxicological significance: toward a molecular understanding of the mercury-selenium antagonism, Environ. Toxicol. Chem. 28 (8) (2009) 1567–1577.

[39] J.G. Melnick, K. Yurkerwich, G.J. Parkin, On the chalcogenophilicity of mercury: evidence for a strong Hg—Se bond in [Tm^{But}]HgSePh and its relevance to the toxicity of mercury, J. Am. Chem. Soc. 132 (2010) 647–656.

[40] Z. Gajdosechova, M.M. Lawan, D.S. Urgast, A. Raab, K.G. Scheckel, E. Lombi, P.M. Kopittke, K. Loeschner, E.H. Larsen, G. Woods, A. Brownlow, F.L. Read, J. Feldmann, E.M. Krupp, In vivo formation of natural HgSe nanoparticles in the liver and brain of pilot whales, Sci. Rep. 6 (2016) 34361.

[41] F. Huggins, S.A. Raverty, O.S. Nielsen, N. Sharp, J.D. Robertson, N.V.C. Ralston, An XAFS investigation of mercury and selenium in beluga whale tissues, Environ. Bioindic. 4 (4) (2009) 291–302.

[42] M. Korbas, J.L. O'Donoghue, G.E. Watson, I.J. Pickering, S.P. Singh, G.J. Myers, T.W. Clarkson, G.N. George, The chemical nature of mercury in human brain following poisoning or environmental exposure, ACS Chem. Neurosci. 1 (12) (2010) 810–818.

[43] A.M. Asaduzzaman, M.A.K. Khan, G. Schreckenbach, F. Wang, Computational studies of structural, electronic, spectroscopic and thermodynamic properties of methylmercury-amino acid complexes and their Se analogues, Inorg. Chem. 49 (2010) 870–878.

[44] R.G. Pearson, Chemical Hardness - Applications From Molecules to Solids, Wiley-VCH, Weinheim, 1997.

[45] K.A. Cupp-Sutton, M.T. Ashby, Biological chemistry of hydrogen selenide, Antioxidants 5 (4) (2016) 42, http://dx.doi.org/10.3390/antiox5040042.

[46] M.A. Freidman, L.R. Eaton, W.H. Carter, Protective effects of freeze-dried swordfish on methylmercury content, Bull. Environ. Contam. Toxicol. 19 (1978) 436–443.

[47] H. Ganther, C. Goudie, M. Sunde, M. Kopeckey, S. Wagner, W. Hoekstra, Selenium: relation to decreased toxicity of methylmercury added to diets containing tuna,

Science 175 (1972) 1122–1124.

[48] C. Watanabe, K. Yin, Y. Kasanuma, H. Satoh, In utero exposure to methylmercury and Se deficiency converge on the neurobehavioral outcome in mice, Neurotoxicol. Teratol. 21 (1) (1999) 83–88.

[49] H.A. Spiller, Rethinking mercury: the role of selenium in the pathophysiology of mercury toxicity, Clin Toxicol (Phila). (2017) 1–14, http://dx.doi.org/10.1080/15563650.2017.1400555 (2017 Nov 10).

[50] K. Beijer, A. Jernelov, Ecological aspects of mercury–selenium interaction in the marine environment, Env. Health Persp. 25 (1978) 43–45.

[51] G. Ohi, S. Nishigaki, H. Seki, Y. Tamura, T. Maki, K. Minowa, Y. Shimamura, I. Mizoguchi, The protective potency of marine animal meat against the neurotoxicity of methylmercury: its relationship with the organ distribution of mercury and selenium in the rat, Food Cosmetics Toxicol. 18 (1980) 139–145.

[52] P.D. Whanger, Selenium in the treatment of heavy metal poisoning and chemical carcinogenesis, J. Trace Elem. Electrolytes–Health Dis. 6 (4) (1992) 209–221.

[53] M.L.A. Cuvin-Aralar, R.W. Furness, Mercury and selenium interaction: a review, Ecotox. Env. Safety. 21 (1991) 348–364.

[54] J. Gailer, Arsenic-selenium and mercury-selenium bonds in biology, Coord. Chem. Rev. 251 (2007) 234–254.

[55] G. Bjørklund, J. Aaseth, O.P. Ajsuvakovad, A.A. Nikonorove, A.V. Skalny, M.G. Skalnay, A.A. Tinkov, Molecular interaction between mercury and selenium in neurotoxicity, Coord. Chem. Rev. 332 (2017) 30–37.

