Concomitant Selenoenzyme Inhibitor Exposures as Etiologic Contributors to Disease: Implications for Preventative Medicine

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Abbreviations:

chimeric antigen receptor (CAR)

cysteine (Cys)

electrophile bound glutathione disulfide (GS-E*-SG)

elemental mercury (Hg^0)

glutathione (GSH)

glutathione disulfide, oxidized GSH; (GS-SG)

glutathione peroxidase (GPx)

glutathione reductase (GRx)

hydrogen peroxide (H_2O_2)

large neutral amino acid transporter (LAT1)

methylmercury (CH_3Hg)

methionine (Met)

methionine sulfoxide reductase B (MsrB1)

oxidized mercury (Hg^+)

hard-soft acid-base (HSAB)

hydroperoxo species (OOH)

inorganic mercury (Hg^+, Hg^{2+})

peroxyl radical ($ROO^{\cdot}$)

selenoate (RSe^-)

selenocysteine (Sec)

selenomethionine (SeMet)

serine (Ser)

S-nitrosothiol (SNO)

thiol (R–SH)

thioredoxin (Trx–$(SH)_2$)

thioredoxin reductase (TRx)

thioredoxin-glutathione reductase (TGR)

tumor-infiltrating lymphocytes (TIL)

Abstract (250 words)

The physiological activities of selenium (Se) occur through enzymes that incorporate selenocysteine (Sec), a rare but important amino acid. The human genome includes 25 genes coding for Sec that employ it to catalyze challenging reactions. Selenoenzymes control thyroid hormones, calcium activities, immune responses, and perform other vital roles, but most are devoted to preventing and reversing oxidative damage. As the most potent intracellular nucleophile (pKa 5.2), Sec is vulnerable to binding by metallic and organic soft electrophiles (E*). These electron poor reactants initially form covalent bonds with nucleophiles such as cysteine (Cys) whose thiol (pKa 8.3) forms adducts which function as suicide substrates for selenoenzymes. These adducts orient E* to interact with Sec and since Se has a higher affinity for E* than sulfur, the E* transfers to Sec and irreversibly inhibits the enzyme's activity. Organic electrophiles have lower Se-binding affinities than metallic E*, but exposure sources are more abundant. Individuals with poor Se status are more vulnerable to the toxic effects of high E* exposures. The relative E*:Se stoichiometries remain undefined, but the aggregate effects of multiple E* exposures are predicted to be additive and possibly synergistic under certain conditions. The potential for the combined Se-binding effects of common pharmaceutical, dietary, or environmental E* require study, but even temporary loss of selenoenzyme activities would accentuate oxidative damage to tissues. As various degenerative diseases are associated with accumulating DNA damage, defining the effects of complementary E* exposures on selenoenzyme activities may enhance the ability of preventative medicine to support healthy aging.

Introduction

Mutations incurred as a result of oxidative damage, ionizing radiation, mistakes in DNA repair, or errors during replication lead to somatic mosaicism, an established cause of cancers [1] and a suspected cause of various other diseases and disorders [2-10]. As these somatic mutations accumulate throughout life, age is directly correlated with risk of developing most noncommunicable diseases. Development of chronic degenerative diseases is an important determinant of longevity, and each additional comorbidity increases mortality risks [11]. Improved understanding of the contributions and consequences of somatic mutations may provide insights regarding the etiologies, pathologies, and progression of diseases that may improve prevention and the effectiveness of therapeutic interventions. Treatment is important, but such interventions are inferior to approaches that would preclude their onset or minimize their effects. The United States' annual health expenditures for 2020 [12] amounted to ~$4.1 trillion ($12,530 per capita). Reducing exposures to causal factors could enhance health system sustainability, but less than 3% of annual expenditures is currently allocated to prevention. There may be ways to obtain a better return on our investment.

Each day, many of the trillions of cells in the human body undergo mitosis to support growth and repair damage. While DNA replication proceeds with high fidelity, stochastic errors still arise that range from aneuploidy or deletion/addition of chromosome sections to small mutational events such as single base substitutions, doublet base substitutions, and small insertions or deletions. Errors which are not inherently lethal or severe enough to result in recognition and elimination by immune cells will survive and be passed along in the progeny of that cell lineage. While DNA replication errors can arise spontaneously, exposure to ionizing radiation, genotoxic agents, or initiators of oxidative damage add to existing errors and magnify risks of developing significant pathology.

Lineages with growing numbers of acquired mutations increase with age as replication errors or inaccurate repairs of DNA damage accumulate. Severe errors prevent cell survival while those that produce aberrant proteins are terminated by immune cells. However, mutation errors which are subtle enough to not attract the attention of immune surveillance will remain in the tissues they reside in even if

121 they are unable to properly perform their normal functions. When somatic cells suffer damage to critical
122 oncogenes, tumor-suppressor genes, and other factors which cause them to lose their response to contact
123 inhibition and propagate uncontrollably, these mutations produce malignancies. Random DNA copy
124 errors account for the majority of these mutations [13], and their single-cell genomes indicate they
125 possess multiple acquired mutations.
126 Among the many factors which protect against cellular damage, certain selenoproteins appear to
127 have particularly important roles. As the most powerful intracellular nucleophile [14], the selenoate of
128 selenocysteine (Sec) directly facilitates the activities of various selenoenzymes that prevent or reverse
129 oxidative damage, communicate redox states, regulate calcium and thyroid hormone status, guide protein
130 folding, transport Se between tissue compartments, and synthesize the selenophosphate required for their
131 own synthesis [14-21]. Cellular respiration spontaneously produces reactive oxygen species (ROS),
132 reactive nitrate species (RNS), free radicals, and other metabolic byproducts which can damage lipids,
133 proteins, and nucleic acids. The unparalleled homeostatic control of Se's tissue kinetics apparently
134 evolved to ensure that brain, endocrine, and certain other tissues are preferentially supplied to support
135 uninterrupted selenoenzyme synthesis and activities regardless of current dietary intakes [22-24].
136 Compared to other essential trace elements, consequences of dietary Se deficiencies develop slowly and
137 have few overt and no acute symptoms. Correlations between low blood Se and increased morbidity
138 and/or mortality due to various pathologies [25-38] may indicate low Se intakes contribute to their
139 development. Low blood Se is associated with diminished anti-viral immunity and sepsis responses as
140 well as autoimmunity, allergic asthma, and chronic inflammation [39, 40], potentially indicating
141 diminished immunocompetence contributes to the onset and progression of certain diseases. In some
142 cases, low Se-status can be linked to functional defects that may contribute to development of these
143 pathologies. However, since inflammation itself will cause Se to redistribute from blood to other tissues
144 [41], some relationships between these disorders and blood Se may reflect consequences of the disease
145 rather than causes. Distinguishing causes from consequences is always important to establish, but these
146 relationships will need to be fully assessed. Furthermore, exposures to certain agents can limit Se's

biological activities and induce deficiencies even though tissue Se levels may remain normal or even increase. Although this Se-sequestration effect has been demonstrated for high exposures to certain agents [20, 42, 43], the potential for other agents to similarly contribute to pathological outcomes remains conjectural.

As the most potent intracellular nucleophile (electron-rich, negatively charged species), Sec is chemically reactive with electron poor soft electrophiles (E*) and forms stable covalent Se-E* bonds. Thus, it is notable but not surprising that other than genetic knockouts, high E* exposures are the only environmental insults capable of substantially diminishing selenoenzyme activities in preferentially supplied tissues [24, 25, 42-44]. Since intracellular thiols are ~10^5 more abundant than Se, mass action effects cause E* to initially bind to the less nucleophilic sulfur of cysteine (Cys) residues. Since many intracellular thiomolecules are substrates for selenoenzymes, this initial binding expedites the transfer of E* to the Se of Sec. Bound to the substrate thiol, the E* is delivered into the selenoenzyme's active site in the proper orientation to directly engage with the Sec. The coordinated structure of the enzyme [45] accentuates Se's reactivity still further, enhancing E* transfer from Cys to form a E*-Sec adduct, thus irreversibly inhibiting the enzyme. Some E* will accumulate and sequester Se in the afflicted tissues. However other E* may bind Se in other tissues of the body, but cause problems by preventing Se from redistributing to where it is needed. Identification of E* of concern will require establishing whether the selenoenzyme inhibition and sequestration effects of the various forms are additive and evaluating which exposures may exacerbate risks of adverse effects. Furthermore, it must be established whether complementarity, cooperativity, or adverse synergies arise from concomitant E* exposures. This will require measurement of the Se-binding affinities of the various metallic and organic E* and establishing the range of concentrations which would be predicted to accompany source exposures. Establishing the extents of these effects will support efforts to protect and improve public health and provide more reliable environmental risk evaluations.

Selenoenzyme Interactions with Reactive Oxygen and Reactive Nitrogen Species

Due to their propensity for binding with various minerals and metals, oxygen, sulfur, Se, and other members of group 16 of the periodic table are known as chalcogens, meaning “ore forming” elements. Metallic elements with larger atomic radii and more diffuse electron shells tend to have higher binding affinities for sulfur than oxygen, but their affinities for Se are higher still due to its greater atomic radius and lower electron density of its outermost shell [46]. The shared physicochemical properties and similarities among the first three members of the chalcogen family are evident in their biochemistry. As illustrated in Figure 1, Serine (Ser) is an amino acid with a terminal hydroxyl on its R group while a terminal thiol produces Cys. The analogous Sec employs the third member of the chalcogen family, although a concerted series of enzyme activities had to evolve to accomplish its synthesis.

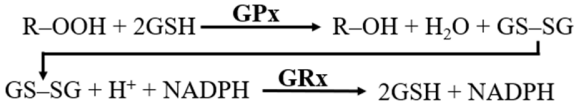
The similarities between sulfur and Se are demonstrated when they are incorporated into methionine (Met) since plants do not distinguish between these elements during synthesis. The abundance of Met and SeMet reflect the sulfur and Se contents of the soils or water the plants are grown in. The Se-form of the molecule is termed selenomethionine (SeMet), and it has no distinct three or single letter designation (See Figure 1.) The sulfur of Met and the Se of SeMet participate in inter and intramolecular chalcogen bonds with backbone and side chain oxygens similarly and appear to equivalent in $tRNA^{Met}$ uptake [47-48], but Se’s higher polarizability enhances the stability of protein structural motifs. When animals consume these plant proteins, Met and SeMet continue to be [49] undistinguished by $tRNA^{Met}$ and are incorporated into animal proteins with no apparent differences, their noncovalent interactions in proteins differ [50, 51]. The biological relevance and physiological importance of Se diverge once these amino acids are degraded to release sulfur and Se.

Once Se is released from SeMet, inorganic selenide is phosphorylated by selenophosphate synthetase (SPS2) which is itself a selenoenzyme. In the presence of a specific stem-loop structure known as the selenocysteine insertion sequence (SECIS) element, an in-frame UGA which would otherwise be read as the opal “stop” codon will instead direct de novo synthesis of Sec and its simultaneous insertion into the selenoprotein being formed. Unique among amino acids, Sec is synthesized while on its transfer RNA ($tRNA^{[Ser]Sec}$). The Ser that is initially bound has its hydroxyl moiety displaced by selenophosphate,

thus converting it into Sec [21, 52, 53]. Humans possess 25 unique genes encoding for insertion of Sec whose expression levels vary among cell types, developmental stages, dietary Se, and other factors [54]. While all cells of all forms of vertebrate life express selenoproteins, their sequence and tissue expression homologies give indications of their importance [21, 51, 54].

Cells require intracellular reducing conditions to be maintained for survival and employ multiple interactive processes to monitor and regulate transcription factors, kinases, and other enzymes to control redox status [56, 57]. The forms of ROS and RNS include multiple highly reactive species produced as metabolic byproducts of essential reactions [58, 59]. While their beneficial roles in signaling and as weapons of the immune system are essential, above the nominally healthy limits, their concentrations are directly linked to increasing tissue damage. Loss of redox balance is a key contributor in development of metabolic and degenerative diseases and disorders [60, 61]. Excessive ROS, RNS, and diminished control of the oxidative damage they cause will adversely affect physiological processes and is thus considered a likely initiator of numerous pathologies. When intracellular concentrations of these agents rise above normal, increasing molecular damage can exceed accommodation by repair mechanisms and endanger cell survival. Major ROS forms include the hydroxyl radical ($^{\bullet}OH$), superoxide (O_2^{-}), hypochlorous acid (HClO), and hydrogen peroxide (H_2O_2). The best known RNS forms are nitrogen dioxide $NO_2^{\bullet}$, nitric oxide ($NO^{\bullet}$), and peroxynitrite ($ONOO^{-}$) – a powerful oxidant [62]. These can cause molecular damage, but also perform regulatory roles in mammalian cells [63]. The modification of Cys by S-nitrosylation [64-66] involves $NO^{\bullet}$ covalently binding to form S-nitrosothiol (SNO). Along with tyrosine nitration, S-nitrosylation is a fundamental mechanism for cell signaling aspects of NO bioactivity [62]. Tyrosine nitration is a posttranslational protein modification mediated by $ONOO^{-}$ and $^{\bullet}NO_2$, formed as secondary products of NO metabolism in the presence of oxidants including superoxide radicals ($O_2^{\bullet-}$), H_2O_2, and transition metal centers. Malfunctions in ferroptosis are linked to diseases with notable ROS production including cancer, neurodegenerative disorders, infections, and inflammatory diseases [67-68]. Disruptions of the balance of these pathways could easily have multiple adverse outcomes.

