Effects of Soft Electrophiles on Selenium Physiology

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Abstract:

This review examines the effects of neurotoxic electrophiles on selenium (Se) metabolism. Selenium-dependent enzymes depend on the unique and elite functions of selenocysteine (Sec), the 21st proteinogenic amino acid, to perform their biochemical roles. Humans possess 25 selenoprotein genes, ~half of which are enzymes (selenoenzymes) required for preventing, controlling, or reversing oxidative damage, while others participate in regulating calcium metabolism, thyroid hormone status, protein folding, cytoskeletal structure, Sec synthesis and Se transport. While selenoproteins are expressed in tissue dependent distributions and levels in all cells of all vertebrates, they are particularly important in brain development, health, and functions. As the most potent intracellular nucleophile, Sec is subject to binding by mercury (Hg) and other electron poor soft neurotoxic electrophiles. Epidemiological and environmental studies of the effects of exposures to methyl-Hg (CH_3Hg^+), elemental Hg (Hg^0), and/or other metallic/organic neurotoxic soft electrophiles need to consider the concomitant effects of all members of this class of toxicants in relation to the Se status of their study populations. The contributions of individual electrophiles' discrete and cooperative rates of Se sequestration need to be evaluated in relation to tissue Se reserves of the exposed populations to identify sensitive subgroups which may be at accentuated risk due to poor Se status. Additional study is required to examine possibilities of inherited, acquired, or degenerative neurological disorders of Se homeostasis that may influence vulnerability to soft electrophile exposures. Investigations of soft electrophile toxicity will be enhanced by considering the concomitant effects of combined exposures on tissue Se-availability in relation to pathological consequences during fetal development or in relation to etiologies of neurological disorders and neurodegenerative diseases. Since selenoenzymes are molecular "targets" of soft electrophiles, concomitant evaluation of aggregate exposures to these toxicants in relation to dietary Se intakes will assist regulatory agencies in their goals of improving protecting public health.

1.0 INTRODUCTION

The first human illness reported in association with selenium (Se)-deficiency was congestive cardiomyopathy observed among children and women of child bearing age living Se-deficient regions of China (Anon, 1979) and also observed among patients on total parenteral nutrition in New Zealand and Finland (van Rij et al., 1979). The poor availability of Se in the soils of affected regions and consumption of the low Se food crops and livestock resulted in significantly Se-deficient populations. In the 1970's, Se was identified in glutathione peroxidase (GPX) (Rotruck et al., 1973) and was soon determined to occur as selenocysteine (Sec), a newly recognized amino acid (Cone et al., 1976). Subsequently determined to be an essential micronutrient, Se's recommended dietary allowance (RDA) in the United States is (55 μg/day) for men and women (National Academies Press, 2000). Homeostatic processes ensure brain, endocrine organs, and the placenta are adequately supplied with Se, even during severe dietary Se deficiency (Schomburg et al., 2003; Burk et al., 2007; Burk et al., 2013), thus preventing development of pathological consequences that would otherwise have arisen. Therefore, the necessity of Se for the normal functions of these tissues was not apparent in earlier studies. However, the roles of Se (See review by Reich and Hondal, 2016) particularly in brain (Buckman et al., 1993; Köhrle et al., 2000; Rayman, 2000; Whanger, 2001; Sun et al., 2001; Chen and Berry 2003; Schweizer et al., 2004; Zhang et al., 2008;) and endocrine tissues (Köhrle et al., 2005; Köhrle and Gärtner, 2009) are well recognized, and the potential for these processes to be involved in pathological disorders and degenerative diseases is receiving increasing consideration (Solovyev, 2015; Dominiak et al., 2016; Oggiano et al., 2018; Maass et al., 2018; Solovyev, 2018). Since the only environmental or dietary insults known to compromise selenoenzyme activities in brain and endocrine tissues are high exposures to certain soft electrophiles, high exposures to metallic and organic soft electrophiles may affect fetal neurodevelopment, adult cardiovascular health, and could contribute to progressive illnesses and neurodegenerative diseases.

As a result of its interactions with sulfur and Se, the best known of these toxic electrophiles is mercury (Hg). Elemental Hg (Hg^0) was known to the ancients, and its toxic effects were familiar to Chinese and Roman physicians (Krebs, 2006). Early alchemists were also familiar with the reversible

reaction that occurs between Hg and sulfur to form cinnabar (HgS) and the harmful outcomes that accompanied consumption of large amounts of cinnabar or prolonged exposures to Hg^0 vapor. Toxic effects from high Hg exposures were encountered by those mining or working with it have been known for centuries, but the mechanisms of its toxicity involving sulfur-dependent delivery of Hg and its subsequent binding of Se (See Figure 1) were not recognized until recently.

The path to understanding the toxicity of Hg and other soft electrophilic neurotoxicants began in 1818, when Jöns Jacob Berzelius (1779–1848) described his discovery of selenium (Se) as a new element. Recognizing its similarities with sulfur as well as tellurium (named for the Earth), he named it after Selene, the Greek goddess of the moon (Trofast, 2011). Ironically, Se's first suspected biological activities were mistakenly associated with toxicity. Livestock that grazed on "loco weed" plants (e.g., *Astragalus bisulcatus*) were known to become ill and demonstrate bizarre behavior. These plants hyperaccumulate Se, and although Se-toxicity (selenosis) does introduce defects in the structure of keratin in hooves and hair, it was not until much later that the adverse neurological effects that characterized this disorder were recognized as being due to swainsonine (Stegelmeier et al., 1995) and other alkaloids that these and related plants produce, not the Se they contained (Cheeke and Shull, 1985; O'toole and Raisbeck, 1995). The first beneficial role reported for Se was its ability to counteract the toxic effects of cadmium (Cd), an electrophile that damages endocrine tissues (Tobias et al., 1946; Kar et al., 1960). Selenium's biological significance as a nutrient was first recognized in 1957 by Klaus Schwarz, who reported it prevented liver necrosis in vitamin E-deficient rats (Schwarz and Foltz, 1957). A year later, Se-deficiency was found to cause a lethal myopathy (white muscle disease) that afflicts livestock grazing in Se-poor pastures (Muth, et al., 1958). Pařízek and Oštádalová (1967) were the first to report that rats treated with otherwise lethal doses of mercury chloride ($HgCl_2$) were saved when provided supplemental Se. Since then, the ability of Se compounds to decrease or abolish the toxicity of various forms of Hg has been established in all investigated species of mammals, birds, and fish (Whanger, 1992; Beijer and Jernelov, 1978; Friedman et al., 1978; Ohi et al., 1980) and described in comprehensive reviews by

Cuvin-Aralar and Furness (1991), Gailer (2007), Bjørklund et al., (2017), Spiller (2017), and Ralston and Raymond (2018).