[56] N.V.C. Ralston, L.J. Raymond, Functional deletion of brain selenoenzymes by methylmercury, in: G.S. Banuelos, Z.-Q. Lin (Eds.), Selenium in the Environment and Human Health, Taylor and Francis, London, 2015.

[57] E.S.J. Arnér, Focus on mammalian thioredoxin reductases - important selenoproteins with versatile functions, Biochim. Biophys. Acta - General Subjects 1790 (2009) 495–526.

[58] C.M.L. Carvalho, E.-H. Chew, S.I. Hashemy, J. Lu, A. Holmgren, Inhibition of the human thioredoxin system: a molecular mechanism of mercury toxicity, J. Biol. Chem. 283 (18) (2008) 11913–11923.

[59] V. Branco, L. Coppo, S. Solá, C. Rodrigues, J. Lu, A. Holmgren, C. Carvalho, Impaired cross-talk between the thioredoxin and glutathione systems is related to ASK-1 mediated apoptosis in neuronal cells exposed to mercury, Redox Biol. 13 (2017) 278–287, http://dx.doi.org/10.1016/j.redox.2017.05.024.

[60] V. Branco, A.G. Santos, J. Rodrigues, J. Gonçalves, J. Lu, A. Holmgren, C. Carvalho, Mitochondrial thioredoxin reductase inhibition, selenium status and Nrf-2 activation are determinant factors modulating the toxicity of mercury compounds, Free Rad. Biol. Med. 73 (2014) 95–105, http://dx.doi.org/10.1016/j.freeradbiomed.2014.04.030.

[61] J. Rodrigues, V. Branco, J. Lu, A. Holmgren, C. Carvalho, Toxicological effects of thiomersal and ethylmercury: inhibition on thioredoxin system and NADP$^+$-dependent dehydrogenases of the pentose phosphate pathway, Toxicol. Appl. Pharmacol. 286 (2015) 216–223, http://dx.doi.org/10.1016/j.taap.2015.05.002.

[62] K. Seppanen, P. Soininen, J.T. Salonen, S. Lotjonen, R. Laatikainen, Does mercury promote lipid peroxidation? An in vitro study concerning mercury, copper, and iron in peroxidation of low-density lipoprotein, Biol. Trace Elem. Res. 101 (2004) 117–132.

[63] L. Baoukhzar, Y. Tanguy, H. Abif, et al., Selonoprotein T: from discovery to functional studies using conditional knockout mice, in: D.L. Hatfield, U. Schweizer, P.A. Tsuji, V.N. Glasyshev (Eds.), Selenium its Molecular Biology and Role in Human Health, 2016 Springer, New York, 2016, pp. 275–286.

[64] Y. Uezono, Y. Toyohira, N. Yanagihara, et al., Inhibition by selenium compounds of catecholamine secretion by inhibition of Ca2þ influx in cultured bovine adrenal chromaffin cells, J. Pharmacol. Sci. 101 (2006) 223–229.

[65] F. Weinberg, U. Bickmeyer, H. Wiegand, Effects of inorganic mercury (Hg2þ) on calcium channel currents and catecholamine release from bovine chromaffin cells, Arch. Toxicol. 69 (1995) 191–196.

[66] D. Behne, H. Pfeifer, D. Rothlein, A. Kyriakopoulos, Cellular and subcellular distribution of selenium and selenium-containing proteins in the rat, in: A.M. Roussel, A.E. Favier, R.A. Anderson (Eds.), Trace Elements in Man and Animals, 10 Kluwer Academic/Plenum Publishers, New York, 2000, pp. 29–34.

[67] C. Wagner, J.H. Sudati, C.W. Nogueira, J.B.T. Rocha, In vivo and in vitro inhibition of mice thioredoxin reductase by methylmercury, Biometals 23 (2010) 1171–1177, http://dx.doi.org/10.1007/s10534-010-9367-4.

[68] I. Falnoga, M. Tusek-Znidaric, M. Horvat, P. Stegnar, Mercury, selenium, and cadmium in human autopsy samples from Idrija residents and mercury mine workers, Environ. Res. 84 (3) (2000) 211–218.

[69] I. Falnoga, M. Tušek-Žnidarič, P. Stegnar, The influence of long-term mercury exposure on selenium availability in tissues: an evaluation of data, Biometals 19 (3) (2006) 283–294.

