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Intrinsic and extrinsic modulators of mercury exposure, bioaccumulation, and adverse effects in wildlife and humans in the context of rapid global change

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Modulators of mercury risk to wildlife and humans in the context of rapid global change

Collin A. Eagles-Smith[1#], Ellen K. Silbergeld[2], Niladri Basu[3*], Paco Bustamante[4*], Fernando Diaz-Barriga[5*], William A. Hopkins[6*], Karen A. Kidd[7,8*], Jennifer F. Nyland[9*]

[1]U.S. Geological Survey, Corvallis, OR, USA
[2]Johns Hopkins University, Baltimore, MD, USA
[3]McGill University, Montreal, Canada
[4]La Rochelle University; La Rochelle, France
[5]Universidad Autónoma de San Luis Potosí, Mexico
[6]Virginia Tech, Blacksburg, VA, USA
[7]University of New Brunswick and Canadian Rivers Institute, Saint John, NB Canada
[8]McMaster University, Hamilton, ON, Canada
[9]Salisbury University, Salisbury, MD, USA

[*]authors listed alphabetically
[#]ceagles-smith@usgs.gov

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Abstract

Understanding ecological and human health risks from mercury (Hg) is an urgent global issue, but one that is difficult to address because of the complex environmental cycling, variable toxicokinetics, and diverse effects of this element. In addition, unprecedented rates of global change are altering many ecological processes, socioeconomic patterns, and the intensity of other health risks (such as infectious disease) that affect dietary and occupational exposures to Hg and realized health outcomes. Extrinsic and intrinsic drivers such as climate change, invasive species, and genetic variability affect both the exposure to and toxicity of Hg to humans and other animals, but are rarely considered when estimating its risks. This is particularly important because global efforts are being made to reduce Hg emission and environmental exposure, and extrinsic and intrinsic drivers of Hg exposure and bioaccumulation can complicate effectiveness monitoring by masking the apparent influence of Hg reduction activities. In this synthesis, we examine the role that key extrinsic and intrinsic drivers have on several aspects of Hg risk to humans and other organisms. We first describe how changes in land use, hydrologic management, invasive species, and climate change affect four key mechanisms known to alter methylmercury movement through food webs – habitat use, bioenergetics, primary production, and food web structure – and the resultant effects on MeHg exposure in animals. Next, at the level of the individual, intrinsic drivers such as genetics and extrinsic ones such as socioeconomics influencing human exposure to both MeHg and inorganic Hg are described. Finally, we address how the manifestation of Hg toxicity in humans and other animals is affected by intrinsic drivers at the individual level such as diet, nutrition, co-exposures to other contaminants or disease, genetics and the microbiome, and discuss the implications of these interactions within the context of a rapidly changing world. To effectively reduce the risk of Hg toxicity, a holistic approach that considers the influences of both broader, globally-occurring drivers as well as individual factors is needed.

1.0 Introduction

The health effects of mercury (Hg) exposure represent a significant threat to ecosystems and human welfare worldwide (Driscoll et al. 2013), but understanding its risks are complicated by this element's varied environmental fate and the overarching influences of environmental, biological, and socioeconomic drivers. In its various forms, Hg causes immunotoxicity (Hawley et al. 2009, Lewis et al. 2013, Hui et al. 2016, Zhang et al. 2016, Crowe et al. 2017) and nephrotoxicity (Tchounwou et al. 2003), diminishes neurological capacity and neurobehavioral function (Steuerwald et al. 2000, Basu et al. 2005, Clarkson and Magos 2006, Mergler et al. 2007a, Scheuhammer and Sandheinrich 2008, Depew et al. 2012a, Bridges et al. 2016, Landler et al. 2017), alters functioning of three major endocrine axes (Wada et al. 2009, Meyer et al. 2014), and impairs reproduction and alters offspring quality (Klaper et al. 2006, Burgess and Meyer 2008, Bergeron et al. 2011, Hopkins et al. 2013, Tartu et al. 2013, Thompson et al. in press). This myriad of adverse effects coupled with the diverse sources, propensity for long-range transport, complex biogeochemical cycling, and mosaic of exposure pathways through food webs and from industrial activities present a labyrinth of challenges to characterizing and managing risk to conservation and public health. Nonetheless, substantial progress has been made over the past several decades, resulting in improved inventories of Hg sources and releases (Streets et al. 2017), and a more robust scientific understanding of the factors influencing Hg fate and transport (Obrist et al. 2017), the processes driving methylmercury (MeHg) production (Hsu-Kim et al. 2017), and the manifestations and mechanisms of many of its toxic effects in biota. This progress has supported global efforts to reduce Hg loading to the environment to protect human and ecological health (Selin et al. 2017).

However, ecological and societal risks from Hg rarely follow a simple linear relationship between Hg releases, uptake/exposure, and adverse outcomes. Instead, a diverse suite of intrinsic biological drivers (herein called "intrinsic drivers", e.g. genetics, microbiome) and extrinsic ecological and socioeconomic drivers (herein called "extrinsic drivers"; e.g. invasive species, culture) alter the availability of Hg to ecological and human receptors, as well as its toxicity to humans and other animals. Some of these drivers – climate change, land use changes, etc. – are occurring at unprecedented global rates and all likely hinder the development of effective control actions, alter recovery trajectories, and confound interpretations of monitoring outcomes. Thus, understanding and accounting for the effects of these drivers on both exposure and effects is a critical component of effectively addressing the global challenges of Hg.

Exposure to MeHg mainly occurs via the diet for most organisms (Mergler et al. 2007b, Wiener 2013), whereas elemental and inorganic Hg exposure (particularly in humans) largely occurs through inhalation, dermal, or oral routes (Clarkson and Magos 2006), and these are primarily associated with industrial processes, such as artisanal and small-scale gold mining (ASGM; (Steckling et al. 2011, Basu et al. 2015b)) and medical uses (Clarkson and Magos 2006). These exposures are influenced by environmental alterations and societal shifts associated with extrinsic drivers (such as climate change, invasive species, hydrologic and land use alterations, and macroeconomic change), although through very different mechanisms. For example, extrinsic drivers that alter trophic processes - such as food web structure, foraging ecology, and ecosystem energetics – influence the magnitude of MeHg transfer to, and degree of bioaccumulation and biomagnification in different organisms through their influence on

exposure (Vander Zanden and Rasmussen 1996, Lavoie et al. 2013, Karimi et al. 2016a, Polito et al. 2016). Conversely, global socioeconomic trends, cultural patterns, and development trajectories affect inorganic Hg exposure risks in human populations (Swain et al. 2007). In this synthesis, we examine intrinsic and extrinsic drivers that influence these routes of exposure, and subsequently alter risks of Hg to human health and the health of organisms in the environment. Although abiotic Hg fate and transport and MeHg production are critical aspects of the Hg cycle, we do not address these processes as they are reviewed in detail elsewhere (Hsu-Kim et al. 2017, Obrist et al. 2017). The growing extent and intensity of some drivers will continue to influence key mechanisms associated with Hg exposure and bioaccumulation in both humans and other animals, thus there is a critical need to understand these interactions to better predict changes in exposure trajectories, and realized adverse health effects.

Here we examine the role of key biological, environmental, and socioeconomic drivers that operate across multiple scales of organization to modulate Hg bioaccumulation in organisms and biomagnification through food webs, exposure in humans, and health outcomes. We do so within a conceptual framework based upon pathways of Hg cycling through the ecosphere (Figure 1), and within three key **domains** of ecological and human health risk. **Domain 1** assesses the *extrinsic global change drivers influencing MeHg bioaccumulation and biomagnification through food webs*. **Domain 2** examines the *extrinsic global, and intrinsic individual and molecular drivers influencing human exposure to both MeHg and inorganic Hg*, and interacts with **Domain 1** through the human consumption of Hg-contaminated foods. **Domain 3** addresses the *extrinsic and intrinsic drivers influencing adverse effects of both MeHg and inorganic Hg in human and ecological health endpoints* across range of scales, and how they interact with the global change drivers described in Domains 1 and 2.