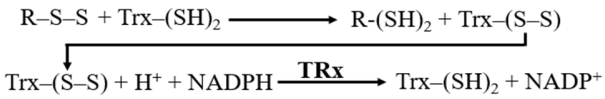
While normal levels of H_2O_2 and lipid peroxides (R-OOH) participate in signaling pathways, high levels can cause oxidative stress and damage. Peroxides are highly reactive species that must be detoxified quickly, and several enzyme systems cooperate in preventing, counteracting, and controlling their damaging effects. Selenium-dependent glutathione peroxidase (GPx) enzymes have vital roles in regulating intracellular redox state as well as preventing and/or reversing oxidative damage. Equation 1 depicts the generalized glutathione (GSH)-dependent reduction of lipid peroxides (R-OOH) or H_2O_2 to an alcohol and water and the role of glutathione reductase (GRx) in restoring GSH to its functional form.



Equation 1.

Glutathione peroxidase 1 (GPx1) is a ubiquitous cytosolic selenoenzyme with concentrations that vary in direct relation to dietary Se intakes. No independent consequences arise in GPx1 knockout mice, although pathologies related to oxidative stress appear to be exacerbated in its absence. In contrast, Glutathione peroxidase 4 (GPx4) knockouts are embryonically lethal at an early stage, and structural compartmentalization becomes disrupted. It is localized to cytosol, mitochondria, and nucleus where it reduces membrane phospholipid hydroperoxides but exhibits broad substrate specificity and acts as a near-universal antioxidant. It is expressed in all tissues and is the most highly expressed selenoenzyme in the brain.

Although thioredoxin reductase (TRx) enzymes are named for their ability to reduce oxidized thioredoxin [Trx–(S-S)] to its active form [Trx–$(SH)_2$], this was just the first of the many substrates they are now known to reduce (See Figure 2). The canonical reaction for which the TRx enzyme is named is shown in Equation 2. Thioredoxin is itself an important antioxidant enzyme, and the reaction between TRx and oxidized substrate disulfides (S-S) restores it to its active thiol form in cytosolic, mitochondrial, and nuclear compartments of the cell.



Equation 2.

Deletion of any of the TRx forms is embryonically lethal, indicating the essentiality of maintaining the reduced state of the broad range of cognate substrates they act upon. Thioredoxin reductase 1 (TRx1), the cytosolic form, is a ubiquitously expressed oxidoreductase flavoprotein with a Sec residue as the penultimate amino acid of its C-terminus. Localized in cytoplasm and translocated into the nucleus during oxidative stress [69-71], TRx1 reduces oxidized forms of a wide range of endogenous substrates including: Trx–$(SH)_2$, dehydroascorbate (vitamin C), lipoic acid/lipoamide, H_2O_2, lipid hydroperoxides, vitamin K, ubiquinone, S-nitrosoglutathione, selenodiglutathione, selenite, methylseleninate, protein disulfide isomerase, glutaredoxin, glutathione peroxidase, NK-lysin/granulysin, selenocystine, and oxidized molecular species of exogenous origin including: HIV Tat protein, ninhydrin, juglone, alloxan, and DTNB as well as dietary polyphenols and additional molecular species [45]. The broad substrate specificity of the TRx enzymes is not exclusively due to the Se of Sec, but also reflects the catalytic power of the enzyme's reaction center [72]. The mitochondrial form, Thioredoxin reductase 2 (TRx2), is a ubiquitous oxidoreductase, and the third form, Thioredoxin glutathione reductase (TGR) reduces diglutathione (GS-SG) and has functions that link Trx–$(SH)_2$ and GSH pathways [73].

The TRx family members cooperatively interact with vitamin E and vitamin C metabolism in protecting against peroxidation and free radical damage. After vitamin E terminates a free radical chain reaction in lipids, it interacts with vitamin C (ascorbate) to be restored to its active form. This oxidizes ascorbate to the dehydroascorbic acid that TRx restores back to ascorbate (See Figure 2). Since many substrates of TRx are important cellular antioxidants themselves, this family of selenoenzymes plays a pivotal role in preserving proper intracellular reducing environments. However, if TRx is synthesized without enough Se to form Sec, the enzyme activity is lost, but more importantly, the molecule acts as a potent apoptosis initiator known as GRIM-12 [74]. Since cells that have too little Se to survive will sacrifice themselves, their Se is redistributed and may enable neighboring cells to persist. This mechanism

appears to represent an evolutionary strategy which enables organisms to survive extended shortfalls in dietary Se availability.

Reversible oxidative modification of Met and SeMet residues has important roles in cell functions Methionine and SeMet [48] act as an antioxidant in several proteins that form reversible diastereomeric methionine sulfoxides (Met-S-SO or Met-R-SO) which are specifically reduced by methionine sulfoxide reductase MsrA or MsrB respectively in a thioredoxin dependent mechanism. Methionine R-sulfoxide reductase (MsrB1) is a selenoenzyme which employs Trx–$(SH)_2$ as the reductant to reverse the oxidation of R-methionine in what is thought to be a signaling mechanism stimulated by oxidative stress. Since the majority of CH_3Hg in the body is bound to Cys [75] and forms a molecular mimic of Met [76, 77], it appears that access and transfer of this and perhaps other forms of E* to Sec may include interaction with and inhibition of MsrB1 activities. Loss of this selenoenzyme is accompanied by increased cellular ROS levels as observed in MsrB1 knockouts and diminishments in their activities are implicated in diseases such as diabetes and neurodegeneration as well as cellular damage associated with aging [78]. Recent studies predict that oxidation of Met may have metabolic functions similar to protein phosphorylation in cell signaling and MsrB1 appears to counteract aging and development of neurological disorders. Several additional selenoenzymes appear to participate in preventing, controlling, or reversing oxidative damage, but have not had their biochemical functions fully characterized but are abundant in brain. A growing number of selenoenzymes are localized in the ER where they appear to participate in homeostasis, protein folding, quality control, calcium homeostasis, and stress response signaling [79, 80]. Loss or diminishment in these selenoenzymes would increase production of aberrant cellular proteins which could elicit recognition by immune cells and initiate an inflammatory response independent of somatic DNA damage.

Metallic and Organic Electrophile Interactions with Selenoenzymes

Electrophiles, also known as Lewis acids, are electron poor and will therefore accept electrons donated by a nucleophile (Lewis base) to form a covalent bond. The outcomes and products of this fundamental

biochemical reaction depend on not just charge, but also the polarizability of the electron shells of the initial participants and will be determined by changes in local electron density and external potential. The Pearson acid-base concept uses hard-soft acid-base (HSAB) terminology to qualitatively distinguish among the relative interactivities of electron shells of various elements [81]. While theoretical reactivity assessments performed with advanced models of density functional theory investigate such interactions with semiquantitative capabilities, HSAB principles provide a qualitative understanding of the properties and reactions of transition metals and organic E* with thiols and selenoates which are sufficient for the present discussion. In this context, "hard" describes electrophiles (e.g., H^+, Li^+, Na^+) or nucleophiles (e.g., F^-, Cl^-) with more concentrated charges and repulsion by electron shells that are less polarizable. Thus, hard electrophiles and hard nucleophiles tend to form ionic bonds with one another while "soft" electrophiles (E*) have larger electron shells whose less concentrated charge distributions can be polarized to permit electron sharing and form covalent bonds. Oxygen and ROS are a subset of the reactive electrophiles that selenoenzymes encounter [82]. While metallic E* have much higher binding affinities than α, β-unsaturated carbonyls or other electronegative structures of organic E* (See examples in Figures 2 and 3) a more complete list of these forms is provided in the review by Saccoccia, et al., [83]. However, it is not the exposures to any individual form that cause the greatest concern. Instead, it is the potential for multiple chronic E* exposures to cooperate in sequestration of tissue Se and diminish selenoenzyme activities through their combined effects.

Since tissue Se concentration are ~1 μM, the aggregate E* exposures that would be required to impair selenoenzyme activities are relatively low. Forms of E* with high Se binding affinities only need to approach equimolar stoichiometries with Se to potentially endanger selenoenzyme activities, particularly when replenishment of Se from dietary sources is limited [42, 84]. The potential for exposures to multiple forms of metallic and organic E* from dietary, environmental, and pharmaceutical sources to cooperatively sequester Se and impair selenoenzyme activities is a health risk worthy of

evaluation [85-90]. The consequences would be predicted to differ depending on the affected tissues, although certain parallels among their pathologies can be expected.

Metallic Electrophiles

Metallic electrophiles are electron-poor and readily accept an electron pair to form covalent bonds with oxides, sulfides, or selenides. In this context, "heavy" metals are thiophilic (and selenophilic) elements with broadly dispersed charge densities such as palladium (Pd), silver (Ag), cadmium (Cd), platinum (Pt), gold (Au), mercury (Hg), or thallium (Th). These have Se-sequestration potentials that would be worrisome as their combined molar concentrations in tissues approach 1 μM (See Table 1). The main sources of exposure to these elements are from industrial sources, pharmaceuticals, or dental alloys, and are expected to be generally low for most populations but will require monitoring since source contributions are rising. For example, typical exposures to the platinum group elements (Pt, Pd, etc.) are not at levels that cause concern [87] but their presence in the environment is steadily increasing due to their use in vehicle catalytic converters. Elements such as molybdenum, manganese, iron, cobalt, nickel, copper, zinc, lead, and bismuth have lower Se-binding affinities so higher exposures would be required to impair Se availability. However, sources of exposure to these forms are more abundant and ought to be critically assessed. It is also important to note that individual elements will often have distinct tissue toxicokinetics. Although their biochemical mechanism of toxicity would all involve selenoenzyme inhibition, the pathological consequences and observed effects could differ between the affected tissues. Certain pharmaceutical agents were specifically designed to exploit their Se-binding capabilities. The effects of Au- and Ag-containing compounds accomplish their therapeutic functions primarily through their irreversible and relatively specific inhibition of thioredoxin reductase (TRx). Other medicinal agents that incorporate accessible metallic E* in their molecular structures appear likely to have similar effects on TRx and/or other selenoenzymes [88-90] but require evaluation on a case-by-case basis.

While all E* will interact with nucleophiles, the interactions between Se and Hg are the best characterized with hundreds of reports since the 1960's [91-95] and increasing attention to details of their

interactions in subsequent years [96-100]. Mercury's binding constant for sulfide is very high (10^{39}), but its affinity for selenide (Ka = 10^{45}) is a million-fold higher [101]. Meanwhile, methylmercury (CH_3Hg^+) has a high binding affinity (10^{17}) with the thiol of Cys but an even higher affinity for Sec [20]. Due to mass action effects of the ~10^5 higher intracellular abundance of Cys than Sec, >95% of intracellular CH_3Hg^+ occurs as CH_3Hg-Cys [75]. Because thiomolecules such as GS-SG and Trx-$(SH)_2$ are selenoenzyme substrates (see Equations 1 and 2), adducts such as GS–E*–SG, GS–E*, Trx-(S_2-E*) are suicide substrates that deliver E* into selenoenzyme active sites. Because of the higher affinity of Hg for Se, it transfers to form CH_3Hg-Sec, irreversibly inhibiting the selenoenzyme [20, 43]. Since the inhibitor truly is irreversibly bound the active site Se and the insoluble HgSe exhibits long term retention in brains [85] and other tissues [102] of highly exposed individuals, it is anticipated that this will soon become the textbook example used to illustrate the mechanism and outcome of irreversible inhibitors.

Because CH_3Hg-Cys resembles Met at the molecular level (see Figure 1), the large neutral amino acid transporter (LAT1) transfers it across membranes [76, 77] and into maternal, placental, fetal, and brain tissues. Once internalized, it is shed from the body in Met-rich materials such as hair, nails, skin, and in sloughed off cells. It degrades slowly and thus accumulates in organisms in quantities that reflect their relative age and trophic level. The CH_3Hg-Cys in fish is absorbed by the consumer and exhibits long term retention in their tissues as a Met mimic although it remains unknown whether pseudomethionine (Figure 1) substitutes for Met in cellular proteins or is simply retained as a molecular bystander.

Table 1. Representative Metallic E*

Form	Examples of Exposure Sources
Pt	Dental alloys and pharmaceuticals used as chemotherapeutic agents
Hg^0	Artisanal mining activities, spills from broken barometers, thermostats
Hg^{2+}	Present in unapproved skin whitening creams and related cosmetics
CH_3HgCH_3	Landfill emissions (very low levels), laboratory reagent spills
CH_3Hg–Cys	Fish, seafoods, large amounts in apex predator whale/shark meats
Cd	Smoking, contaminated water, or foods grown near pollution point sources
Au	Dental alloys and pharmaceuticals used to treat inflammation

Ag	Dental alloys and pharmaceuticals used to treat inflammation
Pb	Paint, contaminated water, dust, and air; gasolines used in some areas
As	Contaminated water, food crops, livestock, cosmetics

Elemental mercury (Hg^0) is uncharged, and its vapor is readily absorbed by the lungs and easily crosses membranes as it is transported throughout the body. It is innocuous in this form since it cannot bind Se. However, it becomes a potent Se-binder once it is oxidized to Hg^+ by catalase [103]. Inorganic Hg formed in this way can initially bind with thiols to form Cys-Hg^+ which can deliver the Hg to Sec and irreversibly inhibit selenoenzyme activities. Because Hg^+ and Hg^{+2} are poorly absorbed and Cys bound forms do not resemble Met at the molecular level, they are not readily transferred across membranes. This limits their neurotoxicity, but their accumulation in other tissues can still sequester Se and reduce its availability for redistribution to brain and other tissues. The toxicokinetics of the various forms of Hg provide useful examples of E* forms in tissue compartments and the specificities of their effects.

Organic Electrophiles

The reactivity of an organic E* depends on the presence of electron withdrawing groups creating a region with low electron densities that enable nucleophiles to approach and donate their electrons. The organic E* vary widely in structure (See Table 2 and Figures 2 and 3) and include carcinogens, classes with recognized neurotoxicity, and other forms known to be associated with neurodegenerative diseases. As with all toxicants, dose is the determining factor, but the defining threshold for adverse effects will in all likelihood depend on the Se-status of the exposed individuals.