[70] K. Anestål, E.S. Arnér, Rapid induction of cell death by selenium-compromised thioredoxin reductase 1 but not by the fully active enzyme containing selenocysteine, J. Biol. Chem. 278 (2003) 15966–15972.

[71] V. Glaser, R.P. Martins, A.J.H. Viera, et al., Diphenyl diselenide administration enhances cortical mitochondrial number and activity by increasing hemeoxygenase type 1 content in a methylmercury induced neurotoxicity mouse model, Mol. Cell. Biochem. 390 (2014) 1–9.

[72] J. Lu, A. Holmgren, The thioredoxin antioxidant system, Free Radic. Biol. Med. 66 (2014) 75–87.

[73] N. Mendelev, S.L. Mehta, H. Idris, et al., Selenite stimulates mitochondrial biogenesis signaling and enhances mitochondrial functional performance in murine hippocampal neuronal cells, PLoS One 7 (2012) e47910.

[74] K. Cui, X. Luo, K. Xu, M.R. Ven-Murthy, Role of oxidative stress in neurodegeneration: recent developments in assay methods for oxidative stress and nutraceutical antioxidants, Prog. Neuro-psychopharmacol. Biol. Psychiatry. 28 (5)

(2004) 771–799, http://dx.doi.org/10.1016/j.pnpbp.2004.05.023.

[75] M. Naziroglu, Role of selenium on calcium signaling and oxidative stress-induced molecular pathways in epilepsy, Neurochem. Res. 34 (12) (2009) 2181–2191, http://dx.doi.org/10.1007/s11064-0090015-8 [PMID: 19513830].

[76] R.F. Burk, D.G. Brown, R.J. Seely, C.C. Scaief, Influence of dietary and injected selenium on whole-body retention, route of excretion, and tissue retention of $^{75}SeO_3{}^{2-}$ in the rat, J. Nutr. 102 (8) (1972) 1049–1055.

[77] Y. Zhang, Y. Zhou, U. Schweizer, N.E. Savaskan, D. Hua, J. Kipnis, D.L. Hatfield, V.N. Gladyshev, Comparative analysis of selenocysteine machinery and selenoproteome gene expression in mouse brain identifies neurons as key functional sites of selenium in mammals, J. Biol. Chem. 283 (4) (2008) 2427–2438, http://dx.doi.org/10.1074/jbc.M707951200 (PMID: 18032379).

[78] A. Nakayama, K.E. Hill, L.M. Austin, A.K. Motley, R.F. Burk, All regions of mouse brain are dependent on selenoprotein P for maintenance of selenium, J. Nutr. 137 (3) (2007) 690–693 17311961.

[79] A.F. Castoldi, T. Coccini, L. Manzo, Neurotoxic and molecular effects of methylmercury in humans, Rev. Env. Health. 18 (1) (2003) 19–31.

[80] K. Eto, H. Tokunaga, K. Nagashima, T. Takeuchi, An autopsy case of Minamata disease (methyl-mercury poisoning) – pathological viewpoints of peripheral nerves, Toxicol. Pathol. 30 (2002) 714–722.

[81] M. Sakamoto, K. Wakabayashi, A. Kakita, T. Hitoshi, T. Adachi, A. Nakano, A widespread neuronal degeneration in rats following oral administration of methylmercury during postnatal developing phase: a model of fetal type Minamata disease, Brain Res. 784 (1998) 351–354.

[82] R.F. Burk, K.E. Hill, G.E. Olson, E.J. Weeber, A.K. Motley, V.P. Winfrey, L.M. Austin, Deletion of apolipoprotein E receptor-2 in mice lowers brain selenium and causes severe neurological dysfunction and death when a low selenium diet is fed, J. Neurosci. 27 (23) (2007) 6207–6211.

[83] W.M. Valentine, T.W. Abel, K.E. Hill, L.M. Austin, R.F. Burk, Neurodegeneration in mice resulting from loss of functional selenoprotein P or its receptor apolipoprotein E receptor 2, J. Neuropath. Exp. Neurology. 67 (1) (2008) 68–77.

[84] K.E. Hill, J. Zhou, W.J. McMahan, A.K. Motley, J.F. Atkins, R.F. Gesteland, R.F. Burk, Deletion of selenoprotein P alters distribution of selenium in the mouse, J. Biol. Chem. 278 (16) (2003) 13640–13646.