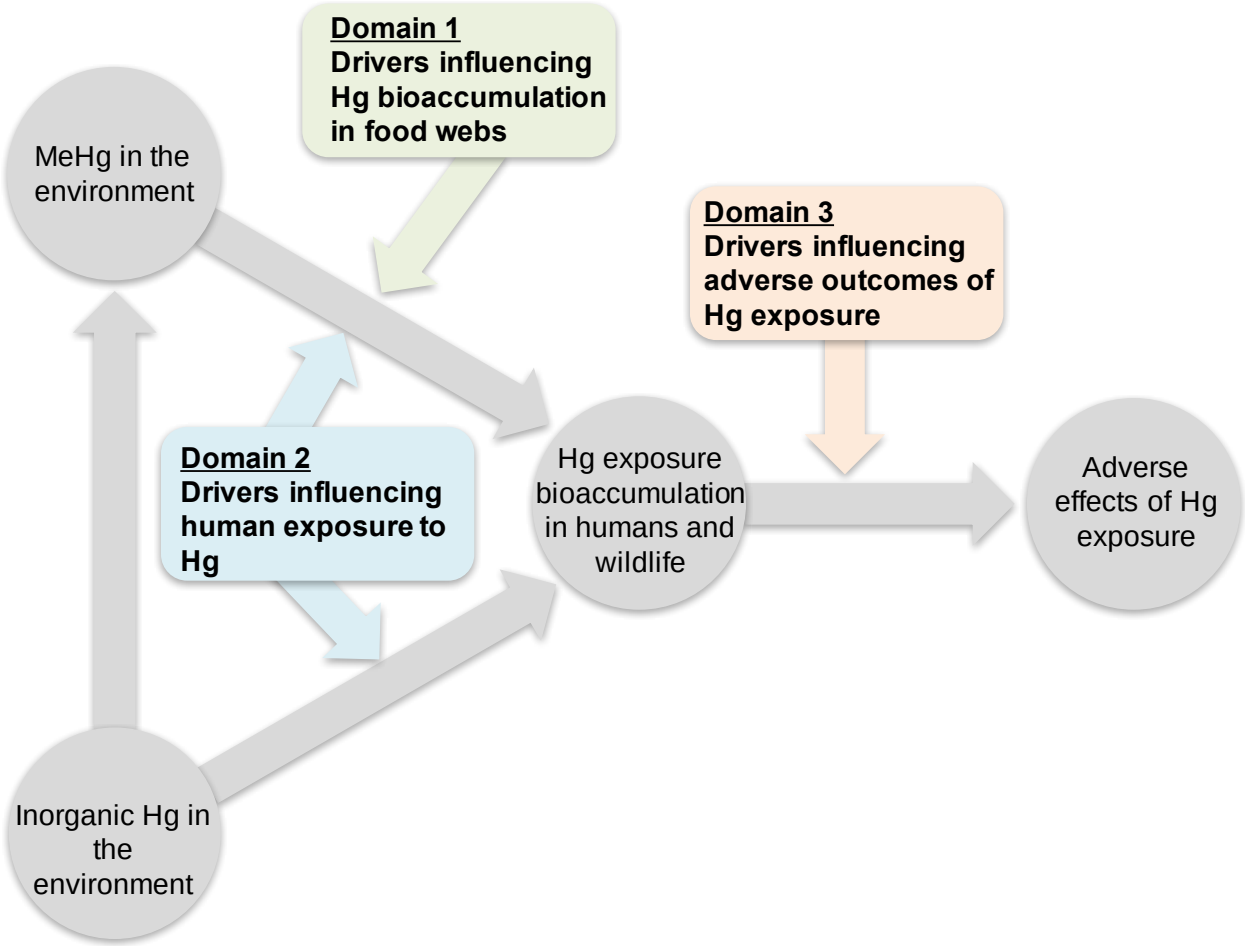

Figure 1*. Conceptual model of mercury (Hg) pathways through the ecosphere and the identification of domains influencing Hg risk. Extrinsic global drivers affecting methylmercury (MeHg) bioaccumulation in Domain 1 include hydrologic alteration, land use change, invasive species, and climate change (see Figure 2). Extrinsic drivers influencing human exposure to inorganic Hg and MeHg in Domain 2 include socio-economics of subsistence and luxury fish consumption and artisanal and small-scale gold mining (ASGM), whereas intrinsic drivers include genetics and gastrointestinal assimilation (see Figure 3). Extrinsic and intrinsic drivers modulating adverse outcomes of MeHg and inorganic Hg exposure in humans and other animals in Domain 3 include pathogens and infectious disease, nutrients and co-contaminants, the microbiome, and genetics.*

2.0 Domain 1 – Global change drivers influencing MeHg bioaccumulation in food webs. The unprecedented rate of human-induced change in climate, hydrology, invasive species, and land use is altering ecosystem processes on a global scale, as well as the distributions and interactions of species across terrestrial, freshwater, and marine habitats (Vitousek 1994, Hooper et al. 2012). Ecosystems respond to extrinsic drivers in many ways, including through changes in food web structure and ecosystem energetics (Petchey et al. 1999, Baxter et al. 2004, Woodward

et al. 2010), which influence MeHg bioaccumulation in food webs and subsequent dietary exposure for humans.

Herein we identify four key ecological mechanisms that modulate MeHg bioaccumulation and risk through their effects on MeHg entry at the base of the food web, trophic transfer of Hg through food webs, and toxicokinetics of Hg within organisms. These mechanisms include: 1) primary productivity, 2) habitat use, 3) bioenergetics, and 4) food web structure. Although there is some inherent overlap among these mechanisms (e.g., hydrology dictates available habitat which can alter food web structure, etc.), their unique influences on Hg exposure and bioaccumulation warrant separate discussions. We then examine how each of these mechanisms can modulate (confound, moderate, or mediate) MeHg bioaccumulation when influenced by widespread global change drivers (Figure 2). The extrinsic drivers considered herein include: a) hydrologic alteration, b) land use change and changes to nitrogen cycling, and c) invasive species. Additionally, each of these extrinsic drivers occur within the context of d) climate change, which modulates many aspects of the other drivers of global change.

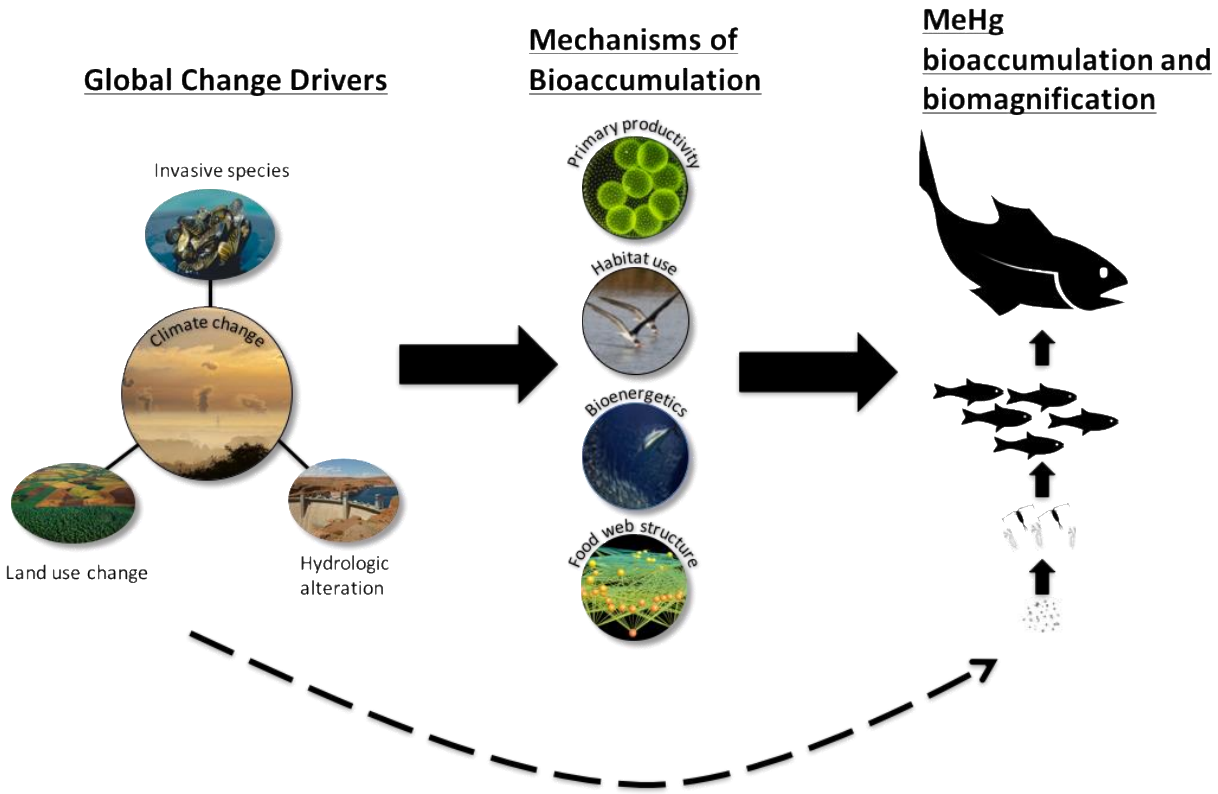

Figure 2. *Major extrinsic drivers of global change (invasive species, land use change, hydologic alteration, and climate change) indirectly (dashed arrow) influence methylmercury (MeHg) bioaccumulation and biomagnification through their direct effects (solid arrow) on key ecological mechanisms of MeHg bioaccumulation (primary productivity, habitat use, bioenergetics, and food web structure).*

2.1 Hydrologic Alteration

Hydrologic alteration is a defining characteristic of the Anthropocene and a major component of global change (Rosenberg et al. 2000). Dam, levee, and canal construction, wetland draining, and restriction of tidal exchange have fundamentally transformed the global water cycle, altering the ecology of freshwater ecosystems (Sahagian 2000), adjacent terrestrial riparian habitats (Poff et al. 2007), and receiving estuaries (Herbert et al. 2015). Globally, approximately 800,000 dams regulate over half of the world's global river systems (Friedl and Wuest 2002, Nilsson 2005). These dams obstruct an estimated two-thirds of freshwater flowing to the oceans (Nilsson and Berggren 2000), and redirect approximately 50% of the planet's accessible freshwater runoff for human use (Postel et al. 1996). Although dam construction has slowed since the 1970s, human population growth and economic development continue to drive a nearly exponential increase in global water use (Vorosmarty and Sahagian 2000). As a result, ongoing management of hydrology through reservoir operations, wetland restoration and management, and agricultural use maintains the global extent of continued hydrologic alteration, particularly in developing regions of the world (Janse et al. 2015).

Aquatic ecosystem functions are profoundly influenced by hydrologic alteration, resulting in changes to habitat connectivity and quality, community composition, and energy flow through ecosystems (Vorosmarty et al. 2000). Dams fragment riverine habitats (Rosenberg et al. 2000), alter water temperatures, and homogenize variation in discharge (Sabo et al. 2010). These physical and chemical changes manifest as ecological outcomes such as enhanced invasion of nonnative species (Havel et al. 2005), community shifts from fluvial specialists to habitat generalists (Haxton and Findlay, 2008), and increased food chain length (Sabo et al. 2010). The impacts of wetland loss on biodiversity and ecological function have been thoroughly described (Zedler and Kercher 2005), but even restored wetlands that are hydrologically managed to mirror pre-disturbance features exhibit both structural and functional biological degradation (Moreno-Mateos et al. 2012). Thus, many of the effects of hydrologic alteration are directly tied to the four key mechanisms associated with Hg bioaccumulation, described herein. The extent and magnitude of hydrologic alteration as a global change driver suggests that it can have an extensive impact on Hg biomagnification through food webs.

Fish and wildlife exposure to Hg inherently differs among waterbody and habitat types (Ackerman et al. 2016, Eagles-Smith et al. 2016a) because hydrology influences the biogeochemical processes associated with MeHg production, as well as habitat availability and use, food web structure, and bioenergetics. As a result, hydrologic alteration is arguably the most well-studied of the global change drivers identified herein with causal ties to altered Hg bioaccumulation in aquatic food webs. Reservoirs in particular have been associated with elevated Hg bioaccumulation. Hg concentrations in reservoir fish are between 40% to several times higher than concentrations in fish from natural lakes (Kamman et al. 2005, Bodaly et al. 2007, Monson et al. 2011, Willacker et al. 2016), and the differences are particularly high in newly-inundated reservoirs where there is a rapid post-impoundment increase in Hg concentrations through aquatic food webs. Studies in Scandinavia (Porvari 1998), North America (Willacker et al. 2016), Europe (Kruzikova et al. 2011), South America (Hylander et al. 2006), and Asia (Li et al. 2013) have all shown that total Hg and MeHg concentrations in aquatic food web components increased 3- to 30-fold within a few years after reservoir creation, with the magnitude of increases tied to amount of flooded area relative to reservoir surface area (Bodaly et al. 2007). Fish Hg concentrations reached their maximum levels 2-14 years after impoundment

across 8 hydroelectric reservoirs in Canada (Bodaly et al. 2007), and an average of 3 years after impoundment across dozens of reservoirs throughout western North America (Willacker et al. 2016). Because Hg concentrations and reproductive risk in piscivorous birds is highly correlated with Hg concentrations in potential prey fish (Evers et al. 2008, Ackerman et al. 2015), waterbird species attracted to reservoirs or their discharge waters may be at particularly high risk to exposure in the years following reservoir creation. Reservoir creation can also enhance the magnitude of aquatic invertebrate emergence, increasing the available biomass of Hg-contaminated prey and associated Hg exposure in insectivorous birds (Gerrard and St Louis 2001), providing biologically-mediated subsidies to adjacent terrestrial habitats. The pulse in MeHg bioaccumulation through food webs does not occur in all newly-impounded reservoirs (Li et al. 2015), and though mechanisms are not well understood, evidence suggests that food chain length of reservoirs may be an important factor regulating responses (Razavi et al. 2014, Ouedraogo et al. 2015).