In addition to Hg, other soft electrophiles such cadmium (Cd), arsenic (As), and lead (Pb) are priority concerns in toxicology studies due to the adverse health effects associated with acute and chronic exposures. These and other soft electrophiles such as various molecular forms of silver (Ag) and gold (Au) share common characteristics such as chemical affinity to proteins and non-protein thiols and their ability to generate cellular oxidative stress (Ganther, 1980; Whanger 1985; Kinraide and Yermiyahu 2007). The health effects of high exposures these soft electrophiles are diverse: kidney and liver damage, specific forms of cancer and irreversible neurological damage. Although the effects of exposures to elemental and organic forms of Hg on Se metabolism are increasingly well studied (See Spiller, 2017 and Ralston and Raymond, 2018 for recent reviews), the possibility that other soft electrophiles might impair selenoenzyme activities and contribute to adverse health effects has received little attention. Examining the possibility of cooperative effects among multiple electrophilic agents acting through the same mode of action is the goal of this article.

On the occasion of the 200th anniversary of the discovery of Se, this review of electrophile interactions with Se-physiology examines Sec as the primary molecular target of Hg toxicity and suggests the possibility that concomitant exposures to other electrophiles may cooperatively contribute to selenoenzyme inhibition and Se sequestration. Since neurotoxic electrophiles tend to co-occur with other persistent bioaccumulative toxicants (PBTs), it is essential to differentiate their toxicokinetic effects, particularly when evaluating agents which cause similar neurological consequences even though the underlying dysfunctions may arise from independent actions on separate biochemical pathways.

1.1 Selenium Physiology

Selenocysteine, the 21st proteinogenic amino acid, is encoded in 25 genes which express unique selenoproteins which employ its nucleophilic selenolate in their active sites (Gladyshev et al., 2004; Kryukov and Gladyshev, 2004). All vertebrate cells exhibit tissue dependent expression levels and

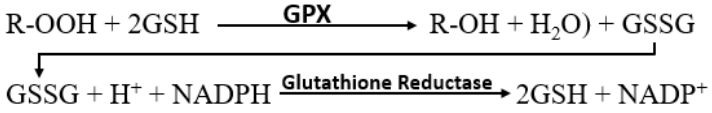
distributions of these proteins, but their functions are particularly important in the brain and endocrine tissues which are preferentially supplied with Se during dietary Se restriction. Selenoprotein functions include; preventing/reversing oxidative damage, regulating calcium metabolism, controlling thyroid hormone status, guiding protein folding, supporting tubulin and actin polymerization, transporting Se, and creating the selenophosphate precursor required for Sec synthesis (See Table 1). For reviews of selenoproteins and their functions see; Reeves and Hoffman (2009), Köhrle and Gärtner, (2009), and Kühbacher et al., (2009), Reich and Hondal (2016), and for updated selenoprotein nomenclature, see Gladyshev et al., (2016).

Selenocysteine is specifically encoded by the UGA codon (alternatively read as the opal stop codon) in coordination with a specific stem-loop structure in the 3' untranslated region that interacts with the Sec Insertion Sequence (SECIS) element together with a unique $tRNA^{[Ser]Sec}$ that brings an aminoacylated serine residue to the ribosome. A high energy selenophosphate is used to displace the serine hydroxyl with a Se, thus forming Sec *de novo* during its cotranslational insertion into the polypeptide chain Leinfelder et al., 1988; Forchhammer et al., 1989; Berry et al., 1991; Hatfield and Diamond, 1993). Because Se supplies to the brain are prioritized and thus protected from developing a Se-deficiency that would spontaneously lead to neurological damage, the only means of inducing Se-deficiencies in brain tissues is either through genetic abolition of the transport and uptake proteins involved in homeostatic maintenance of Se in brain, endocrine, and placental tissues (Schomburg et al., 2003; Burk et al., 2007; Burk et al., 2013), or through exposures to neurotoxic electrophiles (See sections 1.2-1.3).

With 10 Sec/molecule (in humans), selenoprotein P (SELENOP, the main Se transport protein in plasma) delivers Se to brain, endocrine, placental, and other preferentially supplied tissues in the body. Substantial fractions of the body's total Se reservoir are cycled through this molecular form daily (Burk et al., 2005). A receptor protein that was first recognized for its ability to bind and internalize low-density lipoproteins from the plasma; apolipoprotein E receptor 2 (ApoER2), is now known to selectively bind

and internalize SELENOP (Burk et al., 2007; Burk et al., 2013). Defects in ApoER2 metabolism have been recognized in relation to neurological disorders including Alzheimer's Disease (Herz, 2009; Chin et al., 2008 Wang et al., 2017; Solovyev et al., 2018; Mata-Balaguer et al., 2018), antiphospholipid syndrome (de Groot and Derksen, 2005), as well as the most common psychiatric illness; major depressive disorder (Suzuki et al., 2010). Postmortem studies demonstrate intracellular SELENOP (Scharpf et al., 2007) colocalizes with Aβ plaques and neurofibrillary tangles in brains of Alzheimer's disease patients (Bellinger et al., 2008; Rueli et al., 2015). Because ApoER2 is expressed on surfaces of brain, placenta, and endocrine tissues, these tissues selectively capture and internalize SELENOP which subsequently resides within these cells as a readily accessible reserve of Se (Burk et al., 2007; Burk et al., 2013). Although the brain is normally preserved from experiencing Se shortages, inactivation of SELENOP or ApoER2 genes in mice causes severe brain Se-deficiencies that result in neurodegeneration of cerebellum, thalamus, and hippocampus regions, resulting in impaired motor functions, sensory abilities, and learning behaviors, respectively. However, these consequences can be prevented by Se-rich diets that maintain brain Se at levels capable of supporting normal levels of selenoenzyme synthesis (Burk et al., 2007, Hill et al., 2003, Valentine et al., 2008; Caito et al., 2011). Behavioral disorders have been observed in SELENOP knockout mice, with male mice being more vulnerable than females (Raman, et al., 2012).

Normal metabolic production of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) or free radicals such as hydroxyl radicals or superoxides are natural components associated with cell signaling pathways, but excessive production of these agents cause oxidative stress and damage (Pacher et al., 2007). Since peroxides are reactive species, rapid detoxification is required to prevent the oxidative damage they might otherwise cause. As detailed below, selenoenzymes such as the GPX's or TXNRD's regulate redox state and prevent as well as reverse oxidative damage. The generalized reactions shown in Equation 1 reflect the glutathione (GSH)-dependent reduction of lipid peroxides or H_2O_2 to alcohol and water by GSH resulting in formation of glutathione disulfide (GSSG). Glutathione reductase catalyzes reduction of GSSG back to 2GSH in the presence of NADPH (Flohé 1989).



(Equation. 1)

Equation 2 shows the generalized reaction between oxidized protein disulfides and other free radicals being reduced to thiols by the vicinal thiols of thioredoxin (Trx), resulting in an intramolecular disulfide (S_2) which is reduced by TXNRD in the presence of NADPH.