[85] J. Pařízek, I. Oštádalová, J. Kaloušková, A. Babický, L. Pavlík, B. Bíbr, Effect of mercuric compounds on the maternal transmission of selenium in the pregnant and lactating rat, J. Reprod. Fert. 25 (1971) 157–170.

[86] T. Takeuchi, K. Eto, H. Nakayama, A. Sumiyoshi (Eds.), The Pathology of Minamata Disease, Kyushu University Press, 1999, p. 21.

[87] K.S. Crump, T. Kjellstrom, A.M. Shipp, A. Silvers, A. Stewart, Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort, Risk Anal. 18 (1998) 701–713.

[88] P. Grandjean, P. Weihe, R.F. White, F. Debes, S. Araki, K. Murata, Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury, Neurotoxicol. Teratol. 19 (1997) 417–428.

[89] P. Grandjean, P. Weihe, R.F. White, F. Debes, Cognitive performance of children prenatally exposed to "safe" levels of methylmercury, Environ. Res. 77 (1998) 165–172.

[90] F. Debes, E. Budtz-Jorgensen, P. Weihe, R.F. White, P. Grandjean, Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years, Neurotoxicol. Teratol. 28 (3) (2006) 363–375.

[91] F. Debes, E. Budtz-Jorgensen, P. Weihe, R.F. White, P. Grandjean, Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years, Neurotoxicol. Teratol. 28 (5) (2006) 536–547.

[92] P. Weihe, H. Debes-Joensen, Dietary recommendations regarding pilot whale meat and blubber in the Faroe Islands, International Journal of Circumpolar Health. 71 (1) (2012), http://dx.doi.org/10.3402/ijch.v71i0.18594.

[93] C.B. Avella-Garcia, J. Julvez, Seafood intake and neurodevelopment: a systematic review, Curr. Environ. Health Rep. 11 (2014) 46–77.

[94] P.W. Davidson, D.A. Cory-Slechta, S.W. Thurston, L.S. Huang, C.F. Shamlaye, D. Gunzler, G. Watson, E. van Wijngaarden, G. Zareba, J.D. Klein, T.W. Clarkson, J.J. Strain, G.J. Myers, Fish consumption and prenatal methylmercury exposure: cognitive and behavioral outcomes in the main cohort at 17 years from the Seychelles child development study, Neurotoxicology 32 (6) (2011) 711–717, http://dx.doi.org/10.1016/j.neuro.2011.08.003.

[95] J. Golding, J.R. Hibbeln, S.M. Gregory, Y. Iles-Caven, C.M. Taylor, Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: a British prebirth cohort study, Int. J. Hyg. Environ. Health 220 (7) (2017) 1161–1167, http://dx.doi.org/10.1016/j.ijheh.2017.07.004.

[96] J.R. Hibbeln, J.M. Davis, C. Steer, P. Emmett, I. Rogers, C. Williams, J. Golding, Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study, Lancet 369 (9561) (2007) 578–585.

[97] J. Julvez, M. Méndez, S. Fernandez-Barres, D. Romaguera, J. Vioque, S. Llop, I. Riaño, Maternal consumption of seafood in pregnancy and child neuropsychological development: a longitudinal study based on a population with high consumption levels, Am. J. Epidemiol. 183 (2016) 169–182.

[98] S. Llop, F. Ballester, M. Murcia, J. Forns, A. Tardon, A. Andiarena, J. Vioque, J. Ibarluzea, A. Fernández-Somoano, J. Sunyer, J. Julvez, M. Rebagliato, M.J. Lopez-Espinosa, Prenatal exposure to mercury and neuropsychological development in young children: the role of fish consumption, Int. J. Epidemiol. 46 (3) (2017) 827–838, http://dx.doi.org/10.1093/ije/dyw259.

[99] G.J. Myers, P.W. Davidson, J.J. Strain, Nutrient and methyl mercury exposure from consuming fish, J. Nutr. 137 (2007) 2805–2808.

[100] G.J. Myers, P.W. Davidson, Prenatal methylmercury exposure and children:

neurologic, developmental, and behavioral research, Environ. Health Perspect. 106 (3) (1998) 841–847.

[101] S.A. Lederman, R.L. Jones, K.L. Caldwell, V. Rau, S.E. Sheets, D. Tang, S. Viswanathan, M. Becker, J.L. Stein, R.L. Wang, F.P. Perera, Relation between cord blood mercury levels and early child development in a World Trade Center cohort, Environ. Health Perspect. 116 (8) (2008) 1085–1091.