Mercury concentrations in reservoir fish (and likely other taxa) eventually return to near pre-impoundment levels, though it can take several decades (French et al. 1998, Bodaly et al. 2007, Willacker et al. 2016) with rates of decline ranging between 0.5 and 3.9% per year (Green et al. 2016). However, both reservoir management and hydrologic structure can confound any return to background concentrations. Water level management, specifically the magnitude of between-year changes in maximum water levels, is linearly correlated with fish Hg concentrations in subsequent years (Sorensen et al. 2005, Larson et al. 2014, Willacker et al. 2016) and has been associated with up to a 3-fold difference in fish Hg concentrations from reservoirs with low versus high proportional changes in maximum water levels (Willacker et al. 2016). Water column stratification also influences food web Hg bioaccumulation, particularly in dimictic lakes where hypolimnetic MeHg moves rapidly into the food web after fall turnover (Slotton et al. 1995). Reservoir stratification also regulates Hg concentrations in downstream environments, where elevated Hg concentrations in the food webs can extend up to 200 km below dams (Kasper et al. 2014). Thus, the influence of hydrologic alteration on Hg dynamics within food webs extends to other water bodies. For example, fish Hg concentrations have been shown to be highest in wetlands with the greatest degree of water level fluctuation (Snodgrass et al. 2000, Eagles-Smith and Ackerman 2014), white ibis chick Hg concentrations were directly tied to water level fluctuation rates in the Florida Everglades (Herring et al. 2013), and invertebrate MeHg concentration and flux to terrestrial environments differed among ponds with varying water management and presence or absence of fish (Henderson et al. 2012). Further, river geomorphology can influence aquatic-terrestrial Hg transfer through the collective effects on emergent insect body burdens and aquatic insect community composition (Sullivan et al. 2016).

2.2 Land Use Change

Rapid and irreversible conversion of lands for the production of food, extraction of resources and urbanization is occurring globally. This alteration of the landscape has disturbed natural hydrological, geochemical and biological processes due to the production and discharge of wastes, impervious surfaces of cities, conversion of forests to pastures for livestock and crop monocultures, and additions of fertilizers and pesticides to increase food production (Tilman et al. 2001). Our widespread changes to terrestrial systems from a rapidly growing population and unsustainable resource consumption has resulted in global shifts in the nitrogen cycle (Vitousek 1994), unprecedented losses in biodiversity (Phalan et al. 2011), pervasive eutrophication of

aquatic ecosystems (Carpenter and Bennett 2011), and impacts on regional and global climate (Vitousek 1994, IPCC 2014).

These broad-scale changes to the landscape are also altering the fate of Hg through their effects on the structure and function of terrestrial and aquatic systems and the four key mechanisms identified herein (hydrologic alteration, primary productivity, invasive species, and food web structure). For example, direct toxicity, changes in nutrient flow, and habitat loss, each can result in losses of sensitive species and biodiversity, which affects food web structure [urban effluents, (Wenger et al. 2009, Holeton et al. 2011); agricultural pesticides and fertilizers; forestry, (Richardson and Beraud 2014)]. The growth rates and bioenergetics of species shift from changes in food supply, competition, and predation (Brinkmann and Rasmussen 2010). Losses in forest cover and permeable lands alter the timing and magnitude of *water flow* from terrestrial to aquatic systems (Sampaio da Silva et al. 2009, Wenger et al. 2009). Finally, the primary productivity of ecosystems from heavy reliance on fertilizers is increasing the availability of limiting nutrients to terrestrial and aquatic vegetation (Vitousek et al. 1997, Carpenter et al. 1998).

Of the four key mechanisms, alterations in primary productivity and its effects on Hg in consumers is arguably one of the better studied, but controversies remain over the resultant net effects on Hg uptake in biota. Increases in the biomass of primary producers may dilute MeHg in the base of the food web [algae, (Pickhardt et al. 2002, Perron et al. 2014)] and subsequently in predators [zooplankton, (Chen and Folt 2005); fish, (Larsson et al. 1992, Kidd et al. 1999, Essington and Houser 2003)], or alternatively enhances MeHg production through greater abundance of primary producers (Lepak et al. 2015) facilitating *in situ* Hg methylation (Mauro et al. 2002, Paranjape and Hall 2017). Increases in the primary productivity of artificial streams by several orders of magnitude led to similar declines in MeHg concentrations of algae and algal consumers, supporting the biodilution hypothesis (Walters et al. 2015). A review of several case studies examining fish Hg concentrations across a gradient of nutrient loading to coastal waters found examples that both supported and challenged the biodilution hypothesis (Driscoll et al. 2012). Although agricultural runoff and municipal wastewaters are the largest contributors to eutrophication of freshwater and marine coastal systems, there are surprisingly few studies on their impacts on Hg cycling in aquatic ecosystems and in the terrestrial landscape upon which pesticides, wastewater biosolids, fertilizers and manures are applied.

2.3 Invasive and Introduced Species

Long distance transportation and globalization have resulted in the intentional and unintentional transport of microbes, flora, and fauna around the world (Pimentel et al. 2000, Richardson et al. 2000). In some cases, non-native species become established in new geographic localities and outcompete or prey upon native species, carry diseases, alter critical ecosystem functions, influence water and food supplies for humans, and cause extraordinary economic losses (Mack et al. 2000, Pimentel et al. 2000, Richardson et al. 2000, Pimentel et al. 2001, Pimentel et al. 2005). As a result, invasive species are now widely recognized as one of the greatest anthropogenic challenges facing the planet.

Invasive invertebrates, plants, and animals can upend ecosystem-level processes, alter food web composition, and influence the health and survival of native organisms in the receiving

ecosystem. For example, invasive plants can differ from native plants in their physiology and phenology, sometimes producing striking differences in biomass, primary productivity, rhizosphere activity, and fundamental alterations to nutrient and water cycles (Ehrenfeld 2003, Gentes et al. 2013). Invasive invertebrates such as zebra mussels can overwhelm aquatic systems and cause wholesale changes in phytoplankton and zooplankton community structure, driving cascading effects on the diets and growth of fish and other aquatic animals (McNickle et al. 2006). Invasive vertebrates, such as Burmese pythons, brown tree snakes, cane toads, and fish, can alter the growth rates and population densities of native vertebrates, and in extreme cases eliminate native species altogether through predation, pathogen transmission, resource competition, toxicity, and/or competitive exclusion (Vander Zanden et al. 1999, Phillips et al. 2003, Wiles et al. 2003, Dorcas et al. 2012, Willson 2017). Importantly, the effects of invasive species on ecosystem processes and food web structure can vary based on characteristics of the recipient ecosystem, suggesting that a variety of site-specific factors influence the ecological outcomes of species introductions (Ehrenfeld 2003, Occhipinti-Ambrogi and Savini 2003, Vander Zanden et al. 2003, Swanson et al. 2006).

Despite the profound impacts that invasive species have on ecological systems, surprisingly little is known about how they influence the dynamics of co-occurring anthropogenic pollutants such as Hg. One mechanism by which invasive species may influence movement of Hg through food webs is by altering hydrology, biogeochemistry, and microbial processes that control site-specific MeHg production, facilitating subsequent bioaccumulation. For example, saltcedar (*Tamarix* spp.) introductions across the western U.S. may have modified the hydrology of reservoirs, streams, and floodplains due to evapotranspiration (reviewed in Shafroth et al. (2005)). Likewise, the highly invasive common reed (*Phragmites australis*) forms dense monocultures in both freshwater and brackish systems, excluding other plant and animal species, reducing light penetration, and modifying decomposition rates and nutrient cycling (Meyerson et al. 2000). Similarly, introduced aquatic macrophytes can overwhelm aquatic habitats, particularly under eutrophic conditions. The macrophytic rhizosphere is critical to Hg methylation, and thus has the potential to increase bioavailability to local fauna (Gentes et al. 2013). Although the impact of these nonnative plant introductions on Hg accumulation in resident food webs have not been considered, these examples illustrate the broad ecological changes that invasives can have, and the high probability that these alterations could influence Hg dynamics.

Relatively few studies have directly considered how invasive species influence bioaccumulation of Hg in receiving ecosystems, and most of these have focused on changes in feeding ecology and trophic structure due to introductions. One process that invasive species could affect, that would in turn modify Hg fate, is foraging habitat because where an organism feeds can influence Hg exposure and subsequent Hg bioaccumulation (Power et al. 2002, Karimi et al. 2016a). Indeed, threadfin shad (*Dorosoma petenense*) introduced to a lake in California, USA outcompeted native planktivorous species for zooplankton, causing native fishes to shift from pelagic to benthic prey. The dietary shift resulted in a 50% increase in Hg bioaccumulation in native planktivorous species (Eagles-Smith et al. 2008). Alternatively, introduced species could alter the length of trophic pathways and thus influence Hg dynamics with food webs. For example, introduced rainbow smelt (*Osmerus mordax*) in Canadian lakes feed at slightly higher trophic positions than native forage fish and could thus theoretically expose predatory fish to

higher concentrations of dietary Hg. However, support for this hypothesis is mixed (Evans and Loftus 1987, Franzin et al. 1994, Vander Zanden and Rasmussen 1996, Hrabik et al. 1998, Johnston et al. 2003), possibly because localized water chemistry and rapid growth rates of fish (i.e., growth dilution of Hg) may offset relatively fine-scale changes in trophic position (Swanson et al. 2006).

In light of the diverse effects that introduced species can have on ecological systems and their widespread and growing presence, considerable research is needed to understand how invasive species influence Hg bioaccumulation in native species. The examples above suggest this area is ripe for future research, including the need to understand how invasive species influence Hg bioaccumulation in native species by altering methylation processes, food web structure, feeding ecology, hydrology, and bioenergetics of native species. They also clearly highlight the utility of baseline Hg tissue concentrations to elucidate changes in Hg dynamics pre- and post-introduction, and the importance of considering site-specific factors that may interact during species introductions to influence Hg bioaccumulation.

2.4 Climate Change

Whereas the above global change drivers are examples of localized drivers with a global extent, climate change is a global phenomenon with both global and localized impacts. As a result, it both directly and indirectly influences the aforementioned mechanisms of mercury bioaccumulation (Figure 2). It directly influences each mechanism by exerting changes to physical and chemical properties of the environment, which trigger ecological responses. It indirectly influences them because climate change motivates adaptation in land use (Dale 1997, Gao and Liu 2011) and water storage and conveyance (Christensen et al. 2004, Olden and Naiman 2010), while also creating expanded opportunities for nonnative species invasions (Rahel and Olden 2008) – thereby affecting Hg bioaccumulation mechanisms. As a result, the preceding discussion similarly applies to the influence of climate change on MeHg bioaccumulation and biomagnification through altered hydrology, primary productivity, and food web structure. Climate change can also modulate MeHg bioaccumulation and biomagnification through its influence on bioenergetics.