Alkenes conjugated to a carboxylic acid are α, β-unsaturated carbonyls –a common motif among organic molecules, and include methyl vinyl ketones, acrolein, acrylamide, methyl acrylate, maleic acid, fumaric acid, E-crotonaldehyde, testosterone, cinnamaldehyde, cyclohexanone, and paraquinone among many others. Xenobiotic E* include organic products formed during cooking of food, common pharmaceuticals, environmental pollutants, partially combusted constituents in smoke from tobacco,

wood, or diesel exhaust, and many other contaminants present in food or water. Since there are also many endogenously generated "natural" forms, organic E* exposures are pervasive. Several organic E* arise from more than one source, and various endogenously generated forms (e.g., acrolein, 4-hydroxy-2-nonenal), environmental toxicants (e.g., γ-diketones, quinones, unsaturated aldehydes), industrial pollutants (acrolein, acrylonitrile, methyl vinyl ketone), drug metabolites (e.g., acrolein metabolite of cyclophosphamide, NAPQI), and common components present in cooked foods (e.g., acrylamide) are well known for the damage they can cause [104-116] at high concentrations. The unsaturated carbonyls of organic E* will initially form covalent bonds with nucleophilic Cys thiols, and for the reasons stated above, they are expected to bind even better with Sec. However, the necessary studies have not been done to quantitatively compare their relative binding affinities, so this conjecture remains unproven.

Table 2. Representative Organic E*

Form	Examples of exposure sources
Pseudomethionine	(aka CH_3Hg-Cys) Most abundant Hg form in fish and human tissues
Acrylamide	Foods cooked at high temperature, smoking, partially combusted materials
Acrolein	Ubiquitous in cooked foods, smoking partially combusted materials
NAPQI	Byproduct of xenobiotic metabolism of acetaminophen
Aflatoxin	Toxin produced by common forms of mold growing on food
Hydroxyhexenal	Product of lipid peroxidation (exogenous and endogenous)
Neuroketal	Lipoxidation product that forms adducts with cellular proteins
Neuroprostane	Prostaglandin-like product of fatty acid peroxidation
2-Acetylpyrroline	Maillard reaction product formed during baking
Dopamine Quinone	Reactive metabolite formed from oxidation of dopamine
Methamphetamine	Central nervous system stimulant used as recreational drug

While far more varied in sources, forms, and exposures than the metallic E*, the Se-binding affinities of organic E* are expected to be several log orders lower and these products will be more reversible [82]. For this reason, on a mole for mole basis, the risks of selenoenzyme impairment from exposures to any individual α, β-unsaturated carbonyls or other organic E* seem low. However, the wide range of forms and sources may result in exposures to molar quantities that are higher than is typical with

441 metallic E*. It is entirely possible that binding interactions with Se are a common but transitory feature of
442 organic E* physiology which introduce no clinically significant results. This is, in fact, the expectation for
443 organic E* exposures of the majority of individuals through most of the developed world. Provided
444 sufficient Se remains available to support Sec synthesis, few if any consequences would be expected in
445 association with low to moderate E* exposures. However, among subsistence populations living in Se-
446 poor regions of the developing world, there may be too little Se available to overcome losses that would
447 be insignificant for most people. Even in the developed world Se-poor diets may be consumed secondary
448 to chronic alcohol abuse or other causes. It is anticipated that most organic E* will have very low Se-
449 affinities and therefore only high exposures might result in substantial Se-sequestration. Although the
450 population subgroups at risk will be small, examining the Se-binding affinities and anticipated range of
451 human exposures to these numerous and varied forms would at minimum provide prudent reassurance,
452 but could reveal risks that are unexpectedly general in scope and more serious than currently anticipated.
453 There is also a concern regarding recognition that not all reactions between Se and organic
454 molecules seem to require the electron withdrawing structures just discussed. Some far from obvious
455 organic E* react to form highly stable Se-adducts. The selenosugar which is the dominant Se-excretion
456 product in urine [117] is one example. The aldehydes of monosaccharides and amino groups of cellular
457 proteins form a wide range of advanced glycation end products (AGEs) including N-acetyl-D-
458 galactosamine (GalNAc) which is resolved by selenoenzymes and result in formation of 1β-methylseleno-
459 N-acetyl-D-galactosamine, a major Se metabolite formed from GSH combining with Se to form GS–SeH.
460 This will either release the selenide for Sec synthesis or proceed to react with a N-acetyl-α-D-
461 galactosamine (GalNAc). The GalNAc is a carbohydrate necessary for intercellular communication that is
462 concentrated in sensory nerve structures, and it is a common component of antigens and gangliosides. The
463 stability of Se in association with this molecule is remarkable but suggest there are dimensions of Se-
464 reactivity which require much more examination.
465 The cumulative exposures of an individual's lifetime are known as the exposome [118]. This
466 includes all natural and synthetic forms which are acquired from the environment, food, pharmaceuticals,

467 water, air, or through the skin, as well as the metabolites created from these precursors. While the effects
468 of high exposures to a single toxicant can often be easily recognized, quantifying the combined effects of
469 multiple E* that cooperate to impact the same pathway is more challenging. Since the Se-status of the
470 exposed individual is directly associated with resistance to E* toxicity and the latency of their onset, the
471 same dose of E* that has serious consequences in Se-poor populations will have longer delays and less
472 serious or no effects on individuals that receive more Se from their diets. Specific differences in E* tissue
473 compartment distributions could introduce unique effects, but the same "SOS mechanisms" that
474 characterize Hg toxicity [20, 43] are expected to be characteristic of other E*. Each form would be
475 present in various amounts, but their molar concentrations [E*] must be assessed in stoichiometric
476 relation to the concentrations of Se in tissues [Se] to evaluate binding constants (k) for adducts [E*Se] of
477 each form:
478

$$k_1 = \frac{[E^*_1\,Se]}{[Se]\,[E^*_1]} \qquad \text{Equation 3.}$$

480
481
482 The sum of the binding contributions of the individual E* forms in the exposome must be assessed to
483 create a summed value representing their comprehensive Se binding equivalent [E^*_Σ]. While it is
484 impossible to quantify the concentrations and binding affinities of all E* forms present in an exposome, a
485 preliminary assessment of exposures to the most potent and most abundant forms can provide an
486 approximated E^*_Σ for assessment. Concurrent co-exposures to toxicants that promote oxidative damage
487 would be expected to synergistically increase the severity of the adverse effects, although developing
488 equations to take such effects into consideration will require further study.
489 Since these combined effects must be evaluated in relation to Se status, a relative health value
490 (HV_{Se}) can be defined using an equation based on the Health Benefit Value (HBV) criterion currently
491 used to differentiate benefits vs. risks associated with maternal consumption of specific types of fish or
492 seafoods [119]. The HBV index clearly differentiates fish and/or seafoods with positive values indicating

493 consumption benefits that improve the Se-status of consumers in contrast to sources with negative values
494 that indicate consumption risks. This index reliably predicts the effects observed among consumers of
495 meats of apex predators such as toothed whales or great white sharks. Epidemiological studies which have
496 observed harm from seafood Hg exposures have uniformly involved mothers that had eaten seafoods with
497 negative HBVs, i.e., seafoods that contained more Hg than Se. Meanwhile maternal consumption of
498 ocean fish improved their child's IQ by 7.7 points [120]. Based on the same biochemical insights as the
499 HBV, the HV_{Se} indicates the amount of Se available in tissues of the exposed individual is calculated:
500
501 $$HV_{Se} = \left(\frac{[Se] - [E^*_{\Sigma}]}{[Se]}\right) \cdot \left([Se] + [E^*_{\Sigma}]\right)$$ Equation 5.
502
503 Out of an abundance of caution, the current iterations of the HV_{Se} and HBV equations intentionally omit
504 consideration of the amount of E* bound to thiomolecules and other binding partners. This provides a
505 highly conservative estimate of Se health status, but once the effects of additional E* forms have been
506 empirically established, these equations will require updating.
507
508 **Electrophile Interactions with Selenoenzymes as Contributors to Somatic Mutations**
509 Since selenoenzymes have pivotal roles in preventing and/or reversing oxidative damage due to ROS,
510 RNS, and free radicals, E* exposures high enough to diminish their synthesis and activities would
511 accentuate the accumulation of cellular damage. Cancer, cardiovascular, neurodegenerative, and age
512 associated diseases are characterized by increased ROS and RNS [121, 122]. Following the finding that
513 intractable seizures in children with a low GPx could be alleviated by supplemental Se [123], further
514 studies have found correlations between low Se status and seizures, Parkinson's disease (PD), Alzheimer's
515 disease (AD), dementia, cognitive decline [124-126] and neurodevelopmental disorders [127]. In patients
516 with epilepsy and PD, brain Se levels were 40% lower than normal [128] and decreases in plasma Se was
517 associated with reduced GPx activities [126, 129]. However, the redistribution of Se from blood to

518 inflamed tissues is an incompletely understood aspect of the acute phase response of inflammation [130,
519 131], making it difficult to differentiate cause and consequence in these cases.
520 Although inherited genotype variants are clear-cut causes of certain catastrophic medical
521 conditions, the majority of non-communicable diseases responsible for mortalities in the developed world
522 are not associated with clinically significant heritable risk factors [132]. Just as specialization
523 differentiates cellular subtypes during tissue development, somatic mutations that arise in progenitor cells
524 will be propagated throughout their ensuing lineage. While mutations were initially assumed to only arise
525 in association with pathological outcomes, it is now known that individual phenotypically normal human
526 brain cells contain hundreds to a few thousand single-nucleotide variants [133-138]. Similar DNA
527 mosaics seem likely to arise in other tissues, especially among those with rapid turnover. Lineages of
528 somatic variants which are more common within a tissue could indicate they arose earlier [133, 139]
529 while those with comparatively low copy numbers may represent more recent developments [133, 139,
530 140]. These “mosaic patchworks” of genetically related lineages may perturb tissue functions [132, 141,
531 142] and contribute to localized immune recognition, inflammation, and tissue damage well before
532 development of overt disease. Detection of DNA variants in non-cancerous pathologies had to overcome
533 recognition and sampling challenges since lineages can be present in a relatively small number of cells
534 interspersed in pathological tissues [143]. Genomic variants may be inherited through the germline or
535 spontaneously arise in phenotypically normal tissues [133, 140, 144, 145] as well as among pathological
536 cells [132].
537 Mutations in somatic cells produce cancer but the genes involved in control of cell replication are
538 not singularly at risk of damage. As most sources of DNA damage are stochastic, errors in reading and
539 non-reading portions of chromosomes have been recognized in genomes of cells from pathological tissues
540 compared to cells collected from adjacent healthy tissues in cardiovascular disease [146, 147] and a
541 growing number of other diseases. Recent evidence indicates somatic mutations are prevalent in normal
542 tissues of non-symptomatic individuals and clonal expansion of these forms accompany and may
543 contribute to the development of degenerative diseases common among elderly individuals. However,

544 evidence of somatic mutations in pathological cardiovascular tissues was recognized 50 years ago [148]
545 when cells of atherosclerotic plaques were found to be monoclonal variants. Studies in mice have
546 demonstrated that cell clones expand in vascular lesions [146-147] and if atherosclerosis and other
547 vascular lesions accumulate somatic mutations following exposure to injurious stimuli, competent
548 mutants may preferentially expand within the lesion and progress to form monoclonal plaque mosaics.
549 Elimination of the offending mutant cells by immune recognition and response may mitigate some
550 effects, but loss of tissue structure and functions can still have lasting adverse effects even if damaged cell
551 lineages are eliminated. Since genome comparisons of diseased vs. adjacent healthy cells in those tissues
552 reveal the accumulated errors, it appears mutant somatic cells are competent enough to escape detection
553 by immunosurveillance. However, this may indicate inadequacies of the immune response (which can
554 also be an outcome associated with low dietary Se intakes) and indicate that loss of proper immune cell
555 recognition is a contributing factor in development of these diseases.
556 Increased oxidative stress has been implicated in Parkinson's disease, Alzheimer's disease,
557 stroke, and epilepsy, as well as other neurological disorders [149]. While the links between these diseases
558 and Se-status are indirect and lack a clear causal connection, the pivotal importance of selenoenzymes in
559 preventing and reversing oxidative damage suggest their disruption may contribute to these pathologies.
560 Inflammation plays a pivotal role in atherosclerotic plaque formation [150] and its pathophysiology arises
561 in response to injury [151]. Lipid peroxidation by free radicals (e.g., superoxide anion, hydrogen
562 peroxide, and lipid peroxide) and exposures to transition metals that catalyze formation of highly reactive
563 free radicals in Fenton-type reactions [152] are also implicated in aging, neurodegenerative disorders, and
564 neurodegenerative diseases, particularly in relation to mitochondrial dysfunctions.
565 The Se concentrations of most tissues in the body range around 1 μM and E* exposures that
566 result in tissue levels that approach or exceed stoichiometric equivalence with Se will increasing impair
567 selenoenzyme activities [20, 42, 43, 153]. It is crucial to recognize that the effects of E* exposures will
568 not necessarily be proportional to E* dose or tissue concentrations but are instead proportional to E*:Se
569 molar relationships in diet and tissues. If tissue Se reserves and dietary intakes are able to offset the losses

570 due to Se–sequestration by E*, adverse effects would be alleviated or averted. While tissue kinetics and
571 compartmental localization of different E* will differ and sequestration of Se will seldom involve binding
572 affinities that are as high as metallic forms, attritional losses of bioavailable Se from the body's tissue
573 reserves diminish the ability of the body's homeostatic mechanisms to redeploy Se to where it is needed.
574 Several low-Se-affinity E* sequestering fractions of the body's Se would be just as hazardous as a single
575 high-Se-affinity E* sequestering the same amount. However, when exposures to several E* forms are
576 involved, their contributions become harder to evaluate, especially since many arise from common but
577 variable sources.