[102] D.W. Nierenberg, R.E. Nordgren, M.B. Chang, R.W. Siegler, M.B. Blayney, F. Hochberg, T.Y. Toribara, E. Cernichiari, T. Clarkson, Delayed cerebellar disease and death after accidental exposure to dimethylmercury, N. Engl. J. Med. 338 (23) (1998) 1672–1676.

[103] D.C. Rice, Evidence for delayed neurotoxicity produced by methylmercury, Neurotoxicology. 17 (3–4) (1996) 583–596.

[104] N.V.C. Ralston, J.L. Blackwell, L.J. Raymond, Importance of molar ratios in selenium-dependent protection against methylmercury toxicity, Biol. Trace Elem. Res. 119 (3) (2007) 255–268.

[105] N.V.C. Ralston, C.R. Ralston, J.L. Blackwell III, L.J. Raymond, Dietary and tissue selenium in relation to methylmercury toxicity, Neurotoxicology 29 (5) (2008) 802–811.

[106] H.A. Spiller, H.L. Hays, G. Burns, M.J. Casavant, Severe elemental mercury poisoning managed with selenium and *N*-acetylcysteine administration, Toxicology Communications 1 (1) (2017) 24–28, http://dx.doi.org/10.1080/24734306.2017.1392076.

[107] T.L. Limke, J.K.L. Otero-Montanez, W.D. Atchison, Evidence for interaction between intracellular calcium stores during methylmercury-induced intracellular calcium dysregulation in the rat cerebellar granule neurons, J Pharmacol Exper Ther. 304 (2003) 949–958.

[108] X. Tan, C. Tang, A.F. Castoldi, L. Manzo, L.G. Costa, Effects of inorganic and organic mercury on intracellular calcium levels in rat T-lymphocytes, J. Toxicol. Environ. Health 38 (1993) 159–170.

[109] J.J. Kaneko, N.V.C. Ralston, Selenium and mercury in pelagic fish in the central north Pacific near Hawaii, Biol. Trace Element Res. Special Issue 119 (3) (2007) 242–254.

[110] O. Lindqvist, K. Johannson, M. Aastrup, A. Andersson, G. Bringmark, G. Hovsenius, L. Hakenson, A. Iverfelt, M. Meili, B. Timm, Mercury in the Swedish Environment, Kluwer Publishers, Dordrecht, Netherlands, 1991.

[111] Y.W. Chen, N. Belzile, J.M. Gunn, Antagonistic effect of selenium on mercury assimilation by fish populations near Sudbury metal smelters? Limnol. Oceanogr. 46 (7) (2001) 1814–1818.

[112] M. Mailman, R.A. Bodaly, M.J. Paterson, S. Thompson, R.J. Flett, Low-level experimental selenite additions decrease mercury in aquatic food chains and fish muscle but increase selenium in fish gonads, Arch. Environ. Contam. Toxicol. 66 (2014) 32–40.

[113] K. Paulsson, K. Lindbergh, The selenium method for treatment of lakes for elevated levels of mercury in fish, Sci. Total Environ. 87–88 (1989) 495–507.

[114] G.R. Southworth, M.J. Peterson, M.G. Ryon, Long-term increased bioaccumulation of mercury in largemouth bass follows reduction of waterborne selenium, Chemosphere 41 (7) (2000) 1101–1105.

[115] M.A. Turner, J.W.M. Rudd, The English Wabigoon River System III. Selenium in Lake enclosures: its geochemistry, bioaccumulation, and ability to reduce mercury bioaccumulation, Can. J. Fish. Aquat. Sci. 40 (1983) 2228–2240.

[116] M. Lemire, M. Fillion, B. Frenette, C.J. Passos, J.R. Guimarães, Barbosa F. Jr, D. Mergler, Selenium from dietary sources and motor functions in the Brazilian Amazon, Neurotoxicology 32 (2011) 944–953.

[117] M.A. Ali, E.M. Aly, A.I. Elawady, Effectiveness of selenium on acrylamide toxicity to retina, Int J Ophthalmol. 18 (7(4)) (2014) 614–620, http://dx.doi.org/10.3980/j.issn.2222-3959.2014.04.05.