Because diet is the primary exposure route, MeHg follows energetic pathways through food webs and is tied to an organism's energy expenditure, acquisition, and storage. The link between MeHg bioaccumulation and bioenergetics is most commonly exhibited through growth dilution, whereby Hg concentrations are lower in faster growing individuals with higher growth efficiency than those that grow more slowly and have lower growth efficiency. This process has been demonstrated in both fish (Ward et al. 2010) and birds (Ackerman et al. 2011), and is commonly visible through a negative relationship between Hg concentrations and body condition (Eagles-Smith et al. 2016b, Baumann et al. 2017). Growth efficiency and associated bioenergetics can be influenced by either changes in basal metabolic rate (Dijkstra et al. 2013), activity costs, or food quality (Lepak et al. 2012, Johnson et al. 2015, Karimi et al. 2016a). Thus, environmental conditions, such as temperature, that influence these factors can also modulate MeHg bioaccumulation and biomagnification. For example, global average sea surface temperature has increased by 0.11°C per decade between 1971 and 2010, and is projected to further increase by 1-3°C over the next 50 years (IPCC 2014). Many freshwater systems may endure even higher temperature increases (Magnuson et al. 1997). Microcosm and experimental lab studies have

shown that MeHg concentrations in killifish increased substantially over a 3°C and 7°C temperature gradient, respectively, and changes in concentrations were largely due to increased food consumption to maintain the higher basal metabolic rate associated with warmer water temperatures (Dijkstra et al. 2013). Metabolic allometric scaling theory predicts that higher temperatures and associated metabolic rates will also induce community shifts toward smaller body sizes, which has further trickle-down ramifications for ecosystem metabolic processes (Woodward et al. 2010). Among those relevant to MeHg bioaccumulation, are changes in food quality and energy density (Ficke et al. 2007, Atcheson et al. 2012). Lower energy content in food requires higher consumption rates to meet metabolic needs. Thus, even if MeHg concentrations in prey remain unchanged, MeHg exposure in consumers would increase to meet basal energy requirements. These processes have important implications for evaluating the effectiveness of global Hg reductions because changes in Hg concentrations of sentinel species may respond to both changes in Hg releases as well as extrinsic drivers such as climate change. Thus, strategies for incorporating the role of these extrinsic drivers on Hg bioaccumulation are in need of development.

3.0 Domain 2 – Intrinsic and extrinsic drivers of Hg exposure in humans

Most human populations are exposed to Hg through the consumption of MeHg-contaminated fish, shellfish, and marine mammals (Sheehan et al. 2014), though rice has also emerged as a major MeHg vector in some populations (Zhang et al. 2010, Hsu-Kim et al. 2017). Human exposure to elemental or inorganic Hg can occur from sources that may be present in certain occupational settings and contaminated sites as well as from Hg-containing products. As a result, there can be inherent conflicts when trying to minimize Hg exposure in humans because many of these sources have great value for public health, such as seafood and dental amalgams. Thus, limiting use of those potential sources present their own potential health implications. Although alternatives exist (e.g., Hg-free dental restoration options and low Hg fish choices), they are often limited to more economically developed nations or would result in the elimination of culturally important food items. Thus, predicting risk from MeHg and inorganic Hg exposure in human populations is not only complicated by the global change drivers discussed in **Domain 1** that influence Hg concentrations in food items that humans consume, but also by global economic and societal drivers.

Intrinsic drivers such as genetics influence human exposure, as well as the relationship between actual exposure and the commonly accepted biomarkers that are used to estimate it in humans (i.e., blood Hg concentration reflects exposures to both organic and inorganic Hg, and Hg concentrations in hair and urine reflect exposures to organic and inorganic Hg, respectively). This is an important aspect of understanding human exposure to Hg because standard risk assessments often assume a constant and linear relationship between Hg exposure and different biomarker levels despite evidence of tremendous variability in those relationships (Canuel et al. 2006). The potential lack of predictable concordance between MeHg or inorganic Hg exposure in humans and common biomarkers of exposure can have strong implications for the use of these surveillance and monitoring tools in risk assessments of Hg exposure, as well as epidemiological studies of potential health effects.

In this section, we examine the key drivers associated with Hg risk in humans that scale from genetic variability to global socioeconomic influences. Specifically, we describe key

socioeconomic factors that that influence exposure patterns in different cultures and populations as well as extrinsic and intrinsic individual-level factors that modify (i.e., confound, moderate, or mediate) Hg exposure and assimilation.

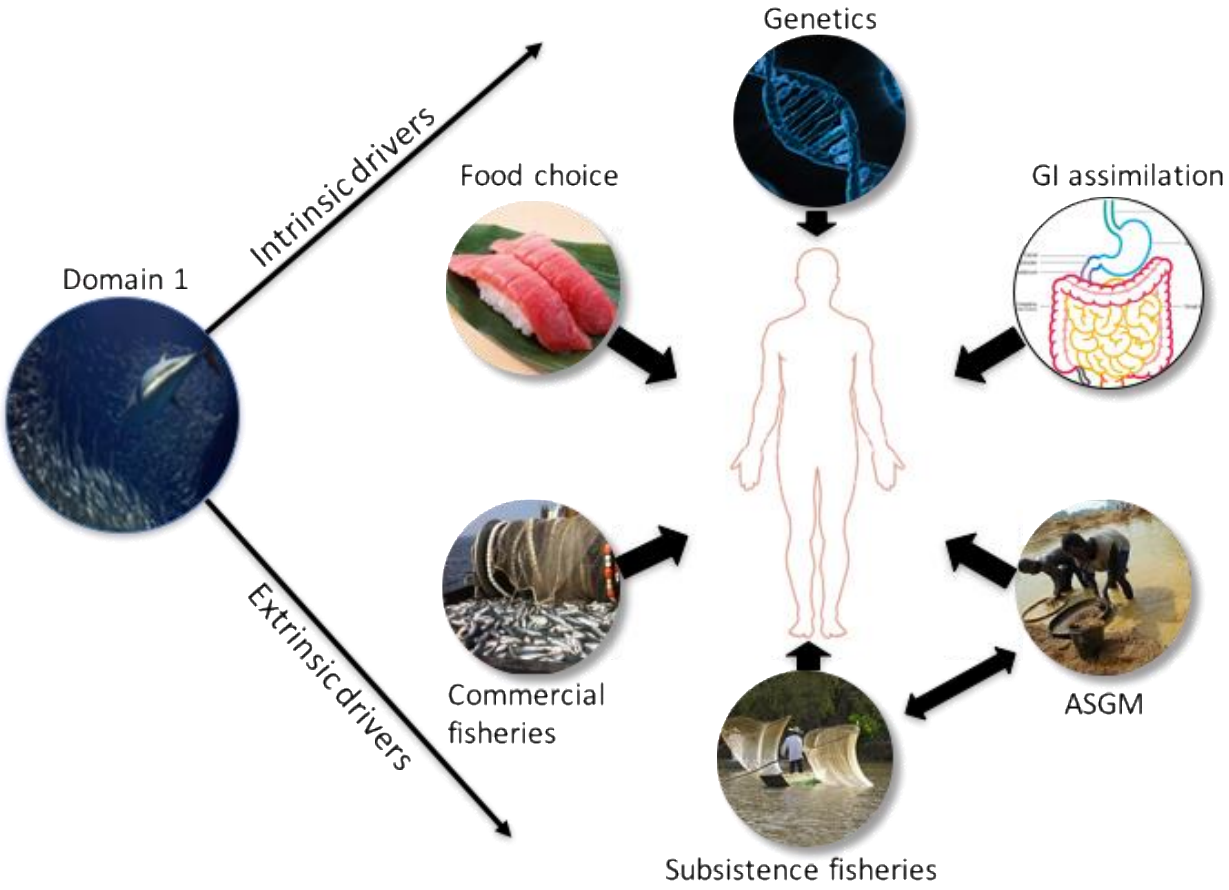

Figure 3*. Domain 2 represents extrinsic and intrinsic drivers that influence mercury exposure in human populations. Domain 2 is influenced by the extrinsic drivers discussed in Domain 1 as they relate to human exposure to MeHg through the consumption of Hg-contaminated fish.*

3.1.0 Socioeconomic drivers - extrinsic

3.1.1 Subsistence fishing, high-end economic fish, and rice

Socioeconomic status is a common factor that drives disparities in mercury exposure among communities (Nriagu et al. 2012). The relationships between socioeconomic status and MeHg exposure in humans does not follow a linear response and is complicated by the numerous pathways of exposure. Both poverty and wealth portend risk for many communities, creating challenges in policies needed to reduce risk, and predicting how risks will change with shifts in global trade and economic development. In industrialized nations, lower income urban anglers, especially minority and immigrant populations, can be at particularly high risk because they are more likely to consume self-caught rather than store-bought fish, and often anglers target predatory species with the highest Hg concentrations (Nriagu et al. 2012, Lauber et al. 2017).

Risks of exposure to Hg and other environmental contaminants are also elevated for these populations because they are less-likely to trust and/or adhere to fish consumption advisories (Perez et al. 2012, Niederdeppe et al. 2015). At the other end of the scale, individuals more frequently consuming tuna steak or swordfish, typically those in higher socioeconomic populations, are also at increased risks for elevated Hg exposures (Hightower and Moore 2003, Mahaffey et al. 2009, Karimi et al. 2014, Goodrich et al. 2016). A third group includes Indigenous populations and rural subsistence fishing communities in resource-limited regions (Chan et al. 2003). Coastal Indigenous groups represent approximately 0.4% of the global human population, but they consume an amount of fish equal to 2% of the global commercial catch (Cisneros-Montemayor et al. 2016), and their average per-capita consumption of seafood is 15 times higher than national averages (Cisneros-Montemayor et al. 2016). One of the most impacted coastal groups are circumpolar Inuit populations who have among the world's highest MeHg exposures due to their particularly high reliance on marine mammals and fish, though rapid changes in climate, food availability, and dietary choices is complicating risk assessments (AMAP 2015). Thus, fish consumption in many of these communities often not only serves as a critical source of protein, but also has a strong cultural connection, presenting unique social justice and risk communication complications. Encouraging those communities to consume alternative fish species with lower Hg concentrations may benefit their health while jeopardizing key aspects of their heritage, whereas maintaining traditional practices may have negative health consequences. Additionally, recent evidence suggests that some rural Asian populations receive the majority of their MeHg exposure through rice consumption (Zhang et al. 2010). The magnitude and extent of MeHg exposure risk through rice is still not yet determined, but appears particularly acute in rural areas with Hg-contaminated soils (Feng et al. 2008). A related, but relatively uninvestigated pathway includes populations that integrate aquaculture with rice agriculture. The propensity of rice paddies to facilitate MeHg production (Windham-Myers et al. 2014) could present unique risks to consumers of fish associated with this practice, particularly in areas with ASGM activities or legacy mining impacts (Feng et al. 2008, Krisnayanti et al. 2012).