578 The toxicokinetics and toxicodynamics of the various E* will differ at organ, tissue, cellular,
579 subcellular, and molecular levels. For example, exposures to As, Cd, or Hg have greater effects on the
580 activities of mitochondrial TRx2 than cytosolic TRx1 [154]. Although TRx activity can become impaired
581 by processes unrelated to Se-sequestration and selenoenzyme inhibition, interactions between Se and E*
582 such as Cd, Au, and other E* will form covalent adducts which are similar in character and affinity to
583 those between Se and Hg. Once a E* becomes bound to the thiol of GSH, Trx–$(SH)_2$, or other substrate
584 molecule or cofactor which directly interacts with the Sec of a selenoenzyme, the E*–thiomolecule adduct
585 will function as a suicide substrate to accomplish the transfer. If tissue concentrations of high Se-affinity
586 E* occur in stoichiometric excess of Se, losses due to attrition would eventually exceed the ability of
587 dietary Se intakes to offset them and oxidative damage would begin to occur. The latency between E*
588 exposures and onset of oxidative damage is proportional to the dietary Se status of the exposed individual
589 and inversely related to the E* dose received and retained.

590 The toxicokinetics and toxicodynamics of E* assessments will require development of more
591 thorough analytical assessments and application of advanced computational methods. Although the
592 physiologically based pharmacokinetic (PBPK) models seemed appropriate to apply in risk assessments
593 when E* toxicity was assumed to involve pseudo-first order reactions, a better model is now required.
594 Since toxic outcomes involve the combined effects of multiple forms of E* acting cooperatively and
595 perhaps synergistically, the dynamic equilibrium between these substrates and the Se cycling that

prevents the onset of toxicity is highly dependent on the rates of Sec–synthesis in target tissues. Since those rates depend on the level of Se reserves in the somatic tissues and concurrent dietary Se intakes of the exposed subject, standard PBPK models are insufficient. To obtain reliably accurate assessments of E*-related risks will require a physiologically oriented interactions of nutrients and toxicants (POINT) model. Versions of POINT models have been demonstrated [20, 155], but further refinement is required.

Discussion

Nosology is the descriptive classification of diseases with the intention of assisting in identification of causal mechanisms, pathological effects, recognized symptoms, and other factors that enable a diagnostic label to be applied. Diseases are often inadequately defined and challenging to clearly classify, especially when their pathogenesis remain incompletely characterized. For this reason, diagnostic terms often describe symptoms or groups of symptoms associated with a disease or syndrome. While a disease usually has a distinct cause or set of contributing causal factors as well as distinguishing symptoms and treatments, a syndrome is a group of symptoms that are associated with a recognized disorder, but often without an identified cause, recognized pathology, or accepted prognosis. The current work is intended to assist in defining potential contributing causes and possible shared mechanisms of multiple pathologies.

The assumption of genetic stability in somatic tissues other than in cancerous tissues has had a pervasive influence on biomedical thinking. It is critical to examine the complex relationships between factors which contribute to DNA damage leading to pathological phenotypes as well as ways to prevent those outcomes. Whether cooperative Se-binding and selenoenzyme inhibition due to E* exposures actually contribute to the somatic DNA mutations associated with various pathologies is an intriguing but speculative conjecture until more evidence can be gathered. Although E*-dependent inhibition of selenoenzyme activities has been confirmed for high Se-affinity forms, other forms under consideration will require research to establish if their Se-binding affinities are high enough to conceivably impair Se availability and activities in a realistic range of exposure concentrations.

621 The factors that determine the relative Se-affinities of the various E* will be reflected in their
622 affinities for thiomolecules, especially thioredoxin, glutathione, and other selenoenzyme substrates. Since
623 intracellular concentrations of thiomolecules are ~10^5 higher, mass action effects drive initial binding to
624 these forms. However, since Se has E* binding affinities which are orders of magnitude higher than those
625 of equivalent thiomolecules, thermodynamic considerations cannot be ignored, particularly since Sec
626 reactivity is potentiated by the enzyme mechanisms. Metallic E* have far higher Se-binding affinities
627 than organic E*, but if the molar abundance of organic E* is sufficiently high, they may still sequester
628 meaningful fractions of intracellular Se. If this outcome is confirmed, this will require development of far
629 better-informed risk evaluations.
630 Significant investment in the development of pharmaceuticals can be lost when adverse
631 consequences result in products being withdrawn from the market [156]. Since idiosyncratic toxicity of
632 pharmaceutical E* forms may arise due to low Se-status or unrecognized concurrent E* coexposures
633 [157], prior identification and remedy of these contraindications may improve clinical outcomes and
634 ensure effective therapeutics can be applied with less risk of adverse reactions. If idiosyncratic
635 consequences due to these effects are recognized, pharmaceuticals which had been withdrawn due to rare
636 and otherwise inexplicable adverse drug reactions might safely be restored to beneficial use.
637 The amount of Se in diets depends on the Se in crops and livestock which reflect its availability
638 from local soils. While certain regions have poor dietary Se availability due to low abundance in parent
639 rock materials or because low pH or other conditions limit availability of the Se from the soil, low Se
640 intakes can also arise as a result of poor dietary choices. Low Se availability in tissues will enhance the
641 risks posed by exposures to E* from foods, environmental sources, or pharmaceuticals and risk
642 evaluations that fail to consider Se-status and dietary intakes cannot provide any meaningful
643 interpretations. Sufficiently high aggregate exposures to E* from foods, metabolites, pharmaceuticals, or
644 environmental insults can impair selenoenzyme activities and reduce their ability to prevent and reverse
645 oxidative damage due to accentuated production of ROS, RNS, and inflammation. However, the
646 pathological consequences of the cooperative effects of multiple E* exposures would be insidious. Not

only would the latency of subtle effects on selenoenzymes be difficult to recognize, but the onset of secondary effects would also be gradual and challenging to differentiate in association with chronic degenerative conditions. Even acutely high exposures to E* with high Se-selectivity is known to demonstrate significant latency due to the slow attrition of tissues Se reserves. The slow but potentially unremitting loss of biologically available Se would cause irreversible inhibition of selenoenzymes and compromise the availability of Se for participation in subsequent cycles of Sec synthesis, but incremental losses would not be attended by dramatic increases in pathology.

Due to the paucity of research in this area, the current discussion of these aspects are hypothetical, but predictable and consistent with clinical observations. Still, it must be emphasized that it is entirely possible that the binding affinities of organic E* are too low to be meaningful and their Se-adducts are too transient for any clinically significant effects to occur. Furthermore, it is likely that exposures to organic E* in amounts sufficient to impair the bioavailability of substantial fractions of tissue Se-reserves will rarely pose risks to populations with normal dietary Se intakes.

Immunotherapy may eventually apply applications based on current work with tumor-infiltrating lymphocytes (TIL) or chimeric antigen receptor (CAR) T-cell approaches [157] to recognize and remove specific somatic mutation lineages that are associated with the pathology being treated. There will be challenges in establishing safe and effective CAR T-cell and TIL therapies, but there are rapid developments in these applications for cancer treatment which may translate well in management of aberrant cell lineages responsible for other pathologies. Various immunotherapies such as immune checkpoint inhibitors, T-cell transfer therapy, monoclonal antibodies, vaccines, and immune system modulators are successfully treating cancers [159,160] and such approaches may prove useful for treatment of other pathologies. In addition to accumulating DNA damage, errors in RNA transcription have been observed to be orders of magnitude higher than DNA mutation rates in yeast [161] and increasing age is similarly expected to accentuate such errors.

The World Health Organization's explanation of aging is; "At the biological level, ageing results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This

673 leads to a gradual decrease in physical and mental capacity, a growing risk of disease and ultimately
674 death. These changes are neither linear nor consistent, and they are only loosely associated with a
675 person's age in years." [162]. Ascertaining the dose-dependent consequences of low levels of individual
676 toxicants has always been challenging but identifying the discrete contributions of multiple low-level
677 toxicants which act on distinct pathways has been considered impossible. If their biochemical
678 mechanisms of toxicity are found to act on the same pathways, assessing the dose-dependent effects of
679 individual E* on selenoenzyme activities individually and in cooperation with other E* will still be a
680 daunting task, but not intractable. Since oxidative damage contributes to DNA mutations which may
681 initiate and/or enhance progression of multiple disease pathologies, defining the potential benefits of
682 reducing E* exposure sources and ensuring proper Se status may enhance outcomes of preventive
683 medicine and improve healthy aging.
684
685 **Conclusions**
686 Based on the above, several aspects must be considered: 1) The Se-binding affinities of the
687 majority of E* remain poorly defined but establishing qualitative and quantitative estimations of these
688 relationships should be relatively straightforward. 2) The complementary effects of multiple E* exposures
689 are assumed to be additive, but since co-exposures to initiators of ferroptosis and other redox active and
690 free radical generating species are common, the risks of synergistic effects should also be considered. 3)
691 Immunotherapy treatment approaches developed for cancer may be applied to recognize and remove
692 specific somatic mutation lineages associated with other pathologies. Establishing safe and effective
693 therapies will be challenging, but the rapid development of these applications for cancer treatment may
694 translate to management of aberrant cell lineages involved in other pathologies. 4) While personalized
695 medicine has long been a goal of biomedical research, the etiologies and pathologies responsible for
696 degenerative diseases and disorders are likely to involve multiple disparate mutational lineages in a single
697 lesion. These distinctions pose therapeutic challenges which will be difficult to overcome and it may be
698 more efficacious to promote preventative medicine approaches until immunotherapeutic interventions

become reliable. 5) Evidence supporting or disproving testable hypotheses based on the projections proposed in this article will have clear implications for nutrition research, toxicological risk assessments, health policies, and environmental regulations.

The intellectual underpinning for personalized medicine is based on recognition of the genetic uniqueness of the individual patients. Now that it is evident that not only the individual, but also the cell lineages of diseased tissues are genetically unique, more refined genomic information is required to define the ongoing pathologies before applying treatment interventions. Identifying ways to diminish the onset of somatic mutations responsible for these conditions would enhance preventive interventions and enhance healthy aging. Establishing whether the conjectured aggregate effects of multiple E* exposures actually impair selenoenzyme-dependent protection against DNA damage will be a challenging, but potentially fruitful avenue of exploration.

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References

1. C.D. Steele, N. Pillay L.B. Alexandrov, 2022. An overview of mutational and copy number signatures in human cancer, J. Pathol. 257(4):454-465. doi: 10.1002/path.5912.

2. K. Yizhak, F. Ague, J. Kim, J.M. Hess K. Kubler, J. Grimsby, R. Frazer, H. Zhang, N.J. Haradhvala, D. Rosebrock, D. Livitz, X. Li, E. Arich-Landkof, N. Shoresh, C. Stewart, A.V. Segre, P.A. Branton, P. Polak, K.G. Ardlie, G. Getz, 2019. RNA sequence analysis reveals macroscopic somatic clonal expansion across normal tissues, Science. 364:eaaw0726.

3. S. Sano, Y. Wang, K Walsh, 2020. Somatic mosaicism: implications for the cardiovascular system, Eur. Heart J. 7;41(30):2904-2907. doi: 10.1093/eurheartj/ehz907.

4. M.J. Lindhurst, J.C. Sapp, J.K.Teer, J.J. Johnston, E.M. Finn, K. Peters, J. Turner, J.L. Cannons, D. Bick, L. Blakemore, C. Blumhorst, K. Brockmann, P. Calder, N. Cherman, M.A. Deardorff, D.B. Everman, G. Golas, R.M. Greenstein, B.M. Kato, K.M. Keppler-Noreuil, S.A. Kuznetsov, R.T. Miyamoto, K. Newman, D. Ng, K. O'Brien, S. Rothenberg, D.J. Schwartzentruber, V. Singhal, R. Tirabosco, J. Upton, S.Wientroub, E.H. Zackai, K. Hoag, T. Whitewood-Neal, P.G. Robey, P.L. Schwartzberg, T.N. Darling, L.L. Tosi, J.C. Mullikin, L.G. Biesecker, 2011. A Mosaic Activating Mutation in AKT1 Associated with the Proteus Syndrome, N. Engl. J. Med. 365:611–619. 10.1056/nejmoa1104017

5. J. A. Couto, A. Y. Huang, D. J. Konczyk, J. A. Goss, S. J. Fishman, J. B. Mulliken, M.L, Warman, A.K. Greene, 2017. Somatic MAP2K1 Mutations Are Associated with Extracranial Arteriovenous Malformation, Am. J. Hum. Genet. 100:546–554. 10.1016/j.ajhg.2017.01.018

6. S.S. Jamuar, A.-T. N. Lam, M. Kircher, A. M. D'Gama, J. Wang, B.J. Barry, X. Zhang, R.S. Hill, J.N. Partlow, A. Rozzo, S. Servattalab, B.K. Mehta, M. Topcu, D. Amrom, E. Andermann, B. Dan, E. Parrini, R. Guerrini, I.E. Scheffer, S.F. Berkovic, R.J. Leventer, Y. Shen, B.L. Wu, A.J. Barkovich, M. Sahin, B.S. Chang, M.D., M. Bamshad, D.A. Nickerson, J. Shendure, A. Poduri, T.W. Yu, C,A. Walsh, 2014. Somatic Mutations in Cerebral Cortical Malformations N. Engl. J. Med. 371, 733–743. 10.1056/nejmoa1314432