[118] H. Akagi, P. Grandjean, Y. Takizawa, P. Weihe, Methylmercury dose estimation from umbilical cord concentrations in patients with Minamata disease, Env. Res. 77 (2) (1998) 98–103.

[120] E. Budtz-Jørgensen, N. Keiding, P. Grandjean, P. Weihe, Confounder selection in environmental epidemiology: assessment of health effects of prenatal mercury exposure, Ann. Epidemiol. 17 (2007) 27–35.

[121] C.M. Carvalho, J. Lu, X. Zhang, E.S. Arnér, A. Holmgren, Effects of selenite and chelating agents on mammalian thioredoxin reductase inhibited by mercury: implications for treatment of mercury poisoning, FASEB J. 25 (1) (2011) 370–381, http://dx.doi.org/10.1096/fj.10-157594.

[122] A.L. Choi, E. Budtz-Jørgensen, P.J. Jørgensen, U. Steuerwald, F. Debes, P. Weihe, P. Grandjeana, Selenium as a potential protective factor against mercury developmental neurotoxicity, Environ. Res. 107 (2008) 45–52.

[123] F. Courtin, F. Chantoux, J. Francon, Thyroid hormone metabolism by glial cells in primary culture, Mol. Cell. Endocrinol. 48 (1986) 167–178.

[124] F.R. Crantz, J.E. Silva, P.R. Larsen, An analysis of the sources and quantity of 3,5,3′-tri-iodothyro-nine specifically bound to nuclear receptors in rat cerebral cortex and cerebellum, Endocrinology 110 (1982) 367–375.

[125] L.E. Davis, M. Kornfeld, H.S. Mooney, K.J. Fiedler, K.Y. Haaland, W.W. Orrison, E. Cernichiari, T.W. Clarkson, Methylmercury poisoning: long-term clinical, radiological, toxicological, and pathological studies of an affected family, Ann Neurol. 35 (6) (1994) 680–688.

[126] M. Farina, J.B. Rocha, M. Aschner, Mechanisms of methylmercury-induced

neurotoxicity: evidence from experimental studies, Life Sci. 89 (2011) 555–563.

[127] V.N. Gladyshev, D.L. Hatfield, Selenocysteine-containing proteins in mammals, J. Biomed. Sci. 6 (3) (1999) 151–160.

[128] J.C. Heath, K.M. Banna, M.N. Reed, E.F. Pesek, N. Cole, J. Li, M.C. Newland, Dietary selenium protects against selected signs of aging and methylmercury exposure, Neurotoxicology 31 (2) (2010) 169–179.

[129] A.V. Lobanov, A.A. Turanov, D.L. Hatfield, V.N. Gladyshev, Dual functions of codons in the genetic code, Crit. Rev. Biochem. Mol. Biol. 45 (4) (2010) 257–265, http://dx.doi.org/10.3109/10409231003786094.

[130] L. Magos, M. Webb, The effect of selenium on the brain uptake of methylmercury, Arch. Toxicol. 38 (3) (1977) 201–207.

[131] B. Møller-Madsen, G. Danscher, Localization of mercury in CNS of the rat. IV. The effect of selenium on orally administered organic and inorganic mercury, Toxicol. Appl. Pharmacol. 108 (3) (1991) 457–473.

[132] M. Navarro-Alarcon, C. Cabrera-Vique, Selenium in food and the human body: a review, Sci. Total Environ. 400 (1–3) (2008) 115–141, http://dx.doi.org/10.1016/j.scitotenv.2008.06.024.

[134] N.V.C. Ralston, L.J. Raymond, Dietary selenium's protective effects against methylmercury toxicity, Toxicology 278 (2010) 112–123.

[135] N.V.C. Ralston, A. Azenkeng, C.R. Ralston, L.J. Raymond, Selenium-health benefit values as seafood safety criteria, in: Se-Kwon Kim (Ed.), Seafood Science; Advances in Chemistry, Technology and Applications, CRC Press, 2015(Chapter 19).

[139] K.T. Suzuki, Equimolar Hg–Se complex binds to selenoprotein P, Biochem. Biophys. Res. Commun. 231 (1) (1997) 7–11.

[140] K.T. Suzuki, C. Sasakura, S. Yoneda, Binding sites for the (Hg-Se) complex on selenoprotein P, Biochem. Biophys. Acta. 1429 (1998) 102–112.