(Equation. 2)

The five Se-dependent GPXs detoxify hydroperoxides using the selenolate ($R\text{-}Se^-$) of their active site Sec to acquire a hydroxyl from the hydroperoxide, thus releasing a water molecule, then displace the hydroxyl with a GSH to release another water molecule. The resulting Sec-SG adduct is released by interacting with a second GSH which reduces the Sec to selenolate while forming GSSG which is subsequently restored to 2 GSH by glutathione reductase. Thioredoxin reductase (TXNRD) is named for its first recognized biochemical substrate; oxidized thioredoxin (Trx), but TXNRDs reduce a broad range of substrates including; hydrogen peroxide, selenite, lipoic acid, ascorbate, ubiquinone, and dietary polyphenols (Arner and Holmgren, 2000). The functions of TXNRD and other selenoenzymes are intimately connected with vitamin E since they both protect against lipid peroxidation (May et al., 2002). It is suggested that once vitamin E has quenched a radical species in lipid bilayers, it requires vitamin C (ascorbic acid) to restore it to its active form, thus forming dehydroascorbic acid which is acted upon by TXNRD to reform ascorbic acid (May et al., 1997). Since many of its substrates are important cellular antioxidants themselves, the activities of TXNRD are crucial in preserving the intracellular reducing environment required for normal metabolism. Although less well characterized, SELENOF, SELENOH, SELENOM, SELENOO, SELENOS, SELENOT, SELENOV, SELENOW, SELENON, and SELENOK appear to have oxidoreductase capabilities (See Table 1), thus it is reasonable to expect that they may similarly interact with thiomolecules.

Although not a selenoprotein, selenocysteine lyase is an important aspect of Sec metabolism since selenoprotein levels in the cell are determined by rates of degradation as well as their rates of synthesis. Selenoprotein half-lives can be as short as minutes, or as long as several days, but eventually the molecule will become damaged, marked for retirement and degraded to its component amino acids. However, Sec cannot be reused in subsequent cycles of protein synthesis since it must be recreated *de novo* immediately prior to incorporation. Regardless of whether a Sec residue originates from recently digested food or from an endogenous source, once a Sec residue is released, Sec lyase catalyzes liberation of inorganic Se. The released Se is almost immediately reduced to selenide, the substrate required for SEPHS2 activity (Xu et al., 2006; Kim et al., 1997; Ogasawara et al., 2005; Carlson et al., 2004) through reactions which are presumed to be mediated by intracellular thiols (Painter, 1941; Ganther, 1968; Ganther 1971; Ganyc and Self, 2008). The selenide substrate is taken up selenophosphate synthetase (SEPHS2) which forms the high energy selenophosphate used to displace the OH of a in Sec biosynthesis during its co-translational incorporation into a nascent selenoprotein (Mihara et al., 2000).

Oxidative damage is a focal aspect of the pathologies that accompany Parkinson's disease, senile and drug-induced deafness, schizophrenia, and Alzheimer's (Floyd, 1999; Dominiak et al., 2016; Pillai et al., 2014; Solovyev et al., 2018). Since the characterized functions of more than half of the selenoenzymes (See Table 1) involve detoxification, prevention, and reversal of oxidative damage, their roles in neurological, endocrine, cardiovascular, and other disease processes are being investigated (Sanmartin et al., 2011; Ruszkiewicz and Albrecht 2015; Solovyev et al., 2018).

Disruption of brain Se homeostasis arising from inherited, acquired, or degenerative neurological disorders would be associated with dysregulation of redox state and increased oxidative damage in the affected tissues. Potentially predisposing genetic differences in selenoenzyme regulation and biosynthetic pathways that affect their vulnerability to soft neurotoxic electrophiles are additional areas of investigation. Further work in this area may reveal novel etiological initiators and pathological pathways, improve diagnosis, enhance pharmaceutical treatments, and improve the prognosis of certain neurological, cardiovascular, and endocrine conditions.

1.2 *Selenium Interactions with Soft Electrophiles*

Although the physical and chemical properties of sulfur and Se are similar in many respects, Se is more readily oxidized and kinetically labile, with biochemical forms which are more reactive than their sulfur analogues (Reich and Hondal, 2016). With a pKa of ~8.3, Cys is largely protonated at physiological pH while the pKa of Sec is ~5.2. Therefore, it is almost exclusively in the anionic selenolate ($R\text{-}Se^-$) form which is recognized as the most powerful soft nucleophile in the cell (Arner, 2010; Wessjohann et al., 2007). This enables Sec to catalyze reactions that cannot be reproduced by Cys analogues, but the same characteristics that enable it to perform these reactions also make it uniquely vulnerable to binding by a variety of metallic and organic toxicants.

Soft electrophiles are positively charged metallic or organic molecules with electron-poor centers that readily react with nucleophilic chalcogens (Group 16 elements of the periodic table such as sulfur or Se) to form covalent bonds. Chalcophiles are elements that react with chalcogens to form sulfides or selenides. They include copper (Cu), lead (Pb), zinc (Zn), Cd, molybdenum (Mo), Hg, Antimony (Sb), tin (Sn), thallium (Tl), technetium (Te), arsenic (As), silver (Ag), gold (Au), and can also include certain other noble metals (Lee 2016). In addition to electron poor metals, a wide variety of organic electrophiles including environmental toxicants (e.g., γ-diketones, quinones, unsaturated aldehydes), industrial pollutants (acrolein, acrylonitrile, methylvinyl ketone), drug metabolites (e.g., acrolein metabolite of cyclophosphamide), dietary contaminants (e.g., acrylamide), and endogenously generated type-2 alkenes (e.g., acrolein, 4-hydroxy-2-nonenal) are known to induce cell damage, quite possibly by interacting with electron rich nucleophiles (Martyniuk et al., 2011, LoPachin et al., 2012, LoPachin and Gavin 2012a, LoPachin and Gavin, 2012b, Martyniuk et al., 2013, Zhang et al., 2013, LoPachin and Gavin 2014, Kosharskyy et al., 2015). Certain pharmaceuticals employ soft electrophiles such as platinum- and Au-containing compounds to interact with Sec and thus inhibit the thioredoxin system (Ouyang et al., 2018).

Unsaturated carbonyls of these soft electrophiles form covalent adducts with nucleophilic Cys sulfhydryls, but are likely to have even higher affinities for selenolates of Sec. While all electrophiles

have the potential to interact with nucleophiles, the interactions between Se and Hg in their various forms are the best characterized. Although the selenoreactivity of organic or metallic soft electrophiles other than Hg are less well studied, information regarding Hg-Se interactions may provide insights regarding effects of high exposures to other metallic chalcophiles and organic electrophiles.

Mercury's association constant for sulfide is high (10^{39}), but its affinity for selenide ($K_a = 10^{45}$) is ~1 million-fold higher (Dyrrsen and Wedborg, 1991). However, methylmercury (CH_3Hg^+) affinities for the thiol (~10^{16}) of Cys (Webb, 1966), vs. its affinity for Sec (estimated to be ~10^{18}) are insufficient to overcome the mass action effects of the ~10^5 higher intracellular abundance of thiols, thus >95% of intracellular CH_3Hg^+ is usually found associated with sulfur (Huggins et al., 2009). If not for the direct interactions that occur between thiomolecules and selenoenzymes, the small difference in their CH_3Hg^+ binding affinities would result in little redistribution of CH_3Hg^+ from Cys to Sec. However, because thiomolecules such as GS-SG and Txr-S_2 are selenoenzyme substrates (see Equations 1 and 2), they carry Hg or other electrophiles (E) GS-E-SG, Trx-(S_2-E) into close proximity with the Se of Sec in enzyme active sites, expediting formation of E-Sec.