7. Y. Dou, X. Yang, Z.J. Li, S. Wang, Z. Zhang, A.Y. Ye, L. Yan, C. Yang, Q. Wu, J. Li, B. Zhao, A.Y. Huang, L. Wei, 2017. Postzygotic Single-nucleotide Mosaicisms Contribute to the Etiology of Autism Spectrum Disorder and Autistic Traits and the Origin of Mutations. Hum. Mutat. 38:1002–1013. 10.1002/humu.23255

8. E.T. Lim, M. Uddin, S. De Rubeis, Y. Chan, A.S. Kamumbu, X. Zhang, A.M. D'Gama, S.N. Kim, R.S. Hill, A.P. Goldberg, C. Poultney, N.J. Minshew, I. Kushima B.Aleksic, N Ozaki, M. Parellada, C. Arango, M.J. Penzol, A. Carracedo, A. Kolevzon, C.M. Hultman, L.A. Weiss, M. Fromer, A.G. Chiocchetti, C.M. Freitag, G.M. Church, S.W. Scherer, J.D. Buxbaum, C.A. Walsh, 2017. Rates, Distribution and Implications of Postzygotic Mosaic Mutations in Autism Spectrum Disorder, Nat. Neurosci. 20:1217–1224. 10.1038/nn.4598

9. J.F. Fullard, A.W. Charney, G. Voloudakis, A.V. Uzilov, V. Haroutunian, P. Roussos, 2019. Assessment of Somatic Single-Nucleotide Variation in Brain Tissue of Cases with Schizophrenia, Transl. Psychiatry 9:21. 10.1038/s41398-018-0342-0

10. A. Hsieh, S.U. Morton, J.A.L. Willcox, J.M. Gorham, A.C. Tai, H. Qi, S. DePalma, D. McKean, E. Griffin, K.B. Manheimer, D. Bernstein, R.W. Kim, J.W. Newburger, G.A. Porter Jr., D. Srivastava, M. Tristani-Firouzi, M. Brueckner, R.P. Lifton, E. Goldmuntz, B.D. Gelb, W.K. Chung, C.E. Seidman, J.G. Seidman, Y. Shen, 2020. EM-mosaic Detects Mosaic Point Mutations that Contribute to Congenital Heart Disease, Genome Med. 12:42. 10.1186/s13073-020-00738-1

11. E.H. DuGoff, V. Canudas-Romo, C. Buttorff, B. Leff, G.F. Anderson, 2014. Multiple chronic conditions and life expectancy: A life table analysis. Med. Care. 52:688–694. doi: 10.1097/MLR.0000000000000166.

12. TFAH, 2020. Trust For American's Health The Impact of Chronic Underfunding on America's Public Health System: Trends, Risks, and Recommendations, 2020. https://www.tfah.org/wp-content/uploads/2020/04/TFAH2020PublicHealthFunding.pdf

13. A.Y. Huang, E.A. Lee, 2022. Identification of Somatic Mutations From Bulk and Single-Cell Sequencing Data. Front Aging. 3;2:800380. doi: 10.3389/fragi.2021.800380. PMID: 35822012; PMCID: PMC9261417.

14. D. L. Hatfield, P. A. Tsuji, B. A. Carlson, V. N. Gladyshev, 2014. Selenium and selenocysteine: Roles in cancer, health, and development. Trends Biochem. Sci. 39, 112–120

15. H.J. Reich, R.J. Hondal, 2016. Why nature chose selenium, ACS Chem. Biol. 11:821-841. https://doi.org/10.1021/acschembio.6b00031.

16. E.S.J. Arnér, 2010. Selenoproteins - what unique properties can arise with selenocysteine in place of cysteine? Experimental Cell Research. 316:1296-1303. https://doi.org/10.1016/j.yexcr.2010.02.032.

17. C. Jacob, G.L. Giles, N.M. Giles, H. Sies, 2003. Sulfur and selenium: The role of oxidation state in protein structure and function. Angewandte Chemie-International Edition. 42 4742-4758.

18. M.A. Reeves, P.R. Hoffmann, 2009. The human selenoproteome: recent insights into functions and regulation. Cellular and Molecular Life Sciences, 66(15):2457–78.

19. M.A. Reeves, F.P. Bellinger, M.J. Berry, 2010. The neuroprotective functions of selenoprotein m and its role in cytosolic calcium regulation. Antioxidants & Redox Signaling, 12(7):809–18.

20. N.V.C. Ralston, 2021. Mercury's Neurotoxic Effects on Brain Selenoenzymes. In "Handbook of Neurotoxicity" Kostrzewa RM. Editor, Springer-Verlag.

21. M. Kühbacher, J. Bartel, B. Hoppe, D. Alber, G. Bukalis, A.U. Bräuer, D. Behne, A. Kyriakopoulos, 2009. The brain selenoproteome: priorities in the hierarchy and different levels of selenium homeostasis in the brain of selenium-deficient rats. Journal of Neurochemistry, 110(1):133–42.

22. R.F. Burk, K.E. Hill, 2005. Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis. Annual Review of Nutrition, 25, 215–235.

23. R.F. Burk, K.E. Hill, A.K. Motley, V.P. Winfrey, S. Kurokawa, S.L. Mitchell, M. Zhang, 2014. Selenoprotein P and apolipoprotein E receptor-2 interact at the blood-brain barrier and also within the brain to maintain an essential selenium pool that protects against neurodegeneration. FASEB Journal, 28, 3579–3588.

24. H. Steinbrenner, H. Sies, 2013. Selenium homeostasis and antioxidant selenoproteins in brain: implications for disorders in the central nervous system. Arch. Biochem. Biophys., 536:152-157.

25. Y. Zhang, Y. Zhou, U. Schweizer, N.E. Savaskan, D. Hua, J. Kipnis, D.L. Hatfield, V.N. Gladyshev, 2008. 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. 283:2427-2438.

26. M.P. Rayman, 2000. The importance of selenium to human health. Lancet 356:233–241.

27. P.D. Whanger, 2004. Selenium and its relationship to cancer: An update. Br. J. Nutr. 91: 11–28.

28. D.L. Hatfield, B.A. Carlson, X.M. Xu, H. Mix, V.N. Gladyshev, 2006. Selenocysteine incorporation machinery and the role of selenoproteins in development and health. Prog. Nucleic Acid Res. Mol. Biol. 81:97–142.

29. L. Latrèche, L. Chavatte, 2008. Selenium incorporation into selenoproteins, implications in human health. Met. Ions Biol. Med. 10:731–737.

30. L.V. Papp, A. Holmgren, K.K. Khanna, 2010, Selenium and selenoproteins in health and disease. Antioxid. Redox Signal. 12:793–795.

31. M.P. Rayman, 2012. Selenium and human health. Lancet. 379:1256–1268.

32. M.I. Jackson, G.F. Combs, 2012. Selenium as a Cancer Preventive Agent. In Selenium: Its Molecular Biology and Role in Human Health, 3rd ed., Hatfield, D.L., Berry, M.J., Gladyshev, V.N., Eds.; Springer: New York, NY, USA, pp. 313–323.

33. S. Kurokawa, M.J. Berry, 2013. Selenium. Role of the essential metalloid in health. Met. Ions Life Sci. 13:499–534.

34. D.L. Hatfield, P.A. Tsuji, B.A. Carlson, V.N. Gladyshev, 2014. Selenium and selenocysteine: Roles in cancer, health, and development. Trends Biochem. Sci. 39:112–120.

35. C. Meplan, J. Hesketh, 2014. Selenium and cancer: A story that should not be forgotten-insights from genomics. Cancer Treat. Res. 159:145–166.

36. Z. Touat-Hamici, Y. Legrain, J. Sonet, A.-L. Bulteau, L.Chavatte, 2016. Alteration of selenoprotein expression during stress and in aging. In Selenium: Its Molecular Biology and Role in Human Health, 4th ed.; Hatfield, D.L., Su, D., Tsuji, P.A., Gladyshev, V.N., Eds.; Springer Science+Business Media, LLC: New York, NY, USA, pp. 539–551.

37. J. Sonet, A.-L. Bulteau, L. Chavatte, 2016. Selenium and Selenoproteins in Human Health and Diseases. In Metallomics: Analytical Techniques and Speciation Methods; Michalke, B., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, pp. 364–381.

38. C. Vindry, T. Ohlmann, L.Chavatte, 2018. Selenium metabolism, regulation, and sex differences in mammals. In Selenium, Molecular and Integartive Toxicology; Michalke, B., Ed.; Springer International Publishing AG, Part of Springer Nature: Cham, Switzerland, pp. 89–107.

39. Avery, J.C.; Hoffmann, P.R. 2018. Selenium, Selenoproteins, and Immunity. Nutrients, 10, 1203.

40. Z. Zhi Huang A.H. Rose, P.R. Hoffmann, 2012. The Role of Selenium in Inflammation and Immunity: From Molecular Mechanisms to Therapeutic Opportunities. Antioxid. Redox. Signal. 16(7):705–743. doi: 10.1089/ars.2011.4145

41. F. Maehira, G.A. Luyo, I. Miyagi, M. Oshiro, N. Yamane, M. Kuba Y. Nakazato, 2002. Alterations of serum selenium concentrations in the acute phase of pathological conditions. Clinica Chimica Acta 316(1–2):137-146.

42. N.V.C. Ralston, 2018. Effects of soft electrophiles on selenium physiology. Free Radicals in Biology and Medicine, 127:134–144.

43. N.V.C. Ralston, L.J. Raymond, 2018. Mercury's neurotoxicity is characterized by its disruption of selenium biochemistry. Biochimica et Biophysica Acta. General subjects, 1862, 2405–2416.

44. M.W. Pitts, C.N. Byrns, A.N. Ogawa-Wong, P. Kremer, M.J. Berry, 2014. Selenoproteins in nervous system development and function. Biol. Trace Elem. Res., 161:231-245.

45. E.S.J. Arnér, A. Holmgren, 2000. Physiological functions of thioredoxin and thioredoxin reductase. European Journal of Biochemistry, 267(20), 6102–9.

46. F. Devillanova, W.W. Du Mont, 2013. Introduction. Handbook of Chalcogen Chemistry: New Perspectives in Sulfur, Selenium and Tellurium Complete Set Second Edition, Devillanova, F., Du Mont, WW. Eds.

47. N.C. Gassner, W.A. Baase, A.C. Hausrath, B.W. Matthews, 1999. Substitution with selenomethionine can enhance the stability of methionine-rich proteins. J. Mol. Biol. 19;294(1):17-20. Doi: 10.1006/jmbi.1999.3220. PMID: 10556025.

48. M.J. Nasim, M.M. Zuraik, A.Y. Abdin, Y. Ney, C. Jacob, 2021. Selenomethionine: A Pink Trojan Redox Horse with Implications in Aging and Various Age-Related Diseases, Antioxidants. 10:882. https://doi.org/10.3390/antiox10060882.

49. M.P. Jedrychowski, G.Z. Lu, J. Szpyt, M. Mariotti, R. Garrity, J.A. Paulo, D.K. Schweppe, D. Laznik-Bogoslavski, L. Kazak, M.P. Murphy, V.N. Gladyshev, S.P. Gygi, E.T. Chouchani, B.M. Spiegelman, 2020. Facultative protein selenation regulates redox sensitivity, adipose tissue thermogenesis, and obesity, Proc. Natl. Acad. Sci. U S A. 117:10789-10796. https://doi.org/10.1073/pnas.2001387117.

50. I.S. Đorđević, M. Popadić, M. Sarvan, M. Petković-Benazzouz, G.V. Janjić, 2020. Supramolecular insight into the substitution of sulfur by selenium, based on crystal structures, quantum-chemical calculations and biosystem recognition, Acta Crystallogr. B Struct. Sci. Cryst. Eng. Mater. 76:122-136. https://doi.org/10.1107/s2052520619016287.

51. O. Carugo, G. Resnati, P. Metrangolo, 2021. Chalcogen Bonds Involving Selenium in Protein Structures, ACS Chem. Biol. 16 :1622-1627.

52. V.N. Gladyshev, D.L. Hatfield, 1999. Selenocysteine-containing proteins in mammals. Journal of Biomedical Sciences, 6(3):151–160.

53. D.L. Hatfield, V.N. Gladyshev, 2002. How selenium has altered our understanding of the genetic code. Molecular and Cellular Biology, 22(11):3565–3576.

54. G. V. Kryukov, V.N. Gladyshev, 2004. The prokaryotic selenoproteome. EMBO Reports, 5(5):538–543.

55. J. Chen, M.J. Berry, 2003. Selenium and selenoproteins in the brain and brain diseases. Journal of Neurochemistry, 86:1–12.

56. A. Acharya, I. Das, D. Chandhok, T. Saha, 2010. Redox regulation in cancer: a double-edged sword with therapeutic potential. Oxid Med Cell Longev 3:23–34. https://doi.org/10.4161/oxim.3.1.10095.

57. H.S. Marinho, C. Real, L. Cyrne, H. Soares, F. Antunes, 2014. Hydrogen peroxide sensing, signaling and regulation of transcription factors. Redox Biol 2:535–562.

58. S. Di Meo, T.T. Reed, P. Venditti, V.M. Victor, 2016. Role of ROS and RNS sources in physiological and pathological conditions. Oxidative Medicine and Cellular Longevity, 2016:1245049. doi: 10.1155/2016/1245049.

59. G. Bartosz, 2009. Reactive oxygen species: destroyers or messengers? Biochemical Pharmacology, 77(8):1303–1315.

60. R.S. Balaban, S. Nemoto, R. Finkel, 2005. Mitochondria, oxidants, and aging. Cell 120:483–495. https://doi.org/10.1016/j.cell.2005.02.001.