[142] S. Verma, F.K. Hoffmann, M. Kumar, Z. Huang, K. Roe, E. Nguyen-Wu, A.S. Hashimoto, P.R. Hoffmann, Selenoprotein K knockout mice exhibit deficient calcium flux in immune cells and impaired immune responses, J. Immunol. 186 (4) (2011) 2127–2137, http://dx.doi.org/10.4049/jimmunol.1002878.

[143] P.D. Whanger, Selenocompounds in plants and animals and their biological significance, J. Am. Coll. Nutr., 2002, 21(3) 223-232 (2002), http://dx.doi.org/10.1080/07315724.2002.10719214.

[144] D.C. Wigfield, S.L. Perkins, Oxidation of mercury by catalase and peroxidase in homogeneous solution, J. Appl. Toxicol. 3 (4) (1983) 185–188.

[145] B.A. Zachara, H. Pawluk, E. Bloch-Boguslawska, K.M. Sliwka, J. Korenkiewicz, Z. Skok, K. Ryć, Tissue level, distribution, and total body selenium content in healthy and diseased humans in Poland, Arch. Environ. Health. 56 (5) (2001) 461–466, http://dx.doi.org/10.1080/00039890109604483.

[146] H. Hintelmann, Organomercurials. Their formation and pathways in the environment, Met Ions Life Sci. 7 (2010) 365–401.

[147] K. Östlund, Studies on the Metabolism of Methyl Mercury and dimethyl mercury in mice, Acta Pharmacologica Et Toxicologica 27 (1) (1969) Suppl 1.

[148] J. Chen, M.J. Berry, Selenium and selenoproteins in the brain and brain diseases, J. Neurochem. 86 (2003) 1–12.

[149] J. Köhrle, Selenium and the control of thyroid hormone metabolism, Thyroid 15 (2005) 841–853.

[150] Y. Sugiura, Y. Tamai, H. Tanaka, Selenium protection against mercury toxicity: high binding affinity of methylmercury by selenium containing ligands in comparison with sulfur containing ligands, Bioinorg. Chem. 9 (1978) 167–180.

[151] C. Watanabe, K. Yoshida, Y. Kasanuma, Y. Kun, H. Satoh, In utero methylmercury exposure differentially affects the activities of selenoenzymes in the fetal mouse brain, Environ Res. 80 (3) (1999) 208–214.

[152] J. Stringari, A.K.C. Nunes, J.L. Franco, D. Bohrer, S.C. Garcia, A.L. Dafre, D. Milatovic, D.O. Souza, J.B.T. Rocha, M. Aschner, M. Farina, Prenatal methylmercury exposure hampers glutathione antioxidant system ontogenesis and causes long-lasting oxidative stress in the mouse brain, Toxicol. Appl. Pharmacol. 227 (2008) 147–154.

[153] D.O. Marsh, T.W. Clarkson, C. Cox, G.J. Myers, L. Amin-Zaki, S. Al-Tikreti, Fetal methylmercury poisoning. Relationship between concentration in single strands of maternal hair and child effects, Arch. Neurol. 44 (1987) 1017–1022.

[154] R.D. Snyder, D.F. Seelinger, Methylmercury poisoning, clinical follow-up and sensory nerve conduction studies, J. Neurol. Neurosurg. Psychiatry 39 (7) (1976) 701–704.

[155] F. Bakir, H. Rustam, S. Tikriti, S.F. Al-Damluji, H. Shihristani, Clinical and epidemiological aspects of methylmercury poisoning, Postgrad. Med. J. 56 (651) (1980) 1–10.

[156] T.K Tsubaki, K. Irukayama, Methylmercury poisoning in Minamata and Niigata, Japan, in: T Tsubaki, K Irukayama (Eds.), Minamata disease, Elsevier, Amsterdam, 1977, pp. 143–253.

[157] N.V.C. Ralston, L.J. Raymond, Fish Selenium-Health Benefit Values in Mercury Risk Management. STAR (Science To Achieve Results). Annual Report to EPA, (2014), pp. 1–7.

[158] Allen Institute for Brain Science, Allen Brain Atlas. Mouse brain SELENOM, (2010) http://mouse.brain-map.org/experiment/siv?id=641541&imageId=593495&initImage=expression&colormap=0.5,1,0,256,4&coordSystem=pixel&x=5816.5&y=3624.5&z=1 Mouse brain SELENOW; http://mouse.brain-map.org/gene/show/20127.