Although organic and metallic soft electrophiles will all interact with chalogens and subsequently inhibit selenoenzymes, the best characterized of the neurotoxic electrophilic metals is Hg. Selenium is present in most tissues at ~1 μM, and exposures to Hg in quantities sufficient to approach or exceed stoichiometric equivalence is sufficient to inhibit tissue activities of GPX (Prohaska and Ganther, 1977; Black et al., 1979; Hirota et al., 1980; Oh and Lee, 1981; Chang and Suber, 1982; Chung et al., 1982; Eide and Severson, 1983: Hirota 1986; Nielsen et al., 1991; Watanabe et al., 1999a; Seppanen et al., 2004; Bulato et al., 2007; Franco et al., 2009: Grotto et al., 2009; Branco et al., 2012; Penglase et al., 2014; Ralston and Raymond 2015a; Branco et al., 2017), TXNRD (Carvalho et al., 2008; Branco et al., 2012; Carvalho et al., 2011; Branco et al., 2014; Ralston and Raymond 2015a; Branco et al., 2017), and/or DIO (Watanabe et al., 1999b). The magnitude of effects of exposures to As, Cd, or Hg has greater impact on mitochondrial TXNRD2 than cytosolic TXNRD1 (Hansen et al., 2006; Branco et al., 2014;). Although TXNRD activity can be inhibited by processes unrelated to Se-sequestration and selenoenzyme

inhibition (e.g., Citta et al., 2012), interactions of Se with soft electrophiles such as Cd form covalent adducts which may not be as strong as with Hg, but are similar in character (Melnick et al., 2010). Certain pharmaceutical agents employ soft electrophiles such as platinum- and Au-containing compounds to inhibit the thioredoxin system (Ouyang et al., 2018).

Once a soft electrophile becomes bound to the thiol of a Cys residue of GSH, Trx, or other substrate or cofactor which directly interacts with the Sec of these selenoenzymes, the thiomolecule acts as a suicide substrate (Ralston et al., 2015, Ralston and Raymond 2015b, Ralston and Raymond 2018). Because the selenoenzyme orients the substrate to bring the thiol into proximity with the selenolate to accomplish the enzyme reaction, a thiol which carries a soft electrophile adduct will enable its transfer to the nucleophilic selenolate to form a covalent bond, which by biochemical definition irreversibly inhibits the enzyme. Although CH_3Hg^+ entered the active site linked to a Cys, it will transfer to the Sec of the selenoenzyme and remain bound. Upon degradation of the inactivated enzyme, the CH_3Hg-Sec form is sufficiently stable to persist intact in tissues and may be excreted from the body in that form, but the bound Se is unavailable for participation in Sec synthesis. The rate of selenoenzyme activities in various tissues appear likely to contribute to the transfer of various soft electrophilic metallic or organic electrophiles from thiols to the Sec of selenoenzymes such as GPX, TXNRD, and/or other oxidoreductase selenoenzymes.

While the inorganic forms (Hg^+, Hg^{2+}) are less able to cross membranes, they are poorly absorbed during digestion and encounter similar barriers at the placental or blood-brain interface. In contrast, Hg^0 vapor is readily absorbed and transported throughout the body until it is oxidized intracellularly by catalase to Hg^+ (Clarkson and Magos, 2006), a form which binds with thiols to form a potent suicide substrate (e.g., Cys-Hg^+) that readily interacts and bind with Sec. Because HgSe is chemically resistant to all acids other than aqua regia, Se in this form remains permanently retired from biological processes. Irreversible inhibitors of enzymes typically form covalent complexes that eventually decompose during degradation of the protein, if not before. But with HgSe, the irreversible inhibition of the enzyme involves formation of a truly irreversible complex, one with the potential to persist for geological epochs.

Because CH_3Hg-Cys biochemically resembles methionine and other neutral amino acids that the LAT1 amino acid transporter binds and moves across membranes (Simmons–Willis et al., 2002), it is readily distributed between maternal/placental/fetal brain compartments (Aschner and Clarkson, 1988; Aschner, 1989; Aschner and Clarkson, 1989; Bridges and Zalups 2010). Since CH_3Hg-Cys mimics essential amino acids, it is retained in tissues and only slowly excreted, persisting and accumulating in aquatic food chains in quantities that depend on the age, size, and trophic level.

Among highly exposed individuals, a blood Hg level of 1 μM is associated with toxicity and 2.5 μM results in severe toxicity (Clarkson and Magos, 2006). Since these amounts are ~equimolar with the 1-2 μM concentration of Se in blood and body tissues, they are stoichiometrically consistent with current understanding of the mechanisms of CH_3Hg^+ toxicity occurring as a consequence of selenoenzyme inhibition and Se-sequestration (Carvalho et al., 2008; Ralston and Raymond, 2010; Branco et al., 2012; Carvalho et al., 2011; Ralston et al., 2015; Branco et al., 2017; Ralston and Raymond 2018). Although Se's protective effect against Hg toxicity was first noted over 50 years ago (Pařízek and Oštádalová, 1967), the significance of this finding was initially overlooked and generally misunderstood. The "Se-protective effect" was thought to involve Se binding to Hg, sequestering it in a stable form that could no longer harm important biomolecules. However, Se is the biochemical "target" of CH_3Hg^+ toxicity, and selenoenzymes are the important biomolecules that are harmed by high Hg exposures (Ralston and Raymond 2007; Ralston et al., 2008; Carvalho et al., 2008; Ralston and Raymond, 2010; Ralston et al., 2014; Spiller, 2017; Spiller et al., 2017 Ralston and Raymond 2018).

Although brain Se availability is normally preserved at optimal levels, there are indications that certain neurological disorders may involve defects in Se distribution to the brain or impaired availability of Se for selenoenzyme synthesis. Children with intractable seizures were found to have low glutathione peroxidase (GPX) activities that were indicative of poor Se status (Weber et al., 1991), but following dietary Se supplementation, their clinical condition improved. This was a small study and the effect of additional dietary Se on the blood GPX of the children was not reported, so further work would clearly be needed to confirm the findings and identify any underlying cause or causes that may have impaired their

Se-status. However, cerebral Se deficiency is associated with neurological phenotypes including ataxia and seizures (Wirth et al., 2010), apparently in relation to loss of GPX4 in parvalbumin expressing neurons. It is important to note that although Se-deficient diets could result in low blood GPX activities, the availability of Se in the brain is usually almost impossible to diminish below optimal levels, so the resolution of the children's clinical symptoms by dietary Se supplementation may have been mistakenly attributed. On the other hand, genetic defects that impair Se absorption, distribution, or metabolism could contribute to functionally diminished Se-status of neurological tissues (Raymond et al., 2014), and the possibility of increased Se-attrition due to exposures to soft electrophiles causing Se-sequestration should also be considered.