61. B.S. Berlett, E.R. Stadtman, 1997. Protein oxidation in aging, disease, and oxidative stress. J. Biol. Chem. 272:20313–20316. https://doi.org/10.1074/jbc.272.33.20313.

62. R. Radi, 2013. Peroxynitrite, a stealthy biological oxidant. J. Biol. Chem. 288(37):26464–26472.

63. P. Anand, J.S. Stamler, 2012. Enzymatic mechanisms regulating protein S-nitrosylation: implications in health and disease. J. Mol. Med. (Berl). 90(3):233-44. doi: 10.1007/s00109-012-0878-z.

64. J.S. Stamler, D.I. Simon, J.A. Osborne, M.E. Mullins, O. Jaraki, 1992. S-nitrosylation of proteins with nitric oxide: synthesis and characterization of biologically active compounds. Proc. Natl. Acad. Sci. USA. 89:444–448.

65. J.S. Stamler, G. Meissner, 2001. Physiology of nitric oxide in skeletal muscle. Physiol. Rev. 81:209–237.

66. R.B. Mikkelsen, P. Wardman, 2003. Biological chemistry of reactive oxygen and nitrogen and radiation-induced signal transduction mechanisms. Oncogene. 22:5734–5754.

67. Y. Xie, W. Hou, X. Song, Y. Yu, J. Huang, X. Sun, R. Kang, D. Tang, 2016. Ferroptosis: process and function. Cell Death Differ. 23(3):369–379.

68. B.R. Stockwell, J.P. Friedmann Angeli, H. Bayir, A.I. Bush, M. Conrad, S.J Dixon, S. Fulda, S. Gascón, S.K. Hatzios, V.E. Kagan, K. Noel, X. Jiang, A. Linkermann, M.E. Murphy, M. Overholtzer, A. Oyagi, G.C. Pagnussat, J. Park, Q. Ran, C.S. Rosenfeld, K. Salnikow, D. Tang, F.M. Torti, S.V. Torti, S. Toyokuni, K.A. Woerpel, D.D. Zhang, 2017. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell. 171(2):273–285.

69. R.J. Arai, H. Masutani, J. Yodoi, V. Debbas, F.R. Laurindo, A. Stern, H.P. Monteiro, 2006. Nitric oxide induces thioredoxin-1 nuclear translocation: Possible association with the p21Ras survival pathway. Biochem. Biophys. Res. Commun. 348:1254–1260.

70. Y.M. Go, S.M. Kang, J.R. Roede, M. Orr, D.P. Jones, 2011. Increased inflammatory signaling and lethality of influenza H1N1 by nuclear thioredoxin-1. PLOS ONE 6: e18918.

71. P. Schroeder, R. Popp, B. Wiegand, J. Altschmied, J. Haendeler, 2007. Nuclear redox-signaling is essential for apoptosis inhibition in endothelial cells–important role for nuclear thioredoxin-1. Arterioscler. Thromb. Vasc. Biol. 27: 2325–2331.

72. A.P. Lothrop, E.L. Ruggles, R.J. Hondal, 2009. No selenium required: reactions catalyzed by mammalian thioredoxin reductase that are independent of a selenocysteine residue. Biochemistry, 48(26):6213–23.

73. C. Brandstaedter, K. Fritz-Wolf, S. Weder, M. Fischer, B. Hecker, S. Rahlfs, K. Becker, 2018. Kinetic characterization of wild-type and mutant human thioredoxin glutathione reductase defines its reaction and regulatory mechanisms. FEBS J. 285(3):542-558. doi: 10.1111/febs.14357.

74. K. Anestål, E.S.J. Arnér, 2003. Rapid induction of cell death by selenium-compromised thioredoxin reductase 1 but not by the fully active enzyme containing selenocysteine. Journal of Biological Chemistry, 278(18):15966–15972.

75. H.H Harris, I.J. Pickering, G.N. George, 2003. The chemical form of mercury in fish. Science, 301(5637), 1203. doi: 10.1126/science.1085941.

76. M. Aschner, T.W. Clarkson, 1988. Uptake of methylmercury in the rat brain: effects of amino acids. Brain Research, 462:31–39.

77. C.C. Bridges, R.K. Zalups, 2010. Transport of inorganic mercury and methylmercury in target tissues and organs. Journal of Toxicology and Environmental Health - Part B: Critical Reviews, 13(5):385–410.

78. A. Koc, V.N. Gladyshev, 2007. Methionine sulfoxide reduction and the aging process. Ann. N Y Acad. Sci. 1100:383–386.

79. C. Jehan, D. Cartier, C. Bucharles, Y. Anouar, L. Lihrmann, 2022. Emerging roles of ER-resident selenoproteins in brain physiology and physiopathology. Redox Biology. 55:102412.

80. A. Ferreiro, S. Quijano-Roy, C. Pichereau, B. Moghadaszadeh, N. Goemans, C. Bönnemann, H. Jungbluth, V. Straub, M. Villanova, J.-P. Leroy, N.B. Romero, J.-J. Martin, F. Muntoni, T. Voit, B. Estournet, P. Richard, M. Fardeau, P. Guicheney, 2002. Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multiminicore disease: reassessing the nosology of early-onset myopathies. Am. J. Hum. Genet. 71(4):739-49.

81. R.G. Pearson, 2005. Chemical hardness and density functional theory. Journal of Chemical Sciences, 117(5):369–377.

82. E.J. Ste. Marie, R.J. Wehrle, D.J. Haupt, N.B. Wood, A. van der Vliet, M.J. Previs, D.S. Masterson, R.J. Hondal, 2020. Can selenoenzymes resist electrophilic modification? Evidence from thioredoxin reductase and a mutant containing α-methylselenocysteine. Biochemistry, 59(36):3300–3315.

83. F. Saccoccia, F. Angelucci, G. Boumis, D. Carotti, G. Desiato, A.E. Miele, A. Bellelli, 2014. Thioredoxin reductase and its inhibitors. Current Protein & Peptide Science, 15(6), 621-646.

84. Y. Ouyang, Y. Peng, J. Li, A. Holmgren, J. Lu, 2018. Modulation of thiol-dependent redox system by metal ions via thioredoxin and glutaredoxin systems. Metallomics, 10(2):218–228.

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

86. X. Xing, M. Xu, L. Yang, C. Shao, Y. Wang, M. Qi, X. Niu, D. Gao, (In press) Association of Selenium and Cadmium with Heart Failure and Mortality Based on the National Health and Nutrition Examination Survey. Journal of Human Nutrition and Dietetics.

87. C.L. Wiseman, F. Zereini, 2009. Airborne particulate matter, platinum group elements and human health: a review of recent evidence. Sci. Total Environ. 1;407(8):2493-500. doi: 10.1016/j.scitotenv.2008.12.057. Epub 2009 Jan 31. PMID: 19181366.

88. J. Lu E. H. Chew A. Holmgren, 2007. Targeting thioredoxin reductase is a basis for cancer therapy by arsenic trioxide. Proc. Natl. Acad. Sci. U.S.A. 104:12288–12293.

89. S. Prast-Nielsen, M. Cebula, I. Pader, E. S. Arner, 2010. Noble metal targeting of thioredoxin reductase--covalent complexes with thioredoxin and thioredoxin-related protein of 14 kDa triggered by cisplatin. Free Radical Biol. Med. 49:1765–1778.

90. A. Ohkoshi, R. Ishii, S. Wakamori, Y. Nakayama, T. Yoshida, K. Higashi, A. Nakanome, T. Ogawa, Y, Katori, 2021. Serum selenium predicts achievement of full-dose cisplatin in concurrent chemoradiotherapy for locally advanced head and neck squamous cell carcinoma: A prospective, observational study. Oral Oncol. 121:105475. doi: 10.1016/j.oraloncology.2021.105475.

91. J. Parizek, I. Ostadalova, 1967. The Protective Effect of Small Amounts of Selenite in Sublimate Intoxication. Experientia, 23:142-143. https://doi.org/10.1007/BF02135970

92. H.E. Ganther, C.A. Baumann, 1962. Selenium metabolism. I. Effects of diet, arsenic and cadmium. J. Nutr. 77(2):210-6. doi: 10.1093/jn/77.2.210.

93. O. Wada, N. Yamaguchi, T. Ono, T. Morimura, Y. Yokoo, 1975. Decrease of activity of glutathione peroxidase in the kidney of mice treated with methyl mercury and the effect of simultaneous administration of selenite. Nihon Eiseigaku Zasshi. 30(1):60.

94. J.R. Prohaska, H.E. Ganther, 1977. Interactions between selenium and methylmercury in rat brain. Chem. Biol. Interact. 16(2):155-67. doi: 10.1016/0009-2797(77)90125-9.

95. J. Parizek, 1978. Interactions between Selenium compounds and those of mercury or cadmium. Environmental Health Perspectives. 25:53-55 https://doi.org/10.2307/3428709

96. V. Branco, L. Coppo, M. Aschner, C. Carvalho, 2022. N-Acetylcysteine or Sodium Selenite Prevent the p38-Mediated Production of Proinflammatory Cytokines by Microglia during Exposure to Mercury (II). Toxics. 29;10(8):433. doi: 10.3390/toxics10080433.

97. B. Branco, C. Carvalho, 2019. The thioredoxin system as a target for mercury compounds. Biochim Biophys Acta Gen. Subj. 1863(12):129255. doi: 10.1016/j.bbagen.2018.11.007.

98. V. Branco, J. Canário, J. Lu, A. Holmgren, C. Carvalho, 2012. Mercury and selenium interaction in vivo: effects on thioredoxin reductase and glutathione peroxidase. Free Radic. Biol. Med. 15;52(4):781-93. doi: 10.1016/j.freeradbiomed.2011.12.002.

99. C.M. Carvalho, E.H. Chew, S.I. Hashemy, J. Lu, A. Holmgren, 2008. Inhibition of the human thioredoxin system. A molecular mechanism of mercury toxicity. J. Biol. Chem. 2;283(18):11913-23. doi: 10.1074/jbc.M710133200.

100. H.A. Spiller, 2018. Rethinking mercury: the role of selenium in the pathophysiology of mercury toxicity. Clin. Toxicol. (Phila). 56(5):313-326. doi: 10.1080/15563650.2017.1400555.

101. D. Dyrssen, M. Wedborg, 1991. The sulfur-mercury(II) system in natural waters. Water, Air, Soil Pollution, 56:507–519.

102. I. Falnoga, M. Tušek-Žnidarič, P Stegnar, 2006. The influence of long-term mercury exposure on selenium availability in tissues: An evaluation of data. BioMetals 19(3):283-294.

103. T.W. Clarkson, L. Magos, 2006. The toxicology of mercury and its chemical compounds. Critical Reviews in Toxicology, 36:608–662.

104. R.M. LoPachin, T. Gavin, B.C. Geohagen, S. Das, 2007. Neurotoxic mechanisms of electrophilic type-2 alkenes: soft–soft interactions described by quantum mechanical parameters. Toxicological Sciences, 98(2):561–570.

105. R.M. LoPachin, T. Gavin, A.P. DeCaprio, D.S. Barber, 2012. Application of the hard and soft, acids and bases theory to toxicant-target interactions. Chemical Research Toxicology, 25:239–251.

106. R.M. LoPachin, T. Gavin, 2012. Acrylamide and related α,β-unsaturated carbonyl derivatives. In: Encyclopedia of Neurological Sciences 2nd Edition; Aminoff, M.J. and Daroff, R.D. (Eds); Elsevier , Oxford England, Chapter 244.

107. Y.H. Jan, D.E. Heck, A-C. Dragomir, C.R. Gardner, D.L. Laskin, J.D. Laskin, 2014. Acetaminophen Reactive Intermediates Target Hepatic Thioredoxin Reductase Chem. Res. Toxicol. 2014, 27, 882−894. dx.doi.org/10.1021/tx5000443

108. Jan Y. H.; Heck D. E.; Gray J. P.; Zheng H.; Casillas R. P.; Laskin D. L.; Laskin J. D. (2010) Selective targeting of selenocysteine in thioredoxin reductase by the half mustard 2-chloroethyl ethyl sulfide in lung epithelial cells. Chem. Res. Toxicol. 23, 1045–1053.

109. Cenas N.; Nivinskas H.; Anusevicius Z.; Sarlauskas J.; Lederer F.; Arner E. S. (2004) Interactions of quinones with thioredoxin reductase: a challenge to the antioxidant role of the mammalian selenoprotein. J. Biol. Chem. 279, 2583–2592.

110. Jan Y. H.; Heck D. E.; Malaviya R.; Casillas R. P.; Laskin D. L.; Laskin J. D. (2014) Cross-linking of thioredoxin reductase by the sulfur mustard analogue mechlorethamine (methylbis(2-chloroethyl)amine) in human lung epithelial cells and rat lung: Selective inhibition of disulfide reduction but not redox cycling. Chem. Res. Toxicol. 27, 61–75.

111. J. Fang, A. Holmgren, 2006. Inhibition of thioredoxin and thioredoxin reductase by 4-hydroxy-2-nonenal in vitro and in vivo. J. Am. Chem. Soc. 128, 1879–1885.

112. J. Fang, J. Lu, A. Holmgren, 2005. Thioredoxin reductase is irreversibly modified by curcumin: A novel molecular mechanism for its anticancer activity. J. Biol. Chem. 280, 25284–25290.

113. J. Lu, L.V. Papp, J. Fang, S. Rodriguez-Nieto, B. Zhivotovsky, A. Holmgren, 2006. Inhibition of mammalian thioredoxin reductase by some flavonoids: Implications for myricetin and quercetin anticancer activity. Cancer Res. 66, 4410–4418.