As countries continue to develop, and economies shift in response to globalization, population growth, and resource availability, the portfolio of exposure risk of distinctive populations will also likely change differentially. Similarly, continued exploitation of fisheries and "fishing down" marine food webs (Pauly et al. 1998, Essington et al. 2006, Baum and Worm 2009) will likely influence MeHg concentrations of common market fish, changing exposure risk of the regions to which those species are commonly sold (see Box 2).

3.1.2 Artisanal small-scale gold mining (ASGM) and mercury mining

Socioeconomic trends can also influence human exposure to inorganic Hg, particularly sources associated with artisanal small-scale gold mining (ASGM). This mining is carried out in over 70 countries (mainly those with low- and middle-income economies) by approximately 10-15 million miners, including approximately 4-5 million women and children (UNEP 2013, WHO 2016). Within ASGM communities, elemental Hg is used to amalgamate gold from processed ore, the amalgam is subsequently heated to burn off the Hg as a vapor, leaving a concentrated gold ore. Annual Hg emissions from ASGM are estimated at 727 tonnes, making this the largest sector accounting for more than 35% of total global anthropogenic emissions of Hg (UNEP 2013). It has been argued that ASGM is a poverty-driven activity with pertinent micro- and

macro-economic drivers as well as push-pull factors (Hilson and Garforth 2012, Wilson et al. 2015). Biomonitoring surveys of ASGM workers and community members show that they have among the highest Hg exposures of any group worldwide (Gibb and O'Leary 2014, Basu et al. 2015b). This is not surprising considering the high amounts of Hg used in the practice, the limited use of personal protective equipment or Hg-free or reduction techniques, and the overall rudimentary nature of most ASGM sites. These are further exacerbated by the fact that most ASGM operations are informal (and illegal in many countries) and thus they sit outside regulatory and public health support programs.

3.1.3 Medical, Personal Care, and Cultural Use

Although fish consumption and ASGM are the dominant drivers of Hg exposure to most humans, other sources such as medical and personal care products can be important contributors for specific subsets of individuals. Historically, Hg was used for therapeutic medical purposes such as treatment for syphilis and as a component in teething powders (Clarkson and Magos 2006). These uses have been phased out, but modern medical applications still exist with Hg as a component of dental amalgams and vaccines. These uses have generated controversy because of the known toxicity of Hg. Public health weight of evidence is somewhat equivocal, but generally has not pointed to adverse health outcomes associated with amalgams (Clarkson and Magos 2006) or vaccines (Stratton et al. 2001). However, newly-developing biomarkers of sensitivity and subtle adverse effects (see Domain 3) may further inform this topic (Branco et al. 2017, Crowe et al. 2017, Dorea 2017, Modabbernia et al. 2017). Voluntary steps to reduce uses of mercury in medicine have been taken by many producers and in many countries, but it still represents a significant source of Hg to many populations and thus should to be considered in cumulative exposure assessments.

Cultural norms, traditions, and religious ceremonies are additional extrinsic drivers that can influence Hg exposure (particularly inorganic and elemental Hg) in certain human populations. Application of skin lightening creams to achieve desired physical appearances is a common practice in some populations, with prevalence rates commonly as high as 50% in some countries (Dlova et al. 2015, Lartey et al. 2017). Unregulated products often contain either Hg or calomel, or Hg is intentionally added by the user (Copan et al. 2015). Mercury exposure also occurs through certain ethno-medical and religious practices such as sprinkling elemental Hg on the floor of the home or burning it in candles to ward off evil spirits (Zayas and Ozuah 1996, Masur 2011). In 2005, a population-based study in New York City, found that women from Dominican and Caribbean cultures had higher urine Hg levels than those from other cultural groups (McKelvey et al. 2011), and this increased exposure was correlated with both the use of Hg-containing skin-lightening creams (as mentioned previously) and the use of elemental Hg in religious and ethnic practices. Similarly, a separate study of prenatal exposures to Hg in a US population of predominately Caribbean immigrants found that maternal urine Hg levels were associated with religious use of Hg during pregnancy including candle burning and religious charm use, while cord blood Hg levels were associated with fish consumption during pregnancy (Geer et al. 2012). These studies from cultures with specific religious uses were conducted in the US, and while public health resources are available to these US immigrants in order to reduce risks for Hg exposure, the founder populations in other countries may not have the same level of access. Thus, these published exposure risks may be significantly higher in other countries (Johnson 1999, Riley et al. 2001, Newby et al. 2006).

3.2.0 Individual level drivers – Intrinsic

3.2.1 Genetics

Exposure biomarkers (e.g. blood, hair, or urine Hg concentrations) are important tools for monitoring and estimating Hg exposure in human populations. However, discrepancies exist in relationships between actual exposure as measured through dietary intake or inhalation estimates and realized exposure as measured through biomarkers (Christensen et al. 2016, Awata et al. 2017, Branco et al. 2017), suggesting that there are other drivers controlling the pathway from actual to realized exposure. Over the past decade research has shown that genetic and epigenetic factors may influence realized Hg exposure (reviewed by (Basu et al. 2014, Llop et al. 2015). For example, using data from a group of 469 dental professionals, Basu et al. (2014) estimated Hg intake through self-reported seafood consumption surveys, measured hair Hg levels, and genotyped all participants to try and better understand whether genetic information can be used to help improve exposure assessments. As expected, estimated Hg intake and hair Hg levels were positively correlated, but there was an interaction between Hg intake and genotype such that the intake-biomarker relationships differed among genotypes. Specifically, among avid fish consumers (i.e., those who ate six cans of tuna per week), there was an 8-fold difference in average hair Hg levels (0.7- 6.2 μg/g) among those with different versions of *SEPP1* (rs7579) gene. Additionally, cross-sectional studies from across the world are showing that polymorphisms in certain environmentally responsive genes (e.g., glutathione, metallothionein, and selenoenzyme families) can be associated with the main effect (i.e., carriers of wildtype and variant forms have different Hg biomarker levels) and gene-environment interactions (i.e., exposure-biomarker relationships are different between carriers of the wildtype and variant form). Such observations have been made on studies involving distinct populations, including dentists (Wang et al. 2011, Parajuli et al. 2016), students (Gundacker et al. 2007, Gundacker et al. 2009), indigenous riverine populations (Barcelos et al. 2013, Barcelos et al. 2015) and gold miners (Custodio et al. 2005, Harari et al. 2012, Engstrom et al. 2013). Despite the expanding breadth of information on this topic, research to date has largely focused on adults and much less is known about either early-life exposure situations or changes across the life course. Further, most of the studies have focused on populations mainly exposed to elevated inorganic Hg sources, with MeHg exposures generally within background levels. Finally, there remain inconsistent findings across studies (see reviews by Basu et al. (2014) and Llop et al. 2015) which is limiting adoption of genetics into Hg risk assessment. If genetics plays a role in pharmacodynamic routing and tissue distribution, then similar exposure profiles among individuals can result in large differences in biomarker concentrations. This not only influences the utility of biomarkers for estimating risk, but may also be important for determining the sensitivity of individuals to Hg exposure. In addition to genetics, there is some emerging evidence from both animals (Pilsner et al. 2010, Basu et al. 2013) and humans (Hanna et al. 2012, Goodrich et al. 2013) to suggest that Hg is epigenetically active, and that Hg-induced methylation of certain genes is also associated with either a main effect of Hg or a gene-environment interaction.

3.3.2 Gastrointestinal Factors

Despite the common assumption that most (>95%) ingested MeHg is bioavailable, substantial evidence exists suggesting that this may be an erroneous assumption. In particular, a review by Bradley et al. (2017) identified a range of MeHg bioavailability in seafood between 12 and 79%

across 20 different studies. Factors such as type of seafood, cooking method, and the presence of certain nutrients all affected Hg bioavailability. More recently the impact of the gut microbiome has received attention for its role in the excretion of MeHg (Rothenberg et al, 2016; Rand et al, 2016) because microbiota in the gut can both affect the speciation of Hg prior to absorption or elimination. Thus, inaccuracies likely exist in estimates of exposure and risk that assume constant assimilation efficiencies.

Box 1: ASGM as an example of extrinsic global drivers of human Hg exposure

The prevalence and extent of ASGM is largely driven by local, community, and cultural factors, but global scale drivers, such as economic market trends are also important determinants. For example, sudden changes in the global price of gold have also been related to the importation of Hg and the expansion of ASGM areas in Peru over the period from 2003 to 2008 (Swenson et al. 2011). Over this period, which included the global economic crash, the price of gold rose markedly and reported Hg imports into Peru increased by 42%. Based upon satellite imagery, rates of forest conversion to mining increased six-fold during this time period. Combining all these data, the authors reported strong correlations among these covariates as shown in Figure 3 in a striking demonstration of the importance of global economics as a driver of Hg use and ecological degradation in ASGM regions.

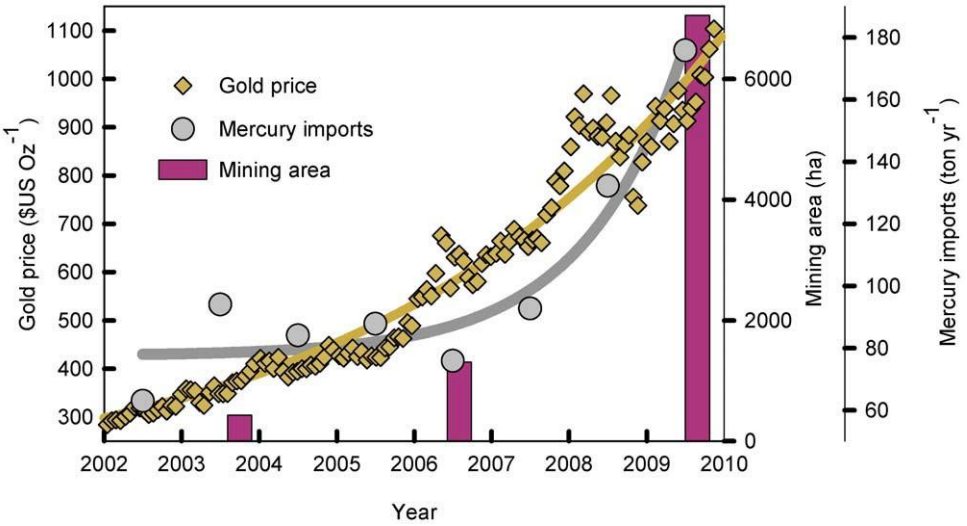

Figure 4*. Relationships between international gold prices, Peruvian Hg imports, and extent of ASGM mining area. Reprinted from Swenson et al. 2011*

Similarly, ASGM gold production in Ghana increased 15-fold between 1995 and 2014 in response to a roughly 6-fold increase in the price of gold. During that time frame, the number of ASGM miners in Ghana rose 33-fold, from approximately 30,000 in 1995 to 1 million workers in 2010, and forest cover decreased from 32.7% to 21.7%. Although estimates of Hg imports are difficult to obtain, limited estimates indicate that they increased from 272 kg Hg in 2010 when approximately 21,000 kg of gold was produced by 1 million ASGM workers to 2015 kg of Hg imported in 2013 when more than 41,000 kg of gold was produced.