Sources and times of soft electrophile exposures are seldom clearly identified, but a recent case involving a patient exposed to large amounts of Hg^0 vapor following a substantial spill of liquid Hg is informative (Spiller, 2017). After ~3 weeks of exposure, the patient developed hypertension and weight loss, experienced muscular, testicular, and abdominal pain, and suffered insomnia, delusions, hallucinations, tachycardia, palmar desquamation, diaphoresis, tremor, and increasingly severe ataxia leading to hospitalization. Supplementation with 500 µg Se/day (~0.1 µMol/kg BW) and 50 mg of N-acetylcysteine per day was initiated. Within 3 days, he showed noticeable improvement, and by day 11, delusions, delirium, tachycardia, and abdominal pain had resolved. After 3 months, all symptoms had resolved except hypertension. In the following 2 months, he regained lost body weight, hypertension relented, and he returned to normal athletic activities. Although Se supplementation continued for 8 months, the patient' serum Se levels did not become elevated, suggesting his tissues had a significant Se deficit, possibly due to continued Se sequestration as HgSe that accumulate in cellular lysosomes and exhibit long term retention, especially following toxic exposures (Korbas et al., 2010). However, so long as tissue Se availability is sufficient to support brain selenoenzyme activities, high levels of HgSe can accumulate in brain and body tissues without adverse consequences (Falnoga et al., 2006).

Evaluating the risks of adverse neurodevelopmental outcomes associated with prenatal exposures to soft electrophiles requires consideration of the molar relationships between toxicants and the Se

available from maternal tissues and dietary Se sources. This is particularly important to note in understanding outcomes of epidemiological studies of the effects of maternal CH_3Hg^+ exposures from seafood consumption on fetal neurodevelopment. Conflicting interpretations based on opposing effects observed in studies of sentinel populations high Hg exposures from seafood consumption have been difficult for regulatory agencies to resolve in making policy decisions. However, these conflicts are largely eliminated once the differences in Hg-Se molar relationships between CH_3Hg^+ and Se in the seafoods consumed by these populations is examined.

1.3 Epidemiological Studies of Soft Electrophile Exposures

The CH_3Hg^+ poisoning incidents of epidemic proportions which occurred in Japan during the 1950's were lethal to many highly exposed adults and revealed the exceptional vulnerability of the developing fetal brain (Clarkson and Magos, 2006). Accentuated fetal vulnerability was first observed in association with catastrophic poisoning events in Minamata, Japan where 75-150 tons of Hg from factory effluents had been dumped into the enclosed confines of the local bay. The contaminated fish that were consumed had Hg concentrations as high as 50 mg/kg (Takeuchi and Eto, 1999). The accentuated sensitivity of the developing fetus to maternal CH_3Hg^+ exposures were confirmed following a poisoning event in Iraq which involved bread prepared from seed grain which had been treated with CH_3Hg^+ as an antifungal agent. Many adults were poisoned, but once again it was observed that the children of pregnant women that were highly exposed to CH_3Hg^+ would often suffer severe brain damage, even in cases where the health of the women themselves had not been noticeably affected. Although catastrophic exposures to high amounts of Hg are extremely rare occurrences, low level exposures are ubiquitous and almost generally without adverse effects.

Findings reported by studies in New Zealand (Crump et al., 1998), and the Faroe Islands (Grandjean et al., 1997; 1998) were indicative of subtle, subclinical harm from CH_3Hg^+ exposures. In contrast, studies performed in the Seychelles showed no harmful effects, even though the Seychellois consume ~12 ocean fish meals per week and had total CH_3Hg^+ exposures that were higher on average

than those of the Faroes population (Van Wijngaarden et al., 2006). Due to the perceived discrepancies in their findings there was considerable controversy regarding which study should be used to generate regulatory policy. To err on the side of caution, the risk assessors from US EPA chose to use the Faroe Islands study to establish the maternal reference dose (Rfd) of 0.1 µg/kg body weight/day, although these values incorporated 10-fold uncertainty multipliers which were established based on risk management guidelines, rather than on estimates of effect thresholds.

Because of the recognized risks associated with the extremely high Hg and PCB contents of the pilot whale meats, seafood safety recommendations in the Faroes currently advise against anyone eating pilot whale meats. However, since increasing ocean fish consumption was found to protect against the adverse effects associated with Hg exposures from pilot whale consumption, the ministry of health in the Faroes encourages maternal consumption of ocean fish during pregnancy (Weihe and Debes-Joensen, 2012). Current U.S. EPA guidelines apply criteria from the Faroes study data which are based on fish Hg contents (EPA-FDA, 2017), although they are aware of the neurodevelopmental benefits of ocean fish consumption which suggest the need for updates to the advisory and have funded work to develop a more reliable seafood safety criterion known as the Health Benefit Value (HBV). The HBV incorporates the total Hg and Se present in the seafood, providing an index which is positive if the food provides more Se than Hg, and negative if the food provides more Hg than Se (Kaneko and Ralston 2007, Ralston et al., 2016). It is calculated using the following equation:

$$HBV_{Se} = ((Se - Hg)/Se) \bullet (Se + Hg) \qquad \text{(Equation 3.)}$$

Average prenatal CH_3Hg^+ exposures were actually higher in the Seychelles than in the Faroe Islands study, but no adverse associations were found between CH_3Hg^+ and 21 health endpoints that were measured (Davidson et al., 2011). Instead, increasing prenatal CH_3Hg^+ correlated with improved scores on neurological endpoints as well as fewer instances of substance abuse or problematic behaviors in

school. Furthermore, increasing maternal seafood consumption was associated with 4-6 points of child IQ benefits in the United Kingdom (Hibbeln et al., 2007) and ~10 IQ points in the United States (Lederman et al., 2008), even though CH_3Hg^+ exposures were greatest among mothers with the highest seafood intakes. Epidemiological studies have consistently found that increasing Hg exposures from ocean fish consumption during pregnancy results in substantial neurological benefits rather than diminishments in their health and that of their children (Hibbeln et al., 2007; Davidson et al., 2011; Myers and Davidson, 1998; Avella-Garcia and Julvez, 2014; Julvez et al., 2016, Llop et al., 2017; Golding et al., 2017). However, it is clear that increased Hg exposures are not responsible for the beneficial outcomes which have been observed. Instead, improved neurological development, motor development, verbal intelligence, perception, social behavior, reduced inattention and diminished hyperactivity appear likely to be due to improved dietary intakes of nutrients provided by ocean fish. A partial attenuation of these positive associations was noted in the highest seafood intake category (Davidson et al., 2011; Avella-Garcia and Julvez, 2014), but it is uncertain whether CH_3Hg-Cys was actually responsible for the slight decrease in the net beneficial effects, or if exposures to other persistent bioaccumulative toxicants (PBTs) from seafood may have been responsible and that blood Hg was simply a surrogate measure of those exposures.

In the ALSPAC study performed in the United Kingdom, children of mothers who complied with the U.S. EPA reference dose (RfD) for CH_3Hg^+ exposure from fish consumption were at substantially increased risk of scoring in the lowest quartile for verbal IQ, compared to children whose mothers had exceeded the recommended fish intake (Hibbeln et al., 2007). 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 so long as dietary Se is in molar excess of CH_3Hg^+ exposure, Hg is not associated with adverse effects. However, diminished maternal consumption of ocean fish during pregnancy causes more harm than had been associated with Hg exposures from consumption of pilot whale meats in the Faroes Islands Study. These findings agree with outcomes of animal studies which found addition of ocean fish to experimental diets which contained otherwise toxic amounts of

CH_3Hg^+ increased the total Hg exposure, but instead of thereby enhancing the severity of the toxicity, the supplemental Se from the fish meat protected against Hg toxicity (Friedman et al. 1978; El-Begearmi et al. 1982; Ohi et al. 1976, 1980; Stillings et al. 1974; Iwata et al. 1973; Sugiura et al. 1978; Zhang et al. 1997; Ralston and Raymond, 2015). This appears to be due to the substantial increases in brain selenoenzyme activity which accompany Se from ocean fish offsetting the amounts lost to Hg-sequestration, thus protecting against selenoenzyme impairments and oxidative damage that otherwise accompanied the lethally high amounts of CH_3Hg that were present in the experimental diets (Ralston, 2010).