114. E.H. Chew, J. Lu, T.D. Bradshaw, A. Holmgren, 2008. Thioredoxin reductase inhibition by antitumor quinols: A quinol pharmacophore effect correlating to antiproliferative activity. FASEB J. 22, 2072–2083.

115. J. Nordberg, L. Zhong, A. Holmgren, E.S. Arner, 1998. Mammalian thioredoxin reductase is irreversibly inhibited by dinitrohalobenzenes by alkylation of both the redox active selenocysteine and its neighboring cysteine residue. J. Biol. Chem. 273, 10835–10842.

116. J. P. Gray, D.E. Heck, V. Mishin, P.J. Smith, J.Y. Hong, M. Thiruchelvam, D.A. Cory-Slechta, D.L. Laskin, J.D. Laskin, 2007. Paraquat increases cyanide-insensitive respiration in murine lung epithelial cells by activating an NAD(P)H:paraquat oxidoreductase: Identification of the enzyme as thioredoxin reductase. J. Biol. Chem. 282, 7939–7949.

117. K.A. Francesconi, F. Pannier, 2004. Selenium metabolites in urine: a critical overview of past work and current status. Clin Chem. 50(12):2240-53. doi: 10.1373/clinchem.2004.039875.

118. R. Vermeulen, E.L. Schymanski, A.L. Barabási, G.W. Miller, 2020. The exposome and health: Where chemistry meets biology. Science, 367(6476):392–396.

119. N.V.C. Ralston, J.J. Kaneko, L.J. Raymond, 2019. Selenium Health Benefit Values: A More Reliable Index of Seafood Benefits vs. Risks. Journal of Trace Elements in Biology and Medicine, 55:50-57.

120. J.R. Hibbeln, P. Spiller, J.T. Brenna, J. Golding, B.J. Holub, W.S. Harris, P. Kris-Etherton, B. Lands, S.L. Connor, G. Myers, J.J. Strain, M.A. Crawford, S.E. Carlson, 2019. Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: Two systematic reviews. Prostaglandins, Leukotrienes and Essential Fatty Acids, Prostaglandins, Leukotrienes and Essential Fatty Acids. 151:14-36.

121. E.E. Battin, J.L. Brumaghim, 2009. Antioxidant activity of sulfur and selenium: a review of reactive oxygen species scavenging, glutathione peroxidase, and metal-binding antioxidant mechanisms. Cell Biochemistry and Biophysics, 55(1):1–23.

122. J. Li, O. Wuliji, W. Li, Z.-G. Jiang, H. Ghanbari, 2013. Oxidative stress and neurodegenerative disorders. International Journal of Molecular Sciences,14(12):24438–24475.

123. G.F. Weber, P. Maertens, X.Z. Meng, C.E. Pippenger, 1991. Glutathione peroxidase deficiency and childhood seizures. Lancet, 337:1443-1444.

124. N.D. Solovyev, 2015. Importance of selenium and selenoprotein for brain function: from antioxidant protection to neuronal signaling. J. Inorg. Biochem., 153:1-12.

125. M.P. Rayman, 2012. Selenium and human health. Lancet. 379:1256-1268.

126. R. Pillai, J.H. Uyehara-Lock, J.P. Bellinger, 2014. Selenium and selenoprotein function in brain disorders. IUBMB Life. 66:229-239.

127. M.A. Ajmone-Cat, R. De Simone, A.M. Tartaglione, A. Di Biase, R. Di Benedetto, M. D'Archivio, R. Vari, L. Ricceri, F. Aureli, F. Iacoponi, A. Raggi, F. Cubadda, S.J. Fairweather-Tait, G. Calamandrei, L. Minghetti, 2022. Critical role of maternal selenium nutrition in neurodevelopment: effects on offspring behavior and neuroinflammatory profile. Nutrients. 14(9):1850.

128. S.R. Varikasuvu, V.S. Prasad, J. Kothapalli, M. Manne, 2019. Brain selenium in Alzheimer's disease (BRAIN SEAD study): a systematic review and meta-analysis. Biol. Trace Elem. Res. 189:361-369.

129. X. Forceville, P. Aouizerate, M. Guizard, 2001. Choc septique et administration de sélénium [Septic shock and selenium administration]. Therapie. 56(6):653-61.

130. C.B. de Almeida, H,P, Leite, J.E. Lopes, T. Konstantyner, 2022. Erythrocyte and plasma selenium in children with acute inflammatory response. J. Trace Elem. Med. Biol. 13;74:127068. doi: 10.1016/j.jtemb.2022.127068.

131. P.L. Carver, 2013. Metal ions and infectious diseases. An overview from the clinic. Met. Ions Life Sci. 13:1-28. doi: 10.1007/978-94-007-7500-8_1.

132. M.J. McConnell, J.V. Moran, A. Abyzov, S. Akbarian, T. Bae, I. Cortes-Ciriano I., J.A. Erwin, L. Fasching, D.A. Flasch, D. Freed, J. Ganz, A.E. Jaffe, K.Y. Kwan, M. Kwon, M.A. Lodato, R.E. Mills, A.C.M. Paquola, R.E. Rodin, C. Rosenbluh, N. Sestan, M.A. Sherman, J.H. Shin, S. Song, R.E. Straub, J. Thorpe, D.R. Weinberger, A.E. Urban, B. Zhou, F.H. Gage, T. Lehner, G. Senthil, C.A. Walsh, A. Chess, E. Courchesne, J.G. Gleeson, J.M. Kidd, P.J. Park, J. Pevsner, F.M. Vaccarino, 2017. Intersection of diverse neuronal genomes and neuropsychiatric disease: The Brain Somatic Mosaicism Network. Science. 2017;356 https://doi.org/10.1126/science.aan8690.

133. T. Bae, L. Tomasini, J. Mariani, B. Zhou, T. Roychowdhury, D. Franjic, M. Pletikos, R. Pattni, B.-J. Chen, E. Venturini, B. Riley-Gillis, N. Sestan, A.E. Urban, A. Abyzov, F.M. Vaccarino, 2018. Different mutational rates and mechanisms in human cells at pregastrulation and neurogenesis. Science. 359:550–5. https://doi.org/10.1038/nature19768.

134. M.A. Lodato, R.E. Rodin, C.L. Bohrson, M.E. Coulter, A.R. Barton, M. Kwon, M.A. Sherman, C.M. Vitzthum, L.J. Luquette, C.N. Yandava, P. Yang, T.W. Chittenden, N.E. Hatem, S.C. Ryu, M.B. Woodworth, P.J. Park, C.A. Walsh, 2018. Aging and neurodegeneration are associated with increased mutations in single human neurons. Science. 359:555–9. https://doi.org/10.1101/gr.215517.116.

135. X. Cai, G.D. Evrony, H.S. Lehmann, P.C. Elhosary, B.K. Mehta, A. Poduri, C.A. Walsh, 2014. Single-cell, genome-wide sequencing identifies clonal somatic copy-number variation in the human brain. Cell Rep. 8:1280–9. https://doi.org/10.1126/science.aal1641.

136. G.D. Evrony, E. Lee, B.K. Mehta, Y. Benjamini, R.M. Johnson, X. Cai, L. Yang, P. Haseley, H.S. Lehmann, P.J. Park, C.A. Walsh, 2015. Cell lineage analysis in human brain using endogenous retroelements. Neuron. 85:49–59. https://doi.org/10.1016/j.celrep.2014.07.043.

137. Erwin JA, A.C.M. Paquola, T. Singer, I. Gallina, M. Novotny, C. Quayle, T.A. Bedrosian, F.I.A. Alves, C.R. Butcher, J.R. Herdy, A. Sarkar, R.S. Lasken, A.R. Muotri, F.H. Gage, 2016. L1-associated genomic regions are deleted in somatic cells of the healthy human brain. Nat. Neurosci. 19:1583–91. https://doi.org/10.1016/j.neuron.2014.12.028.

138. X. Zhu, B. Zhou, R. Pattni, K. Gleason, C. Tan, A. Kalinowski, S. Sloan, A.-S. Fiston-Lavier, J. Mariani, D. Petrov, B.A. Barres, L. Duncan, A. Abyzov, H. Vogel, J.V. Moran, F.M. Vaccarino, C.A Tamminga, D.F. Levinson, A.E. Urban, 2021. Machine learning reveals bilateral distribution of somatic L1 insertions in human neurons and glia. Nat Neurosci. 24:186-96. https://doi.org/10.1101/660779

139. M.A. Lodato, M.B. Woodworth, S. Lee, G.D. Evrony, B.K. Mehta, A. Karger, S. Lee, T.W. Chittenden, A.M. D'Gama, X. Cai, L.J. Luquette, E. Lee, P.J. Park, C.A. Walsh, 2015. Somatic mutation in single human neurons tracks developmental and transcriptional history. Science. 350:94–8. https://doi.org/10.1038/nn.4388.

140. F. Blokzijl, J. de Ligt, M. Jager, V. Sasselli, S. Roerink, N. Sasaki, M. Huch, S. Boymans, E. Kuijk, P. Prins, I.J. Nijman, I. Martincorena, M. Mokry, C.L. Wiegerinck, S. Middendorp, T. Sato, G. Schwank, E.E.S. Nieuwenhuis, M.M.A. Verstegen, L.J.W. van der Laan, J. de Jonge, J.N.M IJzermans, R.G. Vries, M. van de Wetering, M.R. Stratton, H. Clevers, E. Cuppen, R. van Boxtel, 2016. Tissue-specific mutation accumulation in human adult stem cells during life. Nature. 538:260–4. https://doi.org/10.1126/science.aao4426.

141. M. Leija-Salazar, C. Piette, C. Proukakis, 2018. Somatic mutations in neurodegeneration. Neuropathol. Appl. Neurobiol 3:748. https://doi.org/10.1111/nan.12465

142. A. Poduri, G.D. Evrony, X. Cai, C.A. Walsh, 2013. Somatic mutation, genomic variation, and neurological disease. Science 341:1237758. https://doi.org/10.1126/science.12377 58

143. Y. Wang, T. Bae, J. Thorpe, M.A. Sherman, A.G. Jones, S. Cho, K. Daily, Y. Dou, J. Ganz, A. Galor, I. Lobon, R. Pattni, C. Rosenbluh, S. Tomasi, L. Tomasini, X. Yang, B. Zhou, S. Akbarian, L.L. Ball, S. Bizzotto, S.B. Emery, R. Doan, L. Fasching, Y. Jang, D. Juan, E. Lizano, L.J. Luquette, J.B. Moldovan, R. Narurkar, M.T. Oetjens, R.E. Rodin, S. Sekar, J.H. Shin, E. Soriano, R.E. Straub, W. Zhou, A. Chess, J.G. Gleeson, T. Marquès-Bonet, P.J. Park, M.A. Peters, J. Pevsner, C.A. Walsh, D.R. Weinberger, F.M. Vaccarino, J.V. Moran, A.E. Urban, J.M. Kidd, R.E. Mills, A. Abyzov, 2021. Comprehensive identification of somatic nucleotide variants in human brain tissue. Genome Biol. 22:92. https://doi.org/10.1186/s13059-021-02285-3

144. M. O'Huallachain, K.J. Karczewski, S.M. Weissman, A.E. Urban, M.P. Snyder, 2012. Extensive genetic variation in somatic human tissues. Proc. Natl. Acad. Sci. U S A. 109:18018–23. https://doi.org/10.1073/pnas.1213736109.

145. C.E. Bruder, A. Piotrowski, A.A. Gijsbers, R. Andersson, S. Erickson, T. Diaz de Ståhl, U. Menzel, J. Sandgren, D. von Tell, A. Poplawski, M. Crowley, C. Crasto, E.C. Partridge, H. Tiwari, D.B. Allison, J. Komorowski, G.J. van Ommen, D.I. Boomsma, N.L. Pedersen, J.T. den Dunnen, K. Wirdefeldt, J.P. Dumanski, 2008. Phenotypically concordant and discordant monozygotic twins display different DNA copy-number variation profiles. Am. J. Hum. Genet. 82:763–71. https://doi.org/10.1073/pnas.1213736109.

146. Y. Manavski, T. Lucas, S.F. Glaser, L. Dorsheimer, S. Gunther, T. Braun, M.A. Rieger, A.M. Zeiher, R.A. Boon, S. Dimmeler, 2018. Clonal expansion of endothelial cells contributes to ischemia-induced neovascularization. Circ. Res. 122:670–677

147. J. Chappell J.L Harman, V.M. Narasimhan, H. Yu, K. Foote, B.D. Simons, M.R. Bennett, H.F. Jorgensen, 2016. Extensive proliferation of a subset of differentiated, yet plastic, medial vascular smooth muscle cells contributes to neointimal formation in mouse injury and atherosclerosis models. Circ. Res. 119:1313–1323.

148. E.P. Benditt, J.M. Benditt, 1973. Evidence for a monoclonal origin of human atherosclerotic plaques. Proc. Natl. Acad. Sci. USA. 70:1753–1756.

149. B. Uttara, A.V. Singh, P. Zamboni, R.T. Mahajan, 2009. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Current neuropharmacology, 7(1):65–74.

150. P. Libby, 2001. Current concepts of the pathogenesis of the ACS. Circulation. 104(3):365372.

151. R. Ross. 1999. Atherosclerosis—an inflammatory disease. The New England Journal of Medicine. 340:115–126.

152. I. Pinchuk, D. Lichtenberg, 2002. The mechanism of action of antioxidants against lipoprotein peroxidation, evaluation based on kinetic experiments. Progress in Lipid Research. 41(4):279–314.

153. N.V.C. Ralston, 2021. Neurotoxic Effects of Electrophile Interactions with Brain Selenoenzymes. In “Handbook of Neurotoxicity” Kostrzewa RM. Editor, Springer-Verlag.