End Box 1

Box 2: Global scale change for fish

Worldwide the most important source of Hg for human populations is the consumption of contaminated seafood. The amount of Hg that ends up in commercially available seafood is dependent upon a range of ecological factors such as atmospheric loading rates, ecosystem-specific properties, and food web structure (Selin et al. 2010, Sunderland and Selin 2013), as well as socio-economic factors such as market supply and demand. Of all seafood, the presence of Hg in tuna from the commercial market is often the most dominant source for human consumption (e.g., US – (Sunderland 2007, Karimi et al. 2012); Japan – (Nakagawa et al. 1997, Yamashita et al. 2005); Mexico - (Cantoral et al. 2017)). Over the past decades the consumption of tuna associated with sashimi has expanded from the Japanese market to a global one, and associated with this are new distribution systems in which large supermarket and retailors are being favored over fish markets and auctions. Canned tuna production and demand continues to rise, with key markets being the United States, the European Union, and Japan. However, with increasing wealth elsewhere these regions are also declining as a percentage of the world market.

The global demand and preferences for specific fish species has also had substantial effects on the composition and structure of marine food webs (Pauly et al. 2005, Daskalov et al. 2007). In particular, global markets for upper trophic level species has reduced the mean trophic level and average size of fish harvested over the past several decades (Pauly et al. 1998, Pauly et al. 2005). Simultaneously, global demand to support the growing market for fish oil and fishmeal has resulted in substantial increases for harvest of "forage fish" species that occupy lower trophic positions (Essington et al. 2006, McClanahan et al. 2015). These harvest-induced changes to marine food webs certainly have implications for Hg concentrations in market fish and human exposure, but these relationships have not been thoroughly investigated. Finally, aquaculture production has increased dramatically over the past 3 decades, particularly in Asia (Jennings et al. 2016), and currently represents 44% of total global seafood production (Lopes et al. 2017). Farmed seafood has been shown to contain substantially lower Hg concentrations than taxonomically-related wild caught seafood (Karimi et al. 2012), providing a mechanism for reducing Hg exposure in some consumers. However, the context-dependent implications of these trends is uncertain for future trajectories of Hg exposure to different populations. Additionally, responses of fisheries to global change drivers as discussed in Domain 1 represents a key area of uncertainty that is likely to be extremely consequential for influencing human exposure to Hg.

End Box 2

4.0 Domain 3 – Interacting drivers that modulate Hg toxicity and risk to humans and wildlife

Mercury exposure can affect multiple organ systems, and manifests in diverse adverse outcomes in humans, fish, and wildlife. The devastating neurological impacts of acute, high-level MeHg and elemental Hg exposure are well documented, but chronic, low level exposure also has important health impacts that are less well understood. A number of recent reviews have summarized the range of outcomes, known mechanisms, and toxicity benchmarks associated with different levels of Hg exposure or *in situ* Hg concentrations in humans (Karagas et al. 2012, Sheehan et al. 2014, Ha et al. 2017), fish (Depew et al. 2012a, Wiener et al. 2012), and wildlife (Scheuhammer and Sandheinrich 2008, Depew et al. 2012b). Together, this comprehensive collection of reviews highlights both the pervasive occurrence of deleterious effects associated with environmentally-relevant Hg exposures, as well as the tremendous variability in the range

of exposures that induce those effects. The variability in Hg sensitivity suggests that the onset of Hg toxicity is likely mediated by various intrinsic and extrinsic interactive factors. In this section, we examine potential interactions between Hg and other drivers that also affect the processes, mechanisms, and outcomes of Hg toxicity. These drivers represent a range of scales and, where applicable, we relate these drivers that modulate the effects of Hg with the extrinsic drivers described in Domains 1 and 2. Because toxicity of Hg is ultimately a physiological process, we do not separate human outcomes from wildlife or other animals, but instead integrate examples from across taxa where relevant.

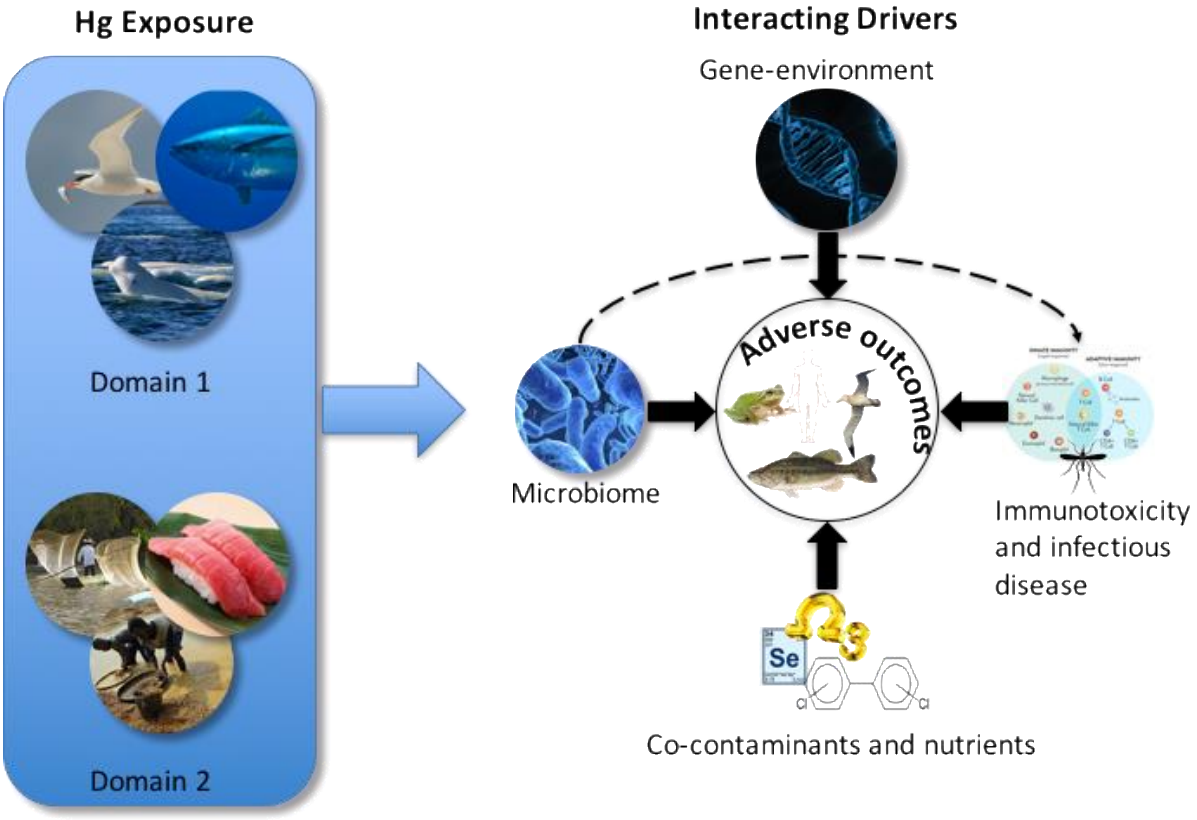

Figure 5*. Conceptual model for Domain 3 evaluating interactions between Hg exposure and its drivers with key intrinsic and extrinsic drivers on adverse outcomes.*

For purposes of this synthesis, we examine the interactions of Hg with various drivers that modulate organism health – such as the microbiome, infectious disease, co-exposures to other toxicants, diet and nutrition, and genetics. These interactions are not exclusive to one another, but for simplicity we evaluate each one independently. The true interactions are possibly much more complex when aspects of more than one of these interactions occur together. Drivers may: 1) chemically modify Hg, as discussed in the topic *microbiological factors*; 2) modify associations between Hg exposure and disease, as discussed in the topic of *infectious disease*; 3) affect risk of adverse effects, as discussed in the topics of *diet and co-contaminants*; or 4) independently increase risks of Hg-associated outcomes, as in the topic of *genetics*.

4.1 Microbiological factors - the microbiome and antibiotic resistance

The microorganisms living commensally in and on humans and other animals exceed the number of somatic cells by a factor of 10 or more (Turnbaugh et al. 2007), and contain a number of genes that code for functions that support host physiology (Huttenhower et al. 2012). The aggregate genetic information encoded by these microbial communities is defined as the microbiome, and its recognition over the past decade has produced a paradigm shift regarding the role it plays in human and animal health (Kau et al. 2011, Muegge et al. 2011) . The gut microbiome, in particular, is critical for immune function (Thaiss et al. 2016), nutrition (David et al. 2014), and xenobiotic metabolism (Dietert and Silbergeld 2015). Much is still unknown about the interaction between the microbiome and Hg exposure, but emerging evidence suggests complex interactions resulting in both positive and negative outcomes related to organism health. For example, the gut microbiome can act as a co-factor that alters the toxicity of Hg by changing its speciation or by sequestering Hg prior to absorption through biosorption and intracellular accumulation (Gadd 2010). The microbial genes responsible for Hg methylation have recently been found in both the vertebrate and invertebrate gut microbiome (Gilmour et al. 2013), and experimental studies have documented substantial Hg methylation within the digestive tracts of vertebrates (Rowland et al. 1975, Wang et al. 2013, Martin-Doimeadios et al. 2017). Moreover, emerging empirical evidence suggests that the gut microbiome also may demethylate Hg (Rowland et al. 1984, Wang et al. 2017), potentially reducing its toxicity.

The relationship between Hg, the gut microbiome, and host organisms extends beyond alterations to the toxicity of Hg to the host. Mercury sensitivity is common among microorganisms, and relatively low exposures may be lethal to many strains. Thus, the gut microbiome can also interact with Hg in a fashion whereby Hg exposure alters the gut microbiome itself, potentially affecting organism health (Madan et al. 2012). Mercury-induced changes to the microbiome can alter certain functional groups that are important for host physiology and health (Li et al. 2008). However, the scientific evidence regarding the extent and importance of these outcomes is only starting to be generated and significant research is still needed. Some of this risk of Hg toxicity to the microbiome is ameliorated by Hg resistant genes that have evolved in many bacterial strains (Pal et al. 2015), and these genes can be exchanged among bacteria through horizontal gene transfer. Importantly, the Hg resistance genes are commonly associated and co-located with genes that also confer antibiotic resistance (Skurnik et al. 2010). Thus, Hg exposure can co-select for microbial communities in the gut that are resistant to both Hg and multiple antimicrobials (Li et al. 2017). The interaction between Hg and antimicrobial resistance may be a particularly significant impact of Hg on the health of biota.