Certain soft electrophiles are known to accumulate along with Hg in top predators. For example, the Cd contents of pilot whale liver and kidney meats eaten by Faroe Islanders were ~442 and ~674 μmol/kg respectively. Furthermore, since pilot whales are the top of the marine food web, these meats (and also the blubber that these mothers consumed) were highly contaminated with PCBs as well as all other PBT's. Since electrophilic metals such as Cd also impair selenoenzyme activities (Kar et al. 1960; Omaye and Tappel, 1975; Jamall and Smith,1985; Gambhir and Nath, 1992; Jamba et al, 2000; Pavlović et al., 2001; Abarikwu et al., 2013; Liu et al., 2014; Binte Hossain et al., 2018), exposures to Se sequestration agents would have been substantial among the Faroes population. Furthermore, electrophilic molecules with α, β-unsaturated carbonyls (e.g., acrylamide, acrolein) also bind thiols well (Lopachin and Barber, 2006; Lopachin et al., 2007a; 2007b). Thus, high exposures to certain organic agents that may have also been present in the pilot whale meat could have also contributed to selenoenzyme impairments, potentially causing or contributing to functional defects observed in Faroese children.

2.0 EVALUATION OF HYPOTHESES

Criteria for evaluating risks associated with CH_3Hg^+, Hg^0, and/or other electrophile exposures need to be based on parameters that reliably predict their combined dose-effect relationships. Exposures to soft electrophiles should be minimized to minimize potential risks, and should be considered in relation to their discrete and aggregate effects on selenoenzyme activities. The Se status and dietary Se intakes of

exposed individuals must also be considered in order to solve the bimolecular equations required to evaluate risks associated with exposures to these electrophiles. It is instructive to compare a series of working hypotheses regarding interpretations of exposure measures in relation to observed outcomes. Following the conventional hypothesis, subsequent hypotheses will indicate the differences between Hypothesis 1 and these alternatives by underlining the relevant text. The following hypotheses are informally worded for convenience and ease of reading:

1) *The conventional hypothesis*: *Maternal CH_3Hg^+ exposures are directly proportional to adverse effects on child neurodevelopmental outcomes.*

This hypothesis is the basis for current regulatory policy and seafood safety advisories in which risk assessments assume that Hg's toxic effects are predictable using the pseudo-first order reaction assumption to evaluate its interactions with cellular thiols or lipids. If this hypothesis is true, predictions of risk can be based on Hg exposures alone.

2) *The Hg-dependent Se-sequestration hypothesis*: *Maternal CH_3Hg^+ exposures <u>in excess of dietary Se intakes</u> are directly proportional to adverse effects on child neurodevelopmental outcomes.*

Since adverse child outcomes associated with increasing maternal CH_3Hg^+ exposures have only been observed in populations which consume foods with negative HBV's (in New Zealand and the Faroe Islands), this hypothesis assumes the adverse consequences which were observed were due to CH_3Hg^+ exposures alone.

3) *The combined electrophiles Se-sequestration hypothesis*: *Maternal exposures to CH_3Hg^+ <u>and other soft electrophiles in cooperative excess of dietary Se intakes</u> are directly proportional to adverse effects on child neurodevelopmental outcomes.*

Since bioaccumulation of CH_3Hg^+ is accompanied by accumulation of various other soft electrophiles in the aquatic food web, the effects attributed to CH_3Hg^+ may reflect consequences due to their combined effects on inhibition of selenoenzymes and sequestration of Se.

4) *The combined concomitant toxicants hypothesis*: *Maternal CH_3Hg^+ exposures and concomitant exposures to other persistent bioaccumulative toxicants (PBT's) are directly proportional to adverse effects on child neurodevelopmental outcomes.*

Since CH_3Hg^+ accumulation is accompanied by coaccumulation of other PBT's in an aquatic food web, the effects currently ascribed to CH_3Hg^+ exposures may actually reflect consequences due to other PBT's, or the combined effects of other PBT's, including, but not limited to inhibition of selenoenzymes and sequestration of Se.

5) *The surrogate measures hypothesis*: *Maternal CH_3Hg^+ exposures are surrogate measures of other persistent bioaccumulative toxicants (PBT's) which concomitantly accumulate in parallel, and are independently directly proportional to adverse effects on child neurodevelopmental outcomes.*

Since CH_3Hg^+ accumulation would parallel accumulation other electrophiles and PBT's in an aquatic food web, the effects attributed to CH_3Hg^+ exposures may be pathological consequences which are independent of Hg and other electrophiles and occur through separate biochemical pathways influenced by PBT's acting independently.

2.1 Evaluation of Hypotheses

Hypothesis 1 has already been repeatedly disproved by the finding that instead of causing harm, increasing CH_3Hg^+ exposures are directly associated with improved social, scholastic, and IQ outcomes in

children (Hibbeln et al., 2007; Davidson et al., 2011; Myers and Davidson, 1998; Myers et al., 2007; Avella-Garcia and Julvez, 2014; Julvez et al., 2016, Llop et al., 2017; Golding et al., 2017). Although these beneficial effects may be partially due to improved dietary Se intakes, they are more likely to result from enhanced access to long-chain omega-3, polyunsaturated fatty acids such as docosahexaenoic acid (DHA) in concert with other essential nutrients obtained from ocean fish.

The discovery that adverse effects reported in association with seafood Hg exposures were only observed in populations that consumed pilot whale meats (HBV= -80) in the Faroe Islands, or great white shark meats (HBV= -120) in New Zealand, while beneficial outcomes have been observed among populations that consume ocean fish with positive HBV's supports hypothesis 2. However, other soft electrophiles such as Cd and a variety of additional metallic and organic soft electrophilic agents that concomitantly bioaccumulate in the marine food web were also present at high levels in the pilot whale and great white shark meats that were associated with adverse child neurodevelopmental outcomes. Therefore, hypothesis 3 is also consistent with the findings of the present studies, but further evaluations must be performed to establish the magnitudes of potential Se-sequestration contributions by the other soft electrophiles. Hypothesis 4 reflects the challenge that all epidemiological studies confront when attempting to identify and apportion potential causality to individual variables when multiple concomitant confounders are present.

Hypothesis 5 considers the possibility that instead of making a causal contribution to the adverse outcomes reported in epidemiological studies associated with seafood consumption, Hg may simply be a surrogate measure of PBT exposures. While maternal exposures to CH_3Hg^+ and other metallic and organic soft electrophiles in the Faroe Islands and New Zealand studies may have been sufficient to impair Se and subtly diminish fetal neurodevelopment as seen in their findings, it is also possible that other agents were responsible for the effects which were observed. Since the amounts of Hg observed in maternal hair or cord blood would be highly correlated with maternal/fetal exposures to all other PBTs, Hg measurements may simply serve as a surrogate measure of those other exposures. If adverse outcomes

arose due to exposures to any other PBTs, some which may currently remain unidentified, we should seek to detect and identify the actual causal agents.