154. V. Branco, A.G. Santos, J. Rodrigues, J. Gonçalves, J. Lu, A. Holmgren, C. Carvalho, 2014. Mitochondrial thioredoxin reductase inhibition, selenium status and Nrf-2 activation are determinant factors modulating the toxicity of mercury compounds. Free Radical Biology and Medicine, 73:95–105.

155. N.V.C. Ralston, L.J. Raymond, 2006. Physiologically Based Pharmacokinetic Model of Hg-Se Interactions. Center for Air Toxic Metals (CATM®) Annual Report to U.S. EPA. 2006:172-184.

156. I.J. Onakpoya, C.J. Heneghan, J.K. Aronson. 2016. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 4;14:10. doi: 10.1186/s12916-016-0553-2.

157. L.R. Whitby, R.S. Obach, G.M. Simon, M.M. Hayward, B.F. Cravatt, Quantitative Chemical Proteomic Profiling of the in Vivo Targets of Reactive Drug Metabolites, ACS Chem. Biol. 12 (2017) 2040-2050.

158. W. Sun, Z. Jiang, W. Jiang R. Yang, 2022. Universal chimeric antigen receptor T cell therapy - The future of cell therapy: A review providing clinical evidence. Cancer Treat. Res. Commun. 22:100638. doi: 10.1016/j.ctarc.2022.100638.

159. J. Eno, 2017. Immunotherapy Through the Years. J. Adv. Pract. Oncol. 8:747. doi:10.6004/jadpro.2017.8.7.8.

160. B. Costa, N.Vale, 2022. Dostarlimab: A Review. Biomolecules. 26;12(8):1031. doi:10.3390/biom12081031.

161. M. Lynch, M.S. Ackerman, J.-F. Gout, H. Long, W. Sung, W.K. Thomas, P.L. Foster, 2016. Genetic drift, selection and the evolution of the mutation rate. Nat. Rev. Genet. 17:704–714. doi: 10.1038/nrg.2016.104

162. WHO (2021) World Health Organization Newsroom Fact Sheets: Aging and health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (Viewed August, 2022.)

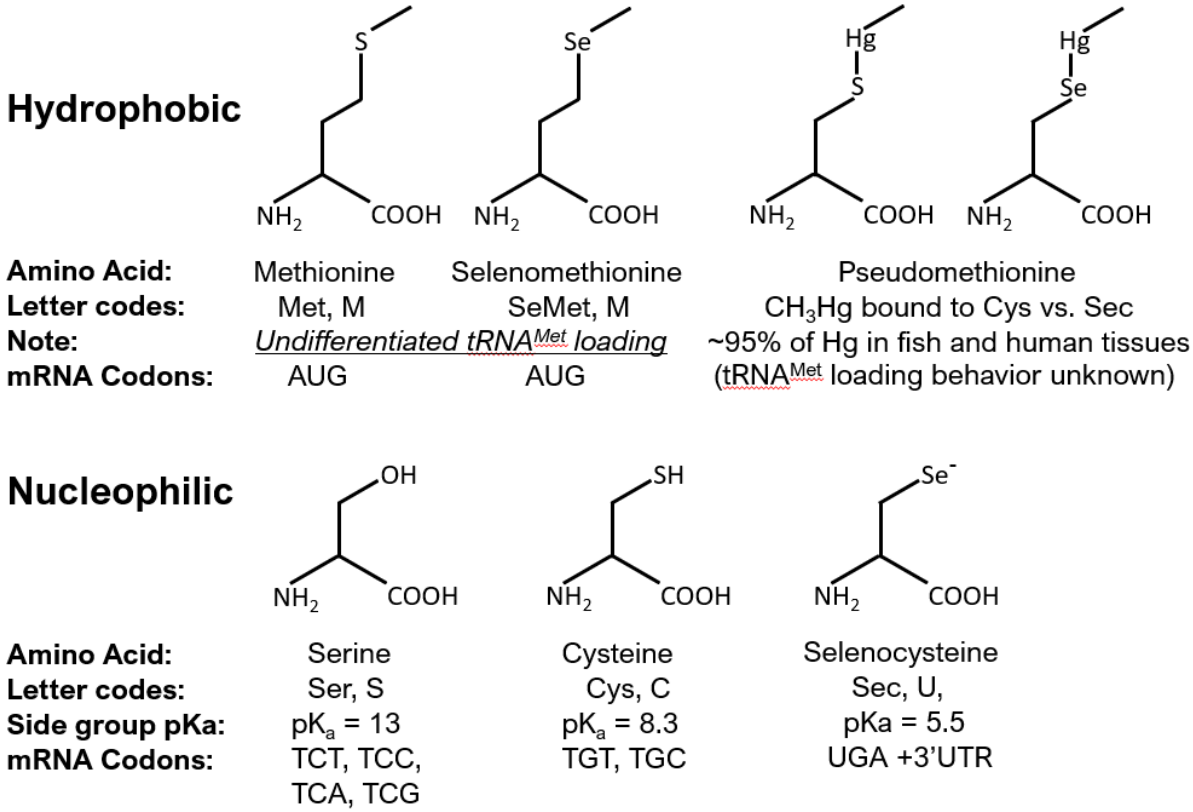

Figure 1. Structures of chalcogen amino acid analogues.

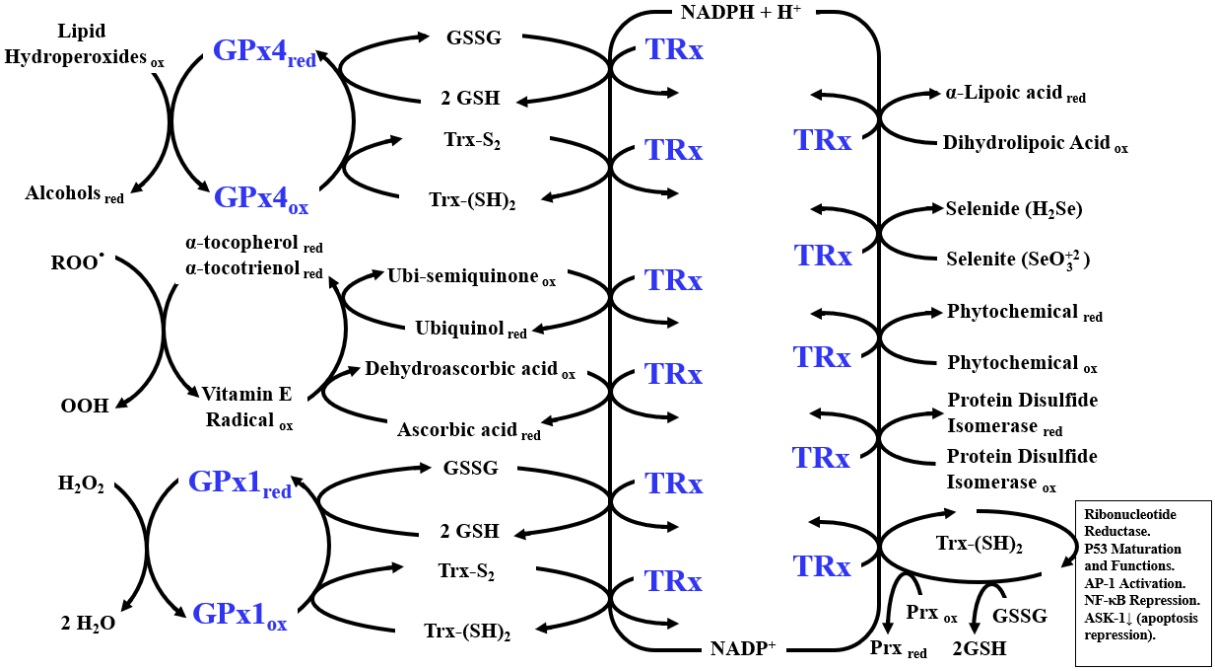

Figure 2. The roles of TRx and GPx enzymes in intracellular redox control.

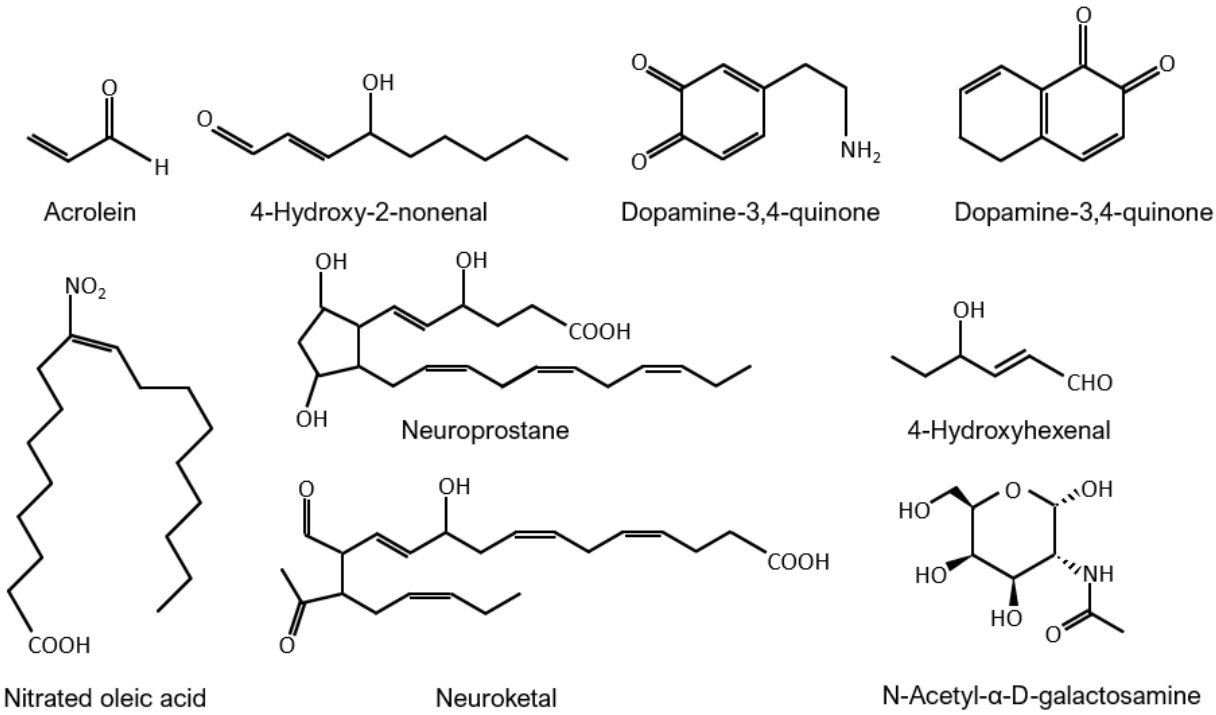

Figure 3. Structures of representative endogenous soft electrophiles

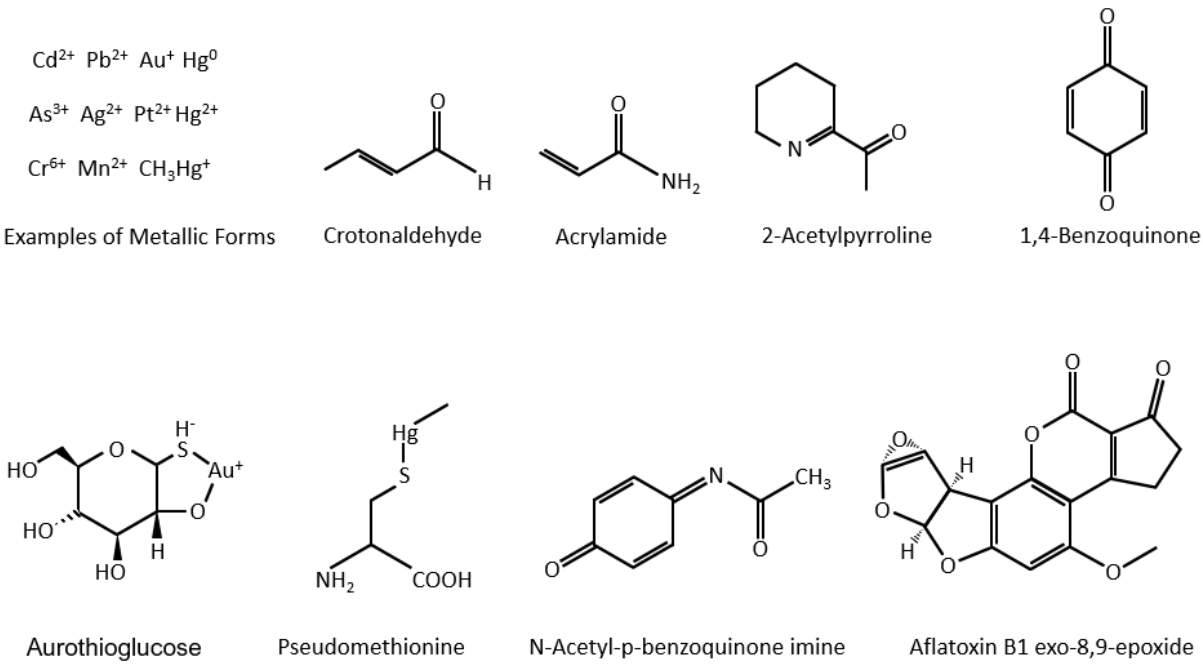

Figure 4 Structures of representative exogenous/xenobiotic soft electrophiles

Electrophile Exposure		Tissue Selenium	Electrophile Bound Se	Selenoenzyme Status	DNA Damage	Somatic Mutant Pathologies
E*	+	Low Se	Se-E*	Se-ENZ	↑	↑
E*	+	Low Se	Se-E*	Se-ENZ	↑↑	↑↑
E*	+	Normal Se	Se-E*	Se-ENZ	↑	↑
E*	+	Rich Se	Se-E*	Se-ENZ	↑	↑