Antibiotic resistance is among the most pressing public health threats (Levy and Marshall 2004), and progress managing it remains a significant challenge. The potential contribution of Hg exposure to this expanding crisis has profound implications for the role of Hg in global health. However, only limited evidence exist regarding the magnitude of Hg's contribution to global antibiotic resistance. The correlation between Hg exposure and antibiotic resistance, emerged in the 1990s with the observation that dental amalgam contributed to shifts in fecal bacteria, with a higher proportion of Hg resistant genes present relative to before amalgam installation (Summers et al. 1993, Wireman et al. 1997). Resistance to antibiotics was substantially more prevalent in Hg resistant strains of bacteria than those that were Hg sensitive (Summers et al. 1993, Wireman

et al. 1997). More recently, is was shown that Wayampi Amerindians from French Guyana, with high Hg exposure but limited access to antibiotic medication and little contact with the outside world had a higher prevalence of antibiotic resistant *E. coli* in fecal samples than Europeans with low Hg exposure and ready access to modern health care (Skurnik et al. 2010). More broadly, a study across 2,522 fully sequenced bacterial genomes and 4,582 plasmids from a range of environments found substantial co-occurrence patterns between Hg resistance and antibiotic resistance genes (Pal et al. 2015). Moreover, antibiotic resistance was 2.5-10 times more prevalent in strains with varying Hg resistance genes than those without Hg resistance genes (Pal et al. 2015). That study also found that humans and domestic animals were among the host environments with the most prevalent co-occurrence of Hg resistance and antibiotic resistance. Moreover, many of the strains that exhibited co-occurrence were of pathogenic clinical significance, such as *Escherichia*, *Staphylococcus*, *Salmonella*, and *Klebsiella*. Still, little is yet known about the prevalence of Hg and antibiotic resistance co-selection across different types of host taxa and its ubiquity in the environment. Recent work does suggest that co-selection extends to fish, where Hg exposure selected for gut microbiomes with up to 8-fold higher abundance of Hg-resistance genes, and resistance to multiple antibiotics was more common in Hg-resistant, as opposed to Hg-sensitive, bacterial colonies (Meredith et al. 2012, Lloyd et al. 2016).

Much more research is needed on the significance of this co-selection, but given the threat posed by antibacterial resistance to the health of humans and the environment, as well food security, it may have substantial, and as yet unquantified, implications regarding the health impacts of Hg exposure. Finally, the antibiotic resistance connection with Hg may have important feedback loops with the adverse effects of Hg too because both inorganic and MeHg exposure can suppress immune function, increasing the likelihood of pathogenic infection.

4.2 Immunotoxic effects of mercury and interactions with pathogens

One of the major health threats associated with global changes such as invasive species and shifting climate is the potential emergence, resurgence, and redistribution of infectious disease (Wu et al. 2016). These anticipated changes create the potential for interacting risks between infectious disease and Hg exposure because Hg also affects immune function (Sweet and Zelikoff 2001, Crowe et al. 2017). Substantially less is known about immunotoxic effects of low level exposures to various Hg species, but within the last decade a growing body of evidence in animal models (Nyland et al. 2012), wild animals (Fallacara et al. 2011, Lewis et al. 2013, Desforges et al. 2016, Becker et al. 2017), and humans (Sweet and Zelikoff 2001, Silbergeld et al. 2010) points to a range of immune system interactions with exposures to elemental, inorganic and methyl Hg. Different Hg species induce different types of immunotoxic responses (Gardner et al. 2010a), and the mechanisms of immunotoxicity depend upon the magnitude of Hg exposure: higher exposures can affect the abundance of those cells responsible for mounting an immune response (dendritic, B, and T cells), impacting the majority of the production of cytokine signals. Conversely, at lower level exposures only the production of those cytokine signals is affected, without changes in cell counts (Silva et al. 2005b). This means that at lower exposure there is a potential for recovery if the cells producing the cytokines can be returned to basal function, but at higher exposures, death of those immune cells that respond appropriately to infection makes cell recovery impossible. Additionally, like the nervous system, the immune system in many species, including humans, undergoes extensive pre- and post-natal development. Early exposures to Hg that are limited to *in utero* and early postnatal stages appear

to reprogram the adult immune system long after exposure ceases (Silva et al. 2005a). This has long-lasting impacts on the ability of the immune system to respond appropriately. The basic immune response is modified by these early exposures differently in males and females and those changes affect the response to stimuli even into adulthood. Thus, males and females exposed to Hg early in life may have different risks in adulthood for autoimmunity and different responses to infection (Silva et al. 2005a).

The complexities of the interactions between immune function, disease, and Hg exposure are exemplified in experimental studies of the interactions between Hg and Coxsackievirus B3 infections. Early evidence indicated that viral infections themselves altered concentrations of Hg in target organs (Ilback et al. 2008), and the interaction between Hg exposure and disease response was dependent upon the relative timing of pathogen and Hg exposure. The virus alone can cause autoimmune myocarditis, whereas Hg alone has no myocarditic effect. However, when Hg exposure occurs prior to viral infection the severity of autoimmune myocarditis is substantially increased despite no changes in viral infectivity (Nyland et al. 2012). Conversely, Hg exposure after viral infection did not alter the severity of myocarditis in comparison to subjects that were not exposed to Hg (Nyland et al. 2012).

Despite experimental, correlational, and epidemiological evidence of Hg immunotoxicity, inconsistencies among studies, particularly those in human populations, have prevented rigorous risk assessments for effects of Hg immunological health. Some of these inconsistencies may be related to failure to account for other interacting cofactors that also are important aspects of the Hg-immunotoxicology link. For example, there was limited evidence of a relationship between blood Hg concentrations and either measles or rubella antibodies in a sample population of 692 children from the U.S., but after stratifying based upon key nutritional status indicators, the population with specific nutritional deficiencies (high MMA, low folate, high homocysteine) exhibited a positive relationship between blood Hg concentrations and antibody titers for the two viruses (Gallagher et al. 2011, Gallagher et al. 2013). Other inconsistencies exist between indices of autoimmunity and Hg exposure. Specifically, increased risks for autoimmune dysfunction, as determined by elevated serum titers of autoantibodies such as anti-nuclear autoantibodies (ANA), have been demonstrated for certain Hg-exposed populations in South America in comparison to unexposed groups (Silva et al. 2004, Gardner et al. 2010b, Nyland et al. 2011). However, no evidence for such an association was found in Hg-exposed European and US populations (Crowe et al. 2015, Monastero et al. 2017). A body of work described below suggests that an interaction between Hg and malaria exposure may be a triggering event that is responsible for Hg-induced autoimmunity in some populations but not others.

Box 3: Mercury and Malaria

The relationship between Hg and malaria represents one of the most complex known interactions between Hg and the immune system, and malaria acts as a global driver that may influence Hg toxicity. Human response to malaria infection involves several layers of immediate and chronic events in the life cycle of the parasite, as well as interactions between activation and suppression of immune response, all of which may be affected by Hg. Specifically, Hg exposure interacts with the human immune system to impair host resistance to the parasite (Silbergeld et al. 2000), increasing the likelihood of infection. Mercury also compromises the development of acquired immunity to malaria and may result in increased severity of symptoms from infection (Silbergeld

et al. 2000). Additionally, Hg exposure that occurs subsequent to malarial infection induces autoimmune dysfunction. Epidemiological studies in areas with endemic malaria coupled with exposures to Hg through artisanal and small-scale gold mining (ASGM) and contaminated fish consumption found increased malaria infection rates in those populations (Dorea et al. 2003, Dorea et al. 2005). Additionally, biomarkers of autoimmune dysfunction were common in Hg exposed populations with a history of malaria contraction, whereas biomarkers were not detected in Hg exposed populations with limited malaria exposure (Motts et al. 2014).

Malaria-endemic areas of the world exhibit a substantial geographic overlap with major regions of ASGM. This creates a nexus for potential interactions between Hg and malaria exposure that can exacerbate the deleterious effects associated with these individual stressors. Evidence of these interactions exist from studies in Brazil (Duarte and Fontes 2002). Increases in gold prices stimulated expansion of ASGM activities throughout Amazonia, and physical activities associated with mining, coupled with increased human occupancy resulting in rapid increases in the incidence of malaria infections. Specifically, the alteration to stream habitats created increased breeding habitat for *Anopheles* mosquito vectors of malaria (de Oliveira et al. 2013). Additionally, much of the population attracted to gold mining in remote areas for work and economic gain were immunologically naïve in terms of exposure to malaria and potentially more likely to contract malaria (Doolan et al. 2009). As the workers moved back and forth between the mining areas and their places of origin, they transported malaria with them, increasing rates of infection outside Amazonia (Silbergeld et al. 2002). Thus, global socioeconomic drivers (gold prices) influenced human exposure to Hg in this region, which indirectly contributed to the spread of malaria to more populated regions. Additionally, given the documented interactions between Hg and malaria, it is conceivable that human health was additionally compromised.

Cumulatively, this series of findings has public health implications and suggests that interactions between Hg and infectious disease may be an understudied but highly relevant aspect of Hg risks to human and ecological health. Additionally, the distribution of many pathogens is currently being altered by climate change, which is facilitating the spread of their intermediate hosts (Wu et al. 2016). Indeed, models predict that under a range of forecasted climate scenarios, the distribution of malaria is likely to expand or change, particularly into higher elevations of tropical latitudes (Caminade et al. 2014). Further quantification of the health implications associated with the malaria-Hg interaction will facilitate estimates of future risks.
End Box 3

4.3Nutrients and co-contaminants

Nutrients and other contaminants can have substantial ameliorative or exacerbating influences on Hg toxicity, complicating risk estimates associated with Hg exposure (Rice 2008). Although there are potentially limitless combinations of co-exposure mixtures that may influence outcomes of Hg exposure, the most common include selenium (Se; (Cuvin-Aralar and Furness 1991, Hu et al. 2017), other biomagnifying contaminants such as PCBs and other halogenated organic compounds (Braune et al. 2005, Burgess et al. 2005), co-occurring contaminants in point-source situations such as lead and arsenic in mining areas (Basu et al. 2011, Basu et al. 2015a), and dietary nutrients like omega-3 fatty acids (Gribble et al. 2016). Of these, Se is arguably the most compelling, because of the potential magnitude of the antagonism, the extreme complexity of the interaction, and of the items listed above it has evoked the greatest discussion

and debate with no clear consensus. The antagonistic relationship between Hg and Se has generated a broad body of literature that has supported numerous review articles (Cuvin-Aralar and Furness 1991, Luque-Garcia et al. 2013, Bjorklund et al. 2017). Both *in vitro* and *in situ* studies from field and lab settings have demonstrated reduced severity of inorganic Hg and MeHg toxicity in response to Se exposure, but the degree of amelioration is at least partially dependent upon the Se species used and its exposure route. Selenite and organic Se compounds (selenocysteine and selenomethionine) tend to be more protective than species such as selenate (Cuvin-Aralar and Furness 1991, Khan and Wang 2009, Dang and Wang 2011). Although a consensus is still lacking, the ameliorative effects of Se on Hg toxicity have been postulated to act through a range of mechanisms, including reducing assimilation and facilitating elimination of MeHg (Bjerregaard et al. 2011, Bjerregaard and Christensen 2012, Li et al. 2012, Huang et al. 2013), rendering Hg biologically unavailable through covalent bonding between Hg and Se (Yang et al. 2008), demethylation of MeHg in the liver or other organs (Eagles-Smith et al. 2009, Khan and Wang 2009), or through supporting the glutathione antioxidant pathway (Sormo et al. 2011). Various degrees of empirical support exist for each of these mechanisms, highlighting both the complexity of the Hg-Se interaction as well as its ubiquity across physiological processes. One commonly referenced concept emerging from the body of work on Hg-Se interactions is the contention that Se:Hg molar ratios greater than 1 confer protection from manifestations of Hg toxicity, whereas molar ratios less than 1 indicate a lack of protection from Se. This hypothesis served as a foundational concept for a more recently posited mechanism that Hg toxicity acts through irreversible binding with Se, thereby interrupting the synthesis of critical selenoenzymes, creating a Se deficiency syndrome that disrupts many aspects of an organism's physiology (Ralston and Raymond 2010). According to this proposed mechanism, amounts of Se sufficient to exceed a Se:Hg molar ratio of 1 in either diet or tissues would confer a protective effect against MeHg toxicity. Though intriguing, there are studies that serve as exceptions to this logic as discussed below, challenging the validity of this hypothesis.