Some notably neurotoxic agents are naturally occurring and already known to occur in seafoods. Although their potential contributions to neurodevelopmental diminishments currently remain undefined, they may present a concrete example of hypothesis 5 in action. For example, in the Seychelle Islands Study, there was a substantial improvement in child outcomes associated with omega-3 fatty acid intakes, but after correcting for these beneficial effects, a subtle decline in neurodevelopmental outcomes that correlated with fetal CH_3Hg^+ exposure remained evident. However, since the fish consumed in the Seychelles have positive HBV's, this consequence may not have been due to CH_3Hg-dependent Se-sequestration. Instead, this may be another case of Hg acting as a surrogate measure of exposure to other PBTs which are present. The seafoods eaten in the Seychelles were primarily reef fish, which bioaccumulate less CH_3Hg^+ than pelagic fish (e.g., tuna). However, coral reefs are populated with dinoflagellates such as *Gambierdiscus toxicus* that produce ciguatoxin (CTX), a naturally occurring toxicant capable of causing gastrointestinal, cardiac, and neurologic symptoms in consumers (Friedman et al, 2017). They are naturally present in the reef ecosystem, growing on the coral, algae, and seaweed at the base of the food web. Although it has no apparent effect on fish, CTX bioaccumulates at the highest levels among top predators of the reef ecosystem and is a notable toxicant that affects fish consumers and has potentially serious, long lasting adverse neurological effects among those with high exposures. Maternal exposures to low levels of CTX is continual among consumers of reef fish, but the effects of such exposures on fetal development remains unexamined. However, similar to other toxic agents, enhanced vulnerability of the developing fetal brain may be characteristic of its effects. Therefore, it remains unclear whether the effects which correlate with Hg exposures in the Seychelles actually reflect the effects of CTX or any other PBT's that coaccumulate in the reef food web.

3.0 DISCUSSION AND CONCLUSIONS

Recognition of the biochemical mechanisms of toxicity of Hg toxicity provides insights into the toxic effects of other metallic and organic electrophiles and may provide a more consistent basis for risk evaluations. The conventional hypothesis of Hg toxicity risks during fetal development has been displaced by more comprehensive concepts which may enable identification of discrete and combined effects of toxicants. Since concomitant exposures to the numerous forms of metallic and organic soft electrophiles is continual throughout life, the potential for aggregate effects of these agents contributing to neurological, endocrine, cardiovascular, and other disease processes is worth investigating. However, the marked vulnerability of the developing fetal brain to Hg indicates maternal exposures to soft electrophiles is a more urgent issue.

Although neuron growth in the fetal brain is a nonlinear process, if averaged throughout pregnancy, it has been estimated that production of the ~100 billion neurons which are the normal complement of a newborn child would require creation of ~250,000 cells per minute (Ackerman, 1992). However, because neuron generation does not begin until ~40 days after conception and thereafter undergoes geometric doubling until ~day 125 in humans, there are times when nutrient deficiencies or toxicant exposures may be expected cause greater harm. The neonatal brain comprises ~10% of the child's total body weight (Jordaan, 1976), but accounts for 25% of total metabolic activity, (Holliday, 1971) and is ~50% lipid by weight (Wainwright 2002), predominantly polyunsaturated long-chain fatty acids including omega-3 fatty acids such as docosahexaenoic acid (DHA) synthesized from precursors or received preformed from the maternal diet (Diau et al., 2005). Since humans have limited abilities to synthesize DHA from precursors, if maternal dietary sources are insufficient, DHA ends up being taken from the mother's brain and redistributed to supply the needs of the child's developing brain, possibly contributing to postpartum depression and other maternal maladies.

Most U.S. women know that ocean fish contain Hg, are aware that Hg is a neurotoxin, and many receive advice to limit their fish intake during pregnancy (Bloomingdale et al., 2010). Far fewer women know that fish contains DHA, the importance of DHA is in the brain, or that increased ocean fish consumption is associated with improved maternal and fetal health. Since few women are told of the

health benefits associated with eating more ocean fish, but most are aware of advice to limit fish intake, many choose to avoid fish rather than risk harming their child. Pregnant women would be willing to eat more ocean fish if their obstetricians advised them to do so, or if they had ready access to a reference indicating which varieties are safe and beneficial to eat (Bloomingdale et al., 2010).

Freshwater fish are far more variable in their Hg and Se contents. Fish from Se-poor watersheds bioaccumulate more CH_3Hg, thus increasing total Hg exposures while simultaneously increasing the risks associated with those exposures since Se-poor fish do not provide consumers with sufficient Se to offset Hg-dependent losses due to Se-sequestration. Therefore, subsistence consumers of low-Se, high-CH_3Hg^+ fresh water fish are at significantly accentuated risk. As blood Hg increased among subsistence freshwater fish consumers in the Amazon, their motor function diminished. However, increasing Se status was protective (Lemire et al., 2011). Since, locally grown foods in Se-deficient regions of the world may fail to provide adequate Se, the risks from exposures to other metallic or organic electrophiles (e.g., Ali et al., 2014) may cooperatively accentuate risks associated with toxic CH_3Hg^+ exposures. Risk assessments based on CH_3Hg^+ exposures of a population without consideration for their concomitant exposures to additional soft electrophiles or the pivotal importance of the Se-status of the exposed populations will fail to adequately identify risks or predict the effects of the soft electrophiles which are present. Suggesting hazards are present when none exist, or failing to recognize the accentuated risks among populations which are more vulnerable to soft electrophile exposures due to poor Se-status are unacceptable errors.

3.1 Conclusions

This review has examined over 50 years of research progress in identifying Se interactions with soft electrophiles. The focus has been on the loss of redox control that can arise from high exposures to soft electrophiles which dysregulate selenoenzyme metabolism and it is clear that risks of high exposures to metallic and/or organic soft electrophiles need to be assessed in relation to dietary Se intakes. While effects of concomitant exposures to soft electrophiles are expected to be additive, the possibility of adverse synergies from certain mixtures of toxic agents are also conceivable. Improved understanding of

the biochemistry and toxicology of organic and metallic soft electrophiles have clear implications for risk assessment research, policy, and regulations.

