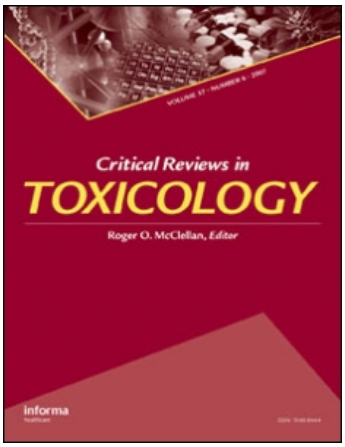

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REVIEW ARTICLE

The endocrine effects of mercury in humans and wildlife

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Abstract

Mercury (Hg) is well studied and research continues as our knowledge of its health risks increases. One expanding area of research not well emphasized to date is the endocrine effects of Hg. This review summarizes the existing literature on the effects of Hg on the endocrine system and identifies gaps in the knowledge. It focuses on the thyroid, adrenal, and reproductive systems, including the accumulation of Hg in the endocrine system, sex differences that are manifested with Hg exposure, reproductive effects in male and female animals including humans, and Hg effects on the thyroid and adrenal systems. We concluded that there are five main endocrine-related mechanisms of Hg across these systems: (a) accumulation in the endocrine system; (b) specific cytotoxicity in endocrine tissues; (c) changes in hormone concentrations; (d) interactions with sex hormones; and (e) up-regulation or down-regulation of enzymes within the steroidogenesis pathway. Recommendations for key areas of research to better understand how the endocrine effects of Hg affect human and wildlife health were developed, and include increasing the amount of basic biological information available about Hg and wildlife species, exploring the role of Hg in the presence of other stressors and chemicals, understanding sublethal and indirect effects of Hg on adverse outcomes, developing better methods to extrapolate effects across species, and understanding the effects of Hg on multiple organ systems following exposure of an animal. Greater inclusion of endocrine endpoints in epidemiological and field studies on humans and wildlife will also advance the research in this area.

Keywords: *Endocrine; hypothalamic–pituitary–adrenal (HPA); reproductive; methylmercury (MeHg); hypothalamic–pituitary–gonadal (HPG); hypothalamic–pituitary–thyroid (HPT); mercury (Hg); mercury chloride ($HgCl_2$)*

Introduction

A toxicant can affect an animal on many different levels, affecting various organ systems in different ways. Effects can be overtly toxic, indirect and subtle, or could have latent effects that are only apparent much later. The more subtle effects can be just as adverse as other, more evident, ones. Such is often the case with endocrine responses to toxicants, and the endocrine data on mercury (Hg) confirm that this is the case. This review is founded on several pieces of information: (a) that Hg is a widespread environmental pollutant that can affect entire ecosystems; (b) that uptake of Hg in the body may lead to preferential retention in endocrine organs; (c) that attention to adverse effects has mainly emphasized neurotoxicity; and (d) that endocrine toxicity is a potential risk to both humans and wildlife. This article reviews the literature on the endocrine effects of Hg and the potential mechanisms involved. Cross-species comparisons of how Hg behaves in different organisms is performed as best as possible with the available information, and the research recommendations made are designed to most efficiently increase knowledge in this area.

Sources of Hg in the environment

Hg occurs in the environment through both natural and anthropogenic sources. Natural sources of Hg include volcanoes, geologic deposits of Hg, and volatilization from the ocean. Anthropogenic sources include release of Hg during alkali and metal processing, incineration of coal, and medical and other waste, and mining of gold and Hg (US Geological Survey, 2000). The majority of environmental Hg exposure occurs through atmospheric deposition of Hg released from both natural and anthropogenic sources.

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However, recent studies indicate that anthropogenic sources have the greatest contribution in the environment. In all, global anthropogenic emissions to air in 2005 was 1930 tonnes (United Nations Environment Programme, 2008) of which slightly more than 50% came from the combination of fossil fuel combustion for power and heating and waste incineration." These sources of Hg in the environment eventually enter the food chain and account for the majority of Hg exposures for humans and wildlife. Hg exposures, toxicity, and effects are discussed below, offering a historical perspective and a summary the current knowledge.

Historical perspective: Hg toxicity (1950–1990)

Between 1950 and 1990, Hg-health-effects research focused mainly on neurological outcomes of Hg exposure, both under controlled conditions with laboratory animals and following environmental exposures to wildlife. To date, relatively little attention has been given to non-neurological changes, with the major exception of renal changes following inorganic Hg exposure. During the 1950s, 1960s, and early 1970s, severe neurological problems among wildlife (Borg et al., 1969; Borg, 1987; Fimreite and Karstad, 1971) and humans (Al Damluji, 1976a, 1976b; Bakir et al., 1973; Harada et al., 1968; Irukayama et al., 1962; Kitamura, 1971; Kurland et al., 1961; Matsumoto et al., 1965) were associated with high levels of methylmercury (MeHg) exposure.

These high concentration exposures came either from severe local pollution of the sea (e.g. Minamata and Niigata, Japan) or treatment of seed grains with Hg-containing anti-fungal compounds—for example, Iraq (Al Damluji, 1976a, 1976b; Bakir et al., 1973), Africa (Derban, 1974), Central America (Ordonez et al., 1966) and North America (Curley et al., 1971; Likosky et al., 1970). Consumption of seed grains treated with organo-mercurial anti-fungals was the cause of a massive epidemic of severe MeHg poisoning among Iraqis during the early 1970s (Bakir et al., 1973). The toxicological assessment of the Iraqi poisoning episode still serves as the basis for the World Health Organization (WHO)'s 1990 dose–response assessment for MeHg (WHO, 1990).

Wildlife also suffered severe neurological damage caused by exposure to organo-mercurials, with massive kills of birds observed in Europe (Borg et al., 1969; Borg, 1987; Fimreite and Karstad, 1971). Organo-mercurials were used as fungicides to protect seeds and plants from fungal diseases (Corrosion Doctors, 2008). Although the toxicity of the Hg-containing anti-fungals was well understood, the massive poisonings of flocks of birds was not fully anticipated. Even though the use of Hg compounds in farming was banned as a registered pesticide by the US Environmental Protection Agency in the 1970s, it continued to be used in countries other than the US (Camara and Corey, 1994).

After the prohibition of organo-mercurials being used as seed dressings, the use of organo-mercurials in paint as anti-fouling agents (Weiss, 1947) and as slimicides for paper pulp actually increased, until the use of Hg compounds in indoor and outdoor latex paints was stopped around 1991 (US Environmental Protection Agency, 1998b).

Current knowledge: Hg exposure and toxicity

Current concerns regarding Hg exposures and toxicity do not involve specific products, rather the environmental bioaccumulation of Hg. MeHg is substantially bioaccumulated at all levels of the food web (among many others see Campbell et al., 2005; Kojadinovic et al., 2006). Other sources of Hg exposure from food and consumer products (excepting some medicinals and biologicals for human and veterinary use) have largely, but not completely, been eliminated (Food and Drug Administration, 2006). People who experience occupational exposure to inorganic Hg and Hg vapor include workers in the chlor-alkali industry, goldsmiths, gold miners, dental technicians and dentists, and people with certain laboratory-based occupations (Mahaffey, 2005; Pirrone and Mahaffey, 2005). Adverse health effects of exposure to lower levels of inorganic Hg are reported for the renal and nervous systems (Mason et al., 2001; Risher and Amler, 2005; Roels et al., 1999). Neurological damage (for MeHg and inorganic Hg) and renal effects (for inorganic Hg) form the basis for occupational and environmental standards aimed at limiting inorganic and MeHg exposures.

Currently, non-occupational inorganic Hg exposure is largely from Hg–silver dental amalgams. Other mercurial compounds (such as ethylmercury or phenylmercury) are found in medicinals and biologicals (e.g. pharmaceuticals including ophthalmological solutions and some vaccines, skin-lightening creams, and 'folk' or traditional medicines; reviewed by Mahaffey, 2005).

The ratio of inorganic Hg to MeHg is characterized by food-chain patterns of predators and prey (Deforest et al., 2007; Dehn et al., 2006; Haines et al., 2003). Bioaccumulation of MeHg at various trophic levels results in substantial increases in tissue Hg concentrations at the highest trophic levels. As shown by biomarkers of exposure, concentrations of MeHg in blood (Schober et al., 2003) and hair (McDowell et al., 2004) reflect differences in quantity, frequency, and species of fish consumed (Mahaffey et al., 2004). Similar patterns exist for wildlife, as demonstrated by the increase in Hg concentrations found in animals at the top of the food chain (Scheuhammer et al., 2007), especially for food webs based on aquatic systems. Examples of high-Hg sources include large pelagic fish such as tuna (Adams, 2004; Kojadinovic et al., 2006, 2007; Licata et al., 2005; Storelli et al., 2005a), shark (Branco et al., 2004, 2007; Penedo de Pinho et al., 2002), marlin (Forsyth et al., 2004), and swordfish (Storelli et al., 2005a), marine mammals such as seals (Beckmen et al., 2002; Campbell et al., 2005; Riget et al., 2007), and birds such as loons (Evers et al., 2003, 2005; Kenow et al., 2003).

Animals including birds, fish, and mammals have a substantially greater risk of exposure to MeHg than to inorganic Hg (Fisk et al., 2005). Although piscivorous animals have the highest MeHg exposures, recent findings show that insectivorous birds, amphibians, and reptiles also have increased

tissue concentrations of MeHg that varies with geographic region and diet (Bank et al., 2005, 2007; Bergeron et al., 2007; Day et al., 2005; Hsu et al., 2006; Storelli et al., 2005b; Storelli and Marcotrigiano, 2003; Unrine and Jagoe, 2004). For humans, nearly all Hg exposures come from inorganic mercurials, methyl-mercurials, and phenyl-mercurials (Bhan and Sarkar, 2005; Dopp et al., 2004; Mahaffey, 2005). For adults with no occupational exposures, MeHg from consumption of fish and shellfish is the predominant route of exposure.

Exposure to inorganic Hg and MeHg has a range of effects, which are dependent upon the exposure period, window, and concentration of Hg. High-level exposures can result in embryo or fetal death and devastating neurological sequellae similar to severe cerebral palsy, accompanied by deafness and visual impairment (Tsubaki and Irukayama, 1977). At the lower end of the dose–response continuum, biochemical indicators such as immuno-toxicological effects occur. Effects on other organ systems, such as the cardiac system, have been explored, yet many of the endocrine effects are not well researched across species. Reproductive effects are an important focus of this review, as they occur through manipulation of both the neuronal and endocrine systems.

General reproductive effects in comparison with changes in other organ systems

Although there are many causes of reproductive impairment, this review addresses those that are primarily of endocrine origin. Risks of adverse reproductive effects have been demonstrated among workers in professions linked to Hg exposures; for example, among female dentists and dental technicians (Lindbohm et al., 2007; Ritchie et al., 2004; Rowland et al., 1994). Regarding wildlife, the US Environmental Protection Agency's *Mercury Study Report to Congress* (1997) integrated terrestrial and aquatic ecosystems, systematically addressing the potential adverse health effects of MeHg on humans and wildlife. While writing this report, the authors noted an absence of 1990s literature from the 1990s on the deaths of birds, fish, and mammals from MeHg exposure. In 2007, a series of position documents (Lindberg et al., 2007; Mergler et al., 2007; Munthe et al., 2007; Scheuhammer et al., 2007) from the Madison Conference (2007), addressed broad-scale issues of energy and contamination of ecosystems as well as cultural and societal concerns (Swain et al., 2007). The assessments included the reproductive and developmental effects of MeHg exposure that occurred at levels lower than those producing overt neurological damage (Mergler et al., 2007).

The current review further describes both laboratory and environmental data on the reproductive effects of both inorganic Hg and MeHg in females and in males, including possible modes of action and sensitive indicators of effects in both sexes across multiple species and taxonomic groups. Isolating the effects of Hg on human reproduction on the basis of epidemiological assessments for women and men has proved complex (Olfert, 2006). Difficulties in understanding the reproductive effects of Hg using epidemiological data include the following: (a) an absence of observed effects for specific reproductive endpoints (Brodsky et al., 1985); (b) no strong associations and absence of dose–response effects (Lindbohm et al., 2007); and (c) significant increases in the risk of adverse reproductive outcomes (Sikorski et al., 1987). For example, the diverse results of combined exposures to multiple chemicals (including organic solvents) with potential adverse reproductive effects (Olfert, 2006) can be seen in dentistry.

Hg and MeHg doses: Endocrine versus other organ systems

It is beyond the scope of this review, and possibly the available data, to construct a quantitative comparison of dose–response relationships by endocrine systems with the full range of effects reported for other organ systems (e.g. neurological effects). The severity of the effects of Hg exposure from previous fungicidal use resulted in substantial limitations to the use of organo-mercurials on seed grains (among others, see United Nations Environment Programme, 2006; WHO, 1974; WHO, 1976; WHO, 1990; WHO, 1991). However, the US Environmental Protection Agency's (1977) *Mercury Study Report to Congress* found that gross mortality among large flocks of birds was not common during the 1990s (i.e. after limitations on treatment of seed grains with organo-mercurials were in place). By contrast, the pattern of toxicity was distinctly different. Instead of reporting mortality, reduction was recorded in the population numbers of fish-consuming avian species high in the aquatic food chain, such as the loon and certain species of wading birds. Many reproductive effects of inorganic Hg and MeHg in multiple species have now been outlined in the literature (Scheuhammer et al., 2007). Cardiac effects, specifically hypertension (Grandjean et al., 2004; Sorensen et al., 2004) and atherosclerosis, have been associated with MeHg exposure in humans (Guallar et al., 2002; Salonen et al., 2000; Virtanen et al., 2005). Inorganic Hg may also play a role, complicating our understanding of cardiac effects when co-exposures with MeHg occur (Yoshizawa et al., 2002).

Risk assessments for MeHg

Neuro-behavioral effects demonstrated psychometrically serve as the basis for current human-health risk assessments for Hg. In the future, endocrine effects of Hg could be confirmed at levels of Hg exposure below those producing adverse neuro-behavioral and intellectual effects. The understanding of the Hg dose–response relationship for the nervous and endocrine systems, and how these systems interact, could change the current understanding of how low-level Hg exposures affect the two organ systems. Further understanding of the endocrine effects of Hg across multiple taxon through increased research, followed by a careful comparison of the sensitivities of endpoints across the neurological and endocrine systems, will allow for a clearer comprehension of the appropriateness of our current risk estimates for Hg.

Occasionally, as more is learned about dose effects, new information can modify which organ system serves as the basis for risk assessment, addressing low-level exposure. Assessments for inorganic lead dose–response relationships serve as an example. Before approximately 1980, virtually all risk assessments for inorganic lead used the hematopoietic system (see Zielhuis, 1977, among others), as effects on this organ system were seen as the most sensitive indicators of exposure to inorganic lead (with blood lead concentrations > 15 μg/dl of whole blood). In the early 1980s, lead-related decrements in IQ and poorer scholastic and societal performance were demonstrated (Needleman et al., 1982) and risk assessments shifted from hematopoietic endpoints to neuro-behavioral and intellectual decrements as the endpoints of concern (with blood lead concentrations < 5 μg/dL). If research finds that the situation with Hg parallels the situation with lead, relevant endpoints considered for risk assessments of MeHg will need to be broadened to include information such as endocrine endpoints.

Approach to this review

Inorganic Hg and MeHg have been clearly shown to adversely affect hormonal or endocrine systems in mammals, fish, and birds, and a growing body of information exists for reptiles, amphibians, and invertebrates. However, an overview of the range of endocrine effects in multiple species has not been undertaken to date. The search strategy used in the current review involved multiple databases and search terms for chemical species of Hg, endocrine, and biological species. For Hg, the following search terms were used: mercury; Hg; methylmercury; MeHg; mercury chloride; $HgCl_2$; inorganic mercury; and organic mercury. The following organ system terms were used: gonadal; neuro-endocrine; brain; kidney; adrenal; thyroid; and liver. For endocrine systems, the following search terms were used: endocrine; hormone; hormonal; development; fertility; reproduction; testes; Leydig; Sertoli; sperm; spermatogenesis; gametogenesis; hypospadia; cryptochidism; ovary; ovulate; oogenesis; menstruation; menstrual period; uterus; uterine; hypothalamus; pituitary; hypothalamo–pituitary–gonadal axis; HPG; hypothalamo–pituitary–thyroid axis; HPT; hypothalamo–pituitary–adrenal axis; HPA; steroidogenesis; steroid; corticosteroid; corticosterone; cortisol; thyroid hormone; thyroxine; T4; triiodthyronine; T3; thyroid-stimulating hormone; TSH; thyrotropin-releasing hormone; TRH; thyroid-binding globulin; TBG; transthyretin; TTR; iodine; iodide; deiodinase; and selenoprotein. The following terms for biological species were used: wildlife; fish; fishes; bird; avian; frog; amphibian; reptile; invertebrate; rodent; rat; mouse; guinea pig; rabbit; human; mammal; field; and laboratory. Databases searched were both specialized databases (including PubMed, Science Direct, Toxnet, and Agricola) and general databases (including Google and Google Scholar). The search terms were confined to English language.

While identifying relevant studies for this review, the authors pinpointed a number of problem areas: (a) study limitations in which only one Hg compound was used and/or a unique endocrine endpoint was assessed; (b) comparison of clinical assessment and field studies of wildlife with exposures under controlled but artificial laboratory conditions; (c) field study conditions often combining inorganic and MeHg exposures; (d) comparisons across studies, even within the same species, that used different exposure windows, doses, and lengths of exposure; and (e) comparisons across animal taxa groups may be difficult because of a paucity of data.

This review of the endocrine effects of inorganic Hg and MeHg allowed us to organize the observed effects reported in the literature by the specific components of the endocrine system (e.g. reproductive axis, thyroid system, adrenal system). Within each hormonal axis of the endocrine system, the main modes of action have been identified where possible and subsections created to describe the observed effects. A parallel approach was maintained for relevant sections. Alternate organizational systems were considered (e.g. steroidogenic effects across the components of the endocrine system), but the consensus was that it was best to maintain the effects observed within each of the major hormone and glandular components of the endocrine system to observe the overall links within that part of the endocrine system. Later, larger comparisons were made within the endocrine system as a whole.

Accumulation of Hg in the endocrine system

Organic and inorganic Hg is known to accumulate in most vertebrate and invertebrate species. Accumulation occurs at particularly high levels in the kidneys and liver of vertebrates, but growing amounts of data show that Hg has a specific affinity for the endocrine system. A complete understanding of the mechanisms and the conditions of this affinity remains largely unknown.

As early as the 1940s and 1950s, scientists were exploring differences in accumulation of organic and inorganic Hg in multiple taxa (for review, see Berlin and Ullberg, 1963). These studies revealed that patterns of accumulation vary greatly, depending on the length of exposure and the period of time between exposure and sampling of the organism's blood, urine, organs, or other tissues of interest, such as hair or feathers. In vertebrates, the kidney and liver traditionally show the greatest accumulation of Hg after chronic or acute exposures to organic and inorganic Hg, but other organs are now recognized to accumulate significant concentrations of Hg.

In 1963, Berlin and Ullberg demonstrated that a one-time injection of $HgCl_2$ in mice led to Hg accumulation in the testes at concentrations higher than those in the liver and second only to those in the kidney. However, these levels of accumulation were only observed when sampling took place 16 days following the injection. In the female endocrine system, accumulation of $HgCl_2$ in the ovary of the Golden Hamster showed greater concentrations in the corpora lutea than in the follicles of the interstitium (Lamperti and Printz,

1974). In the lobster, *Homarus americanus*, a one-time injection of MeHg led to more than 0.1 ppm of Hg accumulated in the egg masses, male gonads, heart, brain, intestine, and tail muscle up to 1 month after the injection of 0.1 mg/kg MeHg (Guarino et al., 1976). These cited papers were some of the first to suggest that organic and inorganic Hg both have a specific affinity for the male and female reproductive organs.

Another endocrine organ that shows $HgCl_2$ accumulation is the hypothalamus, potentially affecting the endocrine system's hypothalamo–pituitary axes (Figure 1). Lamperti and Printz (1974) observed accumulation of Hg in the pituitary lining of the sinusoids and the hypothalamic neurons of the arcuate nucleus when they exposed hamsters to daily injections of 1 mg $HgCl_2$ over a 4-day estrous cycle. Moller-Madsen and Thorlacius-Ussing also demonstrated that Hg accumulates at high concentrations in the anterior pituitary gland of rats exposed to $HgCl_2$ and MeHg, with no structural damage resulting from this accumulation (Moller-Madsen and Thorlacius-Ussing, 1986; Thorlacius-Ussing et al., 1985). These rats were exposed to Hg concentrations frequently used in rodent studies. Humans also have high pituitary-gland levels of Hg when exposed occupationally to Hg vapor (Falnoga et al., 2000; Kosta et al., 1975; Nylander and Weiner, 1991). The pituitary gland may be particularly vulnerable to Hg-vapor accumulation, since it can receive it by direct transport from the nasal cavity (Stortebecker, 1989).

One of the first papers to demonstrate that the organs of the thyroid system accumulate very high concentrations of Hg was a study of retired Hg mine workers who were chronically exposed to Hg vapor for long periods of time (Kosta et al., 1975). Surprisingly, the Hg concentrations in post-mortem mine workers was 3–4 fold greater in the thyroid and pituitary gland than in the kidney. Almost three decades later, a study was performed during the closure of the same mine, and high concentrations of Hg were still observed in the pituitary gland and thyroid of retired mine workers and, to a lesser degree, the residents of the mining town (Falnoga et al., 2000). Because Hg is normally found in high concentrations in the kidney and liver, few studies prior to that by Kosta et al. (1974) compared organ Hg concentrations in other post-mortem human tissue (such as thyroid or other endocrine tissue). It is possible that similar findings would be seen in other occupational studies or following accidental exposures such as Minamata or Nigata, but these tissues have not been systematically examined during these situations. The current depth of information

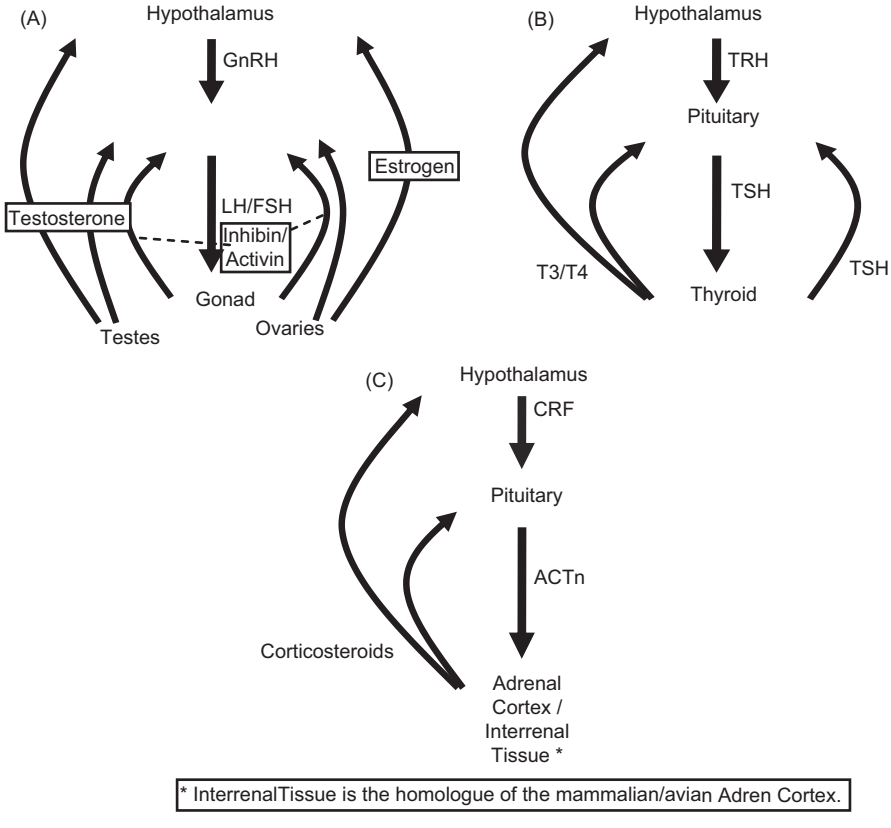

Figure 1. Simplified axes and feedback loops for the (A) hypothalamic–pituitary–gonadal axis (B) hypothalamic–pituitary–thyroid axis and (C) hypothalamic–pituitary–adrenal axis. The gonadal axis includes the male and female gonads and hormones. The adrenal axis contains the inter-renal tissues, which are the fish homolog of the mammalian and avian adrenal cortexes. Abbreviations: ACTH, adrenocorticotropin; CRF, corticotropin-releasing factor; GnRH, gonadotropin-releasing hormone; LH/FSH, leutinizing hormone/follicle-stimulating hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

in this area is limited by a lack of this type of data gathered post mortem.

In birds, a clear and linear accumulation of Hg has been demonstrated in American kestrels (*F. sparverius*) by comparing the dietary exposure of mothers to MeHg with the accumulation of MeHg in their eggs (Albers et al., 2007). Similar accumulation patterns were observed in other raptors, as well as in water fowl, herring gulls, and pheasants. In the kestrel study, a dose-dependent decline in reproductive outcomes (e.g. number of eggs hatched and fledglings produced) was observed for eggs with higher levels of Hg accumulation (Albers et al., 2007).

Inconsistencies in Hg-accumulation patterns exist in the literature, but may simply reflect differences in the taxa studied, sampling times, exposure windows, and forms of Hg used in the study. The studies that demonstrate significant and specific accumulation of Hg in the endocrine system give us reason for concern and highlight the gaps in our understanding of the environmental and internal conditions that lead to high Hg accumulation in specific organs. Many of the studies cited throughout this review have demonstrated that Hg accumulates in endocrine tissues, often at surprisingly high concentrations (Berlin and Ullberg, 1963; Falnoga et al., 2000; Hahn et al., 1989, 1990; Kosta et al., 1975). These studies lead us to question why Hg accumulates in the endocrine system, and what effect this has on endocrine-system function.

Sex differences in susceptibility to Hg

There are numerous papers on the differences observed between sexes of the same species in response to Hg exposure. Most studies use MeHg or $HgCl_2$, and both forms have revealed consistent differences in response between sexes. Sex-linked differences between male and female species of birds, fish, mice, rats, marine mammals, monkeys, and humans were reviewed. Endpoints examined included accumulation and concentration of Hg in different tissues, excretion rates, nephropathology, neurological symptoms, sex ratios at birth or as adults, and behavioral differences between the sexes. Sex-hormone-linked sex differences with Hg exposure were also explored, and when solid links were indicated, they were further discussed and explored. There was a two-part rationale behind our search for studies that specifically identified sex differences: (a) to identify potential sex-linked mechanisms that could lead to differences in the effects of Hg on males versus females and illuminate potential links to the endocrine system; and (b) to look for patterns in sex differences across species and taxa in order to understand whether certain mechanisms are evolutionarily conserved.

The observed differences and the potential mechanisms for the variation between sexes are discussed in the following section. Whether cross-species patterns have been established or not with respect to the sex differences discussed below, the following papers are valuable in determining where Hg exposures may be linked to endocrine effects that are mediated through sex hormones or other secondary mechanisms that are related to sex. It is important to emphasize that, while multitudes of papers exist in the literature on the effects discussed in this section, many of which did not observe sex differences, we chose to focus only on studies that showed sex differences with respect to the endocrine system. By focusing only on these papers it was then possible to look for patterns and trends, which in turn may inform future research.

The results of our search indicate that Hg exposure often leads to different effects for each sex of a species, but sex-specific trends across taxa are difficult to establish at this point in time. The difficulty in establishing trends is in part attributable to a lack of similar studies across taxa (many studies that were intended to explore the effects of Hg in specific taxa led to unexpected sex differences being observed in endpoints that were not necessarily intended as the focus of the study), and the difficulty in comparing field or clinical data with those on laboratory animals. For example, organ accumulation differences have been extensively studied in laboratory rodents and have been linked to sex hormones. However, these studies were performed in controlled environments, whereas the exposure times and concentrations of Hg in humans and wildlife in the field are not possible to control. Still, laboratory data give researchers an indication of effects that may be possible to observe in other mammals, or even other vertebrates, if the same endpoints are studied. Specific mechanisms that occur in one species or across taxa often become apparent when endpoints of interest are systematically observed across studies. For example, human epidemiological studies monitor many of the same endpoints in human populations exposed to elevated Hg levels, and studies that have looked at sex differences in neurological measures show some consistent differences in neurological outcomes between exposed males and females. A review of the literature indicates that a need exists for the study of similar endpoints across taxa to determine if a mechanism well-studied in one species (rodents, for example) applies to other species.

Accumulation

Studies on rats and mice show clear sex differences in accumulation of Hg. Females are believed to have higher body burdens of MeHg at given doses than males (National Research Council, 2000; Nielsen and Andersen, 1991a, 1991b; Thomas et al., 1986, 1987). In rodents, it is generally established that females accumulate more Hg in the brain, while males accumulate higher levels of Hg in the kidney (Table 1; Doherty et al., 1978; Hirayama et al., 1987; Hirayama and Yasutake, 1986; Hultman and Nielsen, 2001; Inouye et al., 1986; Magos et al., 1981; Nielsen et al., 1994; Nielsen and Andersen, 1989, 1990, 1991a, 1991b; Nielsen and Hultman, 2002; Pamphlett et al., 1997; Tanaka et al., 1991, 1992; Yasutake and Hirayama, 1988). One study also found a similar pattern in female bottlenose dolphins, which had higher Hg concentrations in the brain and liver than the males had (Meador et al., 1999). A group of 93 Japanese cranes (*Grus japonensis*) found dead

in Hokkaido, Japan was used in a study that compared Hg accumulation across three life stages (juvenile, sub-adult, and adult) and males versus females (Teraoka et al., 2007). In this comparison, the adult males accumulated more Hg in the kidney and liver than the adult females did. However, in the juveniles, the pattern in the kidney was reversed, with greater accumulation in the kidneys of juvenile females. The same pattern of accumulation has not been documented (to our knowledge) in other species, and it is not clear if this is because the same phenomenon does not occur or because it has not been investigated in other taxa (Table 1). Accumulation differences were observed mainly in rodents in studies using MeHg, but similar trends were seen with $HgCl_2$ and total Hg (Table 1). These trends and their possible effects are discussed below.

Besides greater accumulation of Hg in the brain and motor neurons, it seems that female rodents also tend to have higher Hg concentrations in the blood following Hg exposure (Table 1). This pattern is not observed in humans, but may reflect differences between species, exposure periods, or doses. More studies are needed to understand blood level differences in Hg between males and females across different taxa.

Elimination

While the male rodent kidney seems to accumulate more Hg than the female, it is not clear if this is due to a higher overall rate of accumulation and elimination in the male kidney or faster elimination by the female kidney. Some studies speculate that the comparatively greater accumulation of Hg in the male kidney may be because of faster elimination of Hg from the female kidney. A study of the biological half life of 203Hg in humans showed that females demonstrate faster Hg elimination (Rahola et al., 1973). However, this study had very few subjects, and a similar study (also with small sample size) did not show differences between men and women (Miettinen et al., 1971). Urinary Hg levels were also generally higher in females in a study by Barregard and colleagues (2006) that measured total Hg, and the authors mentioned that this trend could be due to women having lower concentrations of creatinine than men. Another explanation for greater female excretion could be that estrogen can increase glutathione synthesis by the liver and induce increased secretion of MeHg from the kidney (Tanaka et al., 1992). Pamphlett and colleagues (1997), on the other hand, suggest that female mice dosed with $HgCl_2$ may not eliminate Hg from the body as quickly as male mice,

Table 1. Sex Differences in Mercury (Hg) Accumulation.

Species	Hg Type	Higher brain accumulation		Higher kidney accumulation		Higher liver accumulation		Higher blood/plasma concentration		Citation
		Female	Male	Female	Male	Female	Male	Female	Male	
Bird: Loon (*Gavia immer*)	Total Hg	–	–	–	–	–	–	–	X	Evers et al. (1998)
Bird: Crane (*Grus japonensis)*)	Total Hg	–	–	–	X adult	–	X adult	–	–	Teraoka et al. (2007)
Bird: Crane (*G.japonensis)*)	Total Hg	–	–	X juvenile	–	–	X juv.	–	–	Teraoka et al. (2007)
Mammal: mice ($C129F_1$)	MeHg	–	–	–	X	–	–	–	–	Doherty et al. (1978)
Mammal: mice (C57BL/6N)	MeHg	X*	–	–	–	–	–	–	–	Inouye et al. (1986)
Mammal: mice (C57BL/6N & BALB/cA)	MeHg	X	–	X(C57BL/6N)	X	X	–	X	–	Hirayama et al. (1987), Hirayama and Yasutake (1986), Yasutake and Hirayama (1988)
Mammal: mice (ICR)	MeHg	–	–	–	X	–	–	–	–	Tanaka et al. (1992)
Mammal: mice (ICR, BALB/c, C57BL6)	MeHg	–	–	–	X	–	–	–	–	Tanaka et al. (1991)
Mammal: mice (CBA/Bom, Bom:NMRI)	$HgCl_2$	–	–	–	X	–	–	–	–	Nielsen and Andersen (1989, 1990)
Mammal: mice (Bom:NMRI)	MeHg	X	–	–	X	X	–	X	–	Nielsen and Andersen (1991a, 1991b)
Mammal: mice (BALB/c)	$HgCl_2$	motor neurons	–	–	X	–	–	–	–	Pamphlett et al. (1997)
Mammal: rats (Porton–Wistar)	MeHg	X	–	–	–	–	–	–	–	Magos et al. (1981)
Mammal: rats (Long Evans)	MeHg	X	–	X	–	–	–	–	–	Newland and Reile (1999), Thomas et al. (1986, 1987)
	MeHg	X*	X^H	–	–	–	–	–	–	
Mammal: bottlenose dolphin *(Tursiops truncates)*	Total Hg MeHg	X	–	–	–	X	–	–	–	Meador et al. (1999)
Mammal: Humans	Total Hg	–	–	X	–	–	–	X	X	Barregard et al. (1999), Lommel et al. (1992), Mahaffey and Mergler (1998)

*Effect only significant at lowest dose, H significant only at high dose.

but rather may have higher levels of circulating Hg that can then move to other parts of the body, especially the blood, neuronal tissue, and brain, which may partially account for higher levels of Hg in these tissues in female rodents. Nielsen and Andersen performed a series of studies demonstrating that male mice have different toxicokinetics than female mice regarding Hg deposition and elimination, with notable differences between rodent strains. Males generally had shorter half-time retention of MeHg and greater deposition of MeHg and $HgCl_2$ in the kidneys (Nielsen and Andersen, 1990, 1991a, 1991b). Male mice also demonstrated faster elimination of MeHg (Nielsen and Andersen, 1991a, 1991b). In rodents, Hg elimination by the kidneys seems to be generally greater in males, although this varies between rodent strains (Nielsen and Andersen, 1990; Yasutake et al., 1990). Studies in rodents identified specific mechanisms in the kidney that explain why male excretion rates may be greater. These mechanisms are further discussed below.

Renal toxicity

Several papers have addressed the effects of Hg on the kidney as well as resulting differences in effects between the sexes. These papers suggest that differences between the sexes may result from greater Hg accumulation in the male versus the female kidney. In an extensive study by the National Toxicology Program (NTP), rats (strain F344) and mice (B6C3F1) were dosed with $HgCl_2$ over three separate exposure periods (16 days, 6 months, and 2 years), and it was revealed that male mice and rats had greater nephropathy than females. The increased sensitivity of male rodents to acute and chronic nephropathy, including renal tubule necrosis, cytoplasmic vaculolation of the renal tubule epithelial cells, and renal tubule hyperplasia, could be related to greater accumulation of Hg in the male kidney. However, the NTP study did not compare kidney Hg accumulation between males and females. Incidentally, male rats had a lower survival rate than the females in the 2-year study, and the authors attribute this to the accelerated development of chronic nephropathy in males (NTP, 1993). Harber and Jennings (1964, 1965) were the first to demonstrate a sex difference in response to $HgCl_2$, where males were much more susceptible to nephrotoxicity than females (Harber and Jennings, 1964, 1965). Interestingly, testosterone injections to females led to tubular necrosis following Hg exposure, and male rats were protected by estrogen injections. Castration also had similar, although less marked effects as hormone injection (Harber and Jennings, 1965). Estrogen signals the production of metallothionein in the liver and kidneys, and could act to bind Hg and block it from toxic interactions in these organs in females more than males (for discussion, see Oliveira et al., 2006).

Similar long-term-exposure studies on mice have revealed that MeHg also caused renal tumors. Male ICR mice dosed for 2 years with MeHg in their drinking water developed renal tumors (mostly adenocarcinomas; Hirano et al., 1986). Female mice and mice exposed at other doses did not develop renal tumors. A slightly shorter, 80-week study showed that only males had a significantly increased incidence of renal epithelial tumors and tubular cell hyperplasia (Hirano et al., 1988). These effects were not seen in castrated male mice under the same exposure conditions. When castrated males or ovariectomized female ICR mice were injected with testosterone proprionate, a synthetic form of testosterone, under the same MeHg exposure conditions, there was an increase in renal adenocarcinomas and hyperplasia in both male and female mice (Hirano et al., 1988). Mitsumori and colleagues (1990) also found that a different strain of mice (B6C3F1) developed more renal adenomas, carcinomas, and tubular-cell hyperplasia in male mice than in female mice with MeHg exposure, although in this study chronic nephropathy was also seen in females. The described accumulation differences between the sexes probably play a role in the degree of renal toxicity that occurs and where or how Hg is eliminated from the body or accumulates in other organs.

Fowler (1972) found that renal toxicity from MeHg exposure was greater in female than in male Wistar rats, suggesting that sex effects on the renal system may vary between MeHg and $HgCl_2$ depending on age exposed, length of exposure, and the dose level. The author also suggests that sex differences in kidney enzymes are probably responsible for the