The abundance of studies demonstrating antagonism between Hg and Se across taxa and endpoints clearly suggests that Se plays a critical role in modulating Hg risk. However, substantial uncertainty still exists regarding the quantitative protective action of Se against MeHg toxicity. Moreover, contemporary research continues to demonstrate a lack of clarity regarding whether Se provides universal protection for MeHg exposure, or is specific to only some mechanisms of action, such as neurotoxicity. For example, dietary selenocysteine did not reduce MeHg uptake, nor enhance Hg elimination in captive mink (Evans et al. 2016). Additionally, MeHg toxicity in harbor seal lymphocytes was not ameliorated by Se, even at molar ratios up to 10:1 (Das et al. 2016), whereas similar studies in Beluga whales indicated only limited protection from Se at the highest MeHg doses (Frouin et al. 2012). Perhaps most important in terms of deviations from the idea of Hg-Se antagonism is their interaction with respect to reproduction. Recent studies have documented deleterious synergistic relationships between Hg and Se to both bird (Heinz et al. 2012) and fish (Penglase et al. 2014) reproduction. Specifically, at elevated Se exposures Hg appears to exacerbate Se-induced reproductive toxicity. Few studies have experimentally tested this deviance relative to other Hg-Se outcomes, thus it is unclear if these interactions are constrained to only egg laying species, or if viviparous placental reproduction is subject to a similar synergism. Regardless, these experimental findings highlight the need to continue developing a quantitative understanding of the mechanistic role of Se across Hg toxicity

endpoints, and they suggest that application of the Se:Hg molar ratio may not be the panacea some propose for determining Hg risk to humans and wildlife.

Other dietary nutrients may also interact to offset the deleterious effects of MeHg exposure, though not as directly as occurs with Se. Interactions with omega-3 fatty acids, such as eicopentaenoic acid (EPA) and docosahexaenoic acid (DHA), are of particular interest because of their known health benefits and co-occurrence at high concentrations with Hg in many marine fish species (Mozaffarian and Rimm 2006, Gribble et al. 2016). The potential interactions with Hg have largely focused on neurodevelopmental and cardiovascular endpoints. In general, limited evidence exists for substantial antagonism with Hg, though some studies have found that accounting for omega-3 fatty acid or fish intake can improve estimates of Hg impairment for certain populations, suggesting that these fatty acids might have an ameliorating effect (Oken et al. 2008, Choi et al. 2014). Others have found that when populations are stratified by their levels of omega-3 fatty acids, relationships between Hg exposure and adverse outcome biomarkers such as oxidative stress tend to be enhanced in those with low omega-3 levels, and weakened in those with high omega-3 levels (Karimi et al. 2016b). The specific mechanisms underlying any potential protective effects of nutrients on MeHg toxicity is not fully elucidated (Ha et al. 2017). Since MeHg and these nutrients often occur in the same exposure sources and affect the same endpoints, they can confound efforts to quantify their effects. Despite this, the benefits of fish consumption on health parameters is well known, and developing quantitative tools to better determine the risk –benefit coefficient is needed to facilitate recommendations regarding how to balance potential health concerns over MeHg exposure against the benefits afforded by key nutrients found in seafood (Chapman and Chan 2000).

Whereas nutrients such as Se and omega-3 fatty acids can help offset the negative consequences of Hg exposure, co-exposure to other contaminants can have the opposite effects. Of particular concern are other biomagnifying contaminants, such as PCBs and other organohalogenated compounds that may co-accumulate with MeHg and also affect the same physiological systems impaired by Hg. Similar to fatty acids, many other bioaccumulative contaminants in the environment exhibit collinearity with MeHg exposure, which can confound the determination of interactive effects on organism health. *In vitro* and *in vivo* lab studies testing responses to Hg and co-contaminant exposures alone and in combination suggest that PCBs in particular interact with MeHg exposure to elicit neurological effects when isolated exposures do not (Bemis and Seegal 1999, Roegge et al. 2004, Fischer et al. 2008, Cauli et al. 2013). Similarly, epidemiological studies with subjects stratified by Hg or PCB exposure indicate potential interactive effects such as PCB-associated neurological deficits only in the highest tertile of Hg exposure (Grandjean et al. 2001), or negative associations between prenatal MeHg exposure and cognitive abilities only in subjects with elevated prenatal PCB exposure (Stewart et al. 2003). Given the abundance of studies measuring co-exposure of other contaminant with Hg, it is surprising that so few have been implemented to quantitatively test for interactive effects. This is clearly a major data gap for more accurate determination of risk associated with Hg exposure and continued epidemiological and field based studies on humans and wildlife are needed. Although limited, recent field studies with wildlife suggest that MeHg exposure may also interact with other endocrine disrupting compounds to influence hormone expression, disturbance response, and reproduction (Goutte et al. 2015, Tartu et al. 2015a, Tartu et al. 2015b). Similarly, there is emerging evidence that many ASGM sites are co-contaminated with lead, arsenic and cadmium

(Basu et al. 2015b, Tirima et al. 2016) and more work is needed to better understand the toxicological implications of these co-exposures.

4.5 Genetics

Although external environmental factors can influence individual sensitivity to Hg exposure, genetic and epigenetic factors may influence Hg exposure-outcome associations through alterations in toxicokinetics and toxicodynamics. Earlier (Section 3.3.1) we outlined how carriers of certain genetic polymorphisms may have altered Hg exposure biomarkers. Other researchers have shown that neurodevelopmental disorders (Mitchell 2011) and cardiovascular disease (Ehret et al. 2011), both of which are arguably the most relevant in terms of Hg risk, have genetic underpinnings and more importantly, are driven by complex gene-environment interactions. There is a limited, though slowly-growing body of evidence to show Hg gene-environment interactions are an important feature to be considered in future studies. For example, several studies have reported that Hg-associated effects on atypical urinary porphyrin excretion, neurobehavioral tests, and visual-motor performance were modified by genetic polymorphisms (reviewed by Basu et al. (2014)). Another study reported that offspring of mothers with *GSTM1* and *GSTT1* deletions (genes involved in glutathione function) and higher blood Hg levels had increased risk for low birth weight (Lee et al. 2010). Variation responses to MeHg exposure among families suggests that susceptibility to Hg exposure may be heritable (Varian-Ramos et al. 2013). Importantly, recent work with zebrafish demonstrated transgenerational abnormalities in neurobehavior of unexposed F2 generation fish, and proximate cause was sperm epimutations in exposed parents (Carvan et al. 2017). These findings suggest that pulsed exposure in wild populations may have multi-generational effects to fitness, even if exposure is reduced. The prevalence of heritable neurodeficits due to Hg exposure in previous generations is unknown, but these findings indicated that germ line genes appear to be targets for MeHg genotoxicity.

5.0 Summary and Research Needs

The disparities that can exist between Hg releases and the risks of deleterious health impacts to humans and other animals can create substantial uncertainty regarding the efficacy of Hg reduction and mitigation actions. Intrinsic biological factors and extrinsic ecological and socioeconomic factors can be important for modulating realized exposures to methyl and inorganic Hg, as well as the manifestations of health impacts on exposed organisms. Therefore, as Hg reductions and mitigation efforts proceed, a quantitative understanding of how global change drivers interact to influence Hg risk is needed. Incorporating additional metrics that are informative of these factors into monitoring programs would facilitate tractable approaches to statistically account for interactive effects on Hg risk. Specifically, parameters related to the four mechanisms of MeHg bioaccumulation and biomagnification (primary productivity, habitat use, bioenergetics, and food web structure) will help partition out their effects on changing Hg concentrations in ecosystems in responses to extrinsic global change drivers. Development of data application tools that facilitate incorporating these metrics into monitoring programs with a standardized approach is an important need, and would enable more robust comparisons of analogous temporal trends of Hg bioaccumulation among geographically diverse locations.

The emergence of high throughput genetic tools has opened new avenues for understanding: 1) how intrinsic genetic factors influence assimilation of and sensitivity to Hg; 2) epigenetic

responses to Hg exposure which can better inform specific mechanisms of action; and 3) interactions between the gut microbiome and Hg. These emerging areas represent potentially important contributions for refining risk estimates based upon genetic variation among populations, and for developing more effective biomarkers of Hg exposure. Substantial research in these areas is still needed for them to be applicable to public health and ecological conservation. Similarly, not enough is yet known about the interactions between Hg exposure, immunotoxicity, and infectious disease. Clearly the immune system is highly sensitive to both inorganic and methyl Hg exposure, but extrapolating that sensitivity to the toxicological implications at the whole organism scale is an important next step, particularly as it relates to infectious disease interactions. Finally, despite nearly 5 decades of research, and evidence from hundreds of scientific articles supporting Se as strong antagonist to Hg toxicity, there is still no consensus regarding the efficacy of Se in ameliorating different manifestations of Hg toxicity, nor have widely accepted tools been implemented that incorporate Se into health risk assessments for Hg. New criteria are emerging that take into account some of the mechanisms of the Hg-Se antagonism (Zhang et al. 2014, Ralston et al. 2016). However, extensive epidemiologic research is still needed to validate their safety for health risk assessments and their applicability to wildlife health. This is an important research direction that deserves continued focus. This synthesis demonstrates that the context within which Hg exposure occurs in the environment is a critical aspect that influences risk of exposure and adverse health outcomes. Future efforts to develop context-dependent assessments will facilitate improved risk estimates for humans and wildlife.

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