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Graphical Abstract for FRBM

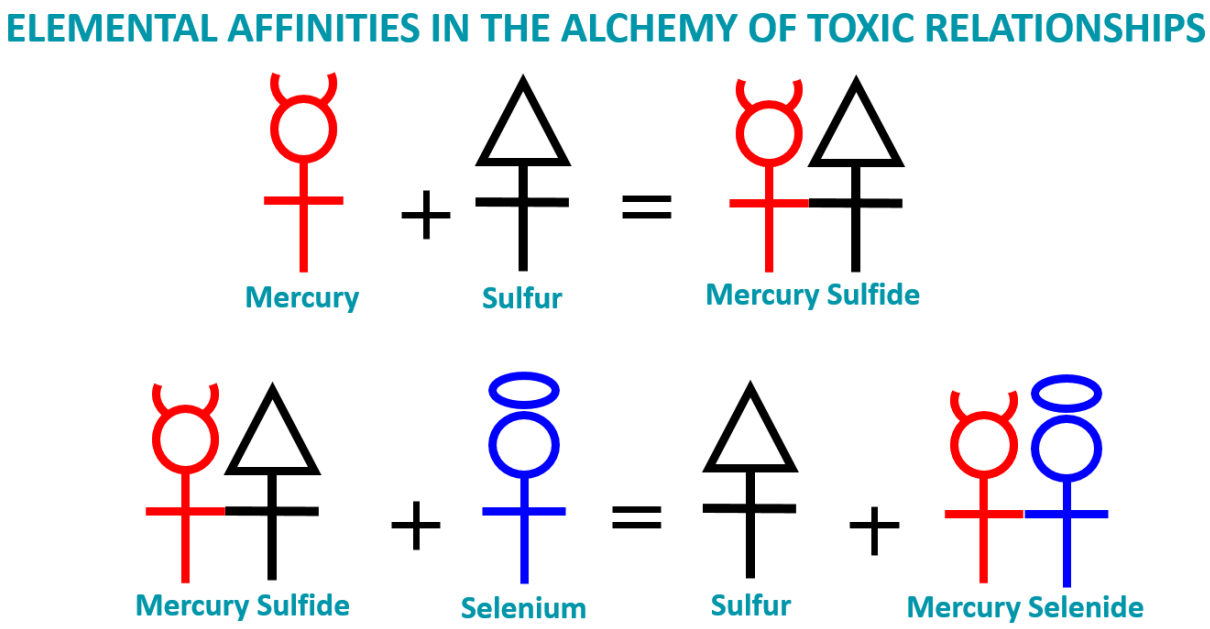

Figure 1. Figure 1. The symbols for mercury and sulfur originate from the era of the early alchemists. The “horns” of the mercury symbol actually indicate the winged helmet of the Roman god Mercury, and the triangle of the figure denoting sulfur originally symbolized “fire” from which sulfur was believed to originate. The alchemists were not aware of selenium, so its symbol is a recent creation. The symbols are used to depict the initial formation of the mercury-sulfur conjugated thiomolecule which brings the mercury into close proximity with the selenium of the selenoenzyme, resulting in mercury’s association with the thiol being exchanged for the selenoate. Other soft electrophiles would similarly bind to sulfur initially and subsequently be transferred to form a covalent adduct with selenium.

Table 1. Mammalian selenoprotein gene names, locations, and functions[1]

Name	Subcellular Location	Tissue Location	Functions	Comments
DIO1	ER	Th, K, L	Activates/inactivates TH	3,5,3'-triiodo-L-thyronine + I^- + A + H^+ = L-thyroxine + AH_2
DIO2	memb	Th, E, B, llUb.	Activates thyroid hormone	Provides brain with T_3 during development
DIO3	endo, memb	U, Pl, B, Fe	Deactivates thyroid hormone	Important in regulating thyroid hormone status in fetus
GPX1	cyto[2]	Ub, B, F	Detoxifies peroxides	H_2O_2 + 2 GSH → GSSG + 2 H_2O
GPX2	cyto	Gb, St, C, llUb	Detoxifies peroxides	H_2O_2 + 2 GSH → GSSG + 2 H_2O
GPX3	plasma	K, llUb,→Pl	Se transport to/from body tissues	Secreted into plasma to redistribute Se to somatic tissues.
GPX4	memb, cyto	Ub, B, T	Phospholipid peroxidase	H_2O_2 or fatty acid peroxides + 2 GSH → GSSG + 2 H_2O or fatty acid
GPX6	secreted (?)	ll, F	Detoxifies peroxides	H_2O_2 + 2 GSH → GSSG + 2 H_2O
MSRB1	Nu, cyto	Ub, K, L	Reduces Met-R-sulfoxides	Promotes actin polymerization, Zn^{2+} cofactor
SELENOF	ER	Ub, Th	Oxidoreductase (?)	May assist in disulfide formation and protein folding
SELENOH	Nu	Ub	Oxidoreductase (?)	Promotes mitochondrial biogenesis
SELENOI	(?)	Ub, B, S, SI	Ethanolamine-P-transferase 1	Synthesizes phosphatidylethanolamine
SELENOK	ER	Ub, A, H, T	Oxidoreductase (?)	Functions in T-cell proliferation, involved in calcium regulation
SELENOM	ER, Gg	Ub, Pr, B, En	Oxidoreductase (?)	May participate in disulfide bond formation
SELENON	ER	Ub	Oxidoreductase (?)	Regulates redox-related calcium homeostasis
SELENOO	mito	Ub	Oxidoreductase (?)	Largest mammalian selenoprotein
SELENOP	plasma	Ub, B, L,→Pl	Primary Se transporter in plasma	10 Sec/molecule in humans, delivers Se to brain, placenta, etc.
SELENOS	ER	Ub, B, T	Participates in detoxification	May be involved in controlling inflammation
SELENOT	ER (?)	Ub, A, B, Th	Oxidoreductase (?), Ca^+ release	Protects dopaminergic neurons against oxidative stress
SELENOV	(?)	T, Th, B, Pr	GPX/TXNRD activities	Member of the SELENOW protein family
SELENOW	cyto	Ub; H, B	Oxidoreductase (?)	May regulate redox state of 14-3-3 proteins in brain
SEPHS2	cyto	Ub	Forms Se-phosphates	Creates high energy precursor required for synthesis of Sec
TXNRD1	cyto	Ub, B, A, Gb	Reduces Trx, glutaredoxin, etc.	Induces actin and tubulin polymerization
TXNRD2	mito	Ub, B, A, Pr	Reduces Trx, glutaredoxin, etc.	Trx + $NADP^+$ → Trx disulfide + NADPH (FAD cofactor)
TXNRD3	N, ER (?)	Ub, T	Reduces Trx, glutaredoxin, etc.	GSSG reductase, also catalyzes disulfide bond isomerization

[1]Information presented in this table was compiled from: Aachmann et al. 2007; Dikiy et al. 2007; Gao et al. 2007; Gereben et al. 2008; Gladyshev et al. 2004; Gromer, 2005; Labunskyy et al. 2009; Linster and Van Schaftingen, 2007; Lu, et al. 2006; Moghadaszadeh and Beggs 2006; Reeves et al., 2009; Reeves et al., 2010; Shchedrina et al. 2010 and UniProt Knowledgebase/National Center for Biotechnology Information. Information regarding the tissue location, subcellular location, and protein functions are indicative, rather than exhaustive.

[2]Abbreviations used in this table: A, adrenal; B, brain; C, colon; cyto, cytoplasm; E, endometrium; ER, endoplasmic reticulum; Es, esophagus; FA, fatty acid; Fe, fetus; F, fat; GSH, glutathione, Gb, gall bladder; Gg, golgi apparatus; Pr, prostate; L, liver; memb, cellular membrane; mito, mitochondria; N, nucleus; Nu, nucleolar; S, skin; SI, small intestine; T, testis; Th, thyroid; Trx, thioredoxin, U, uterus; Ub, ubiquitously expressed; llUb, ubiquitous low level expression, (?), incompletely characterized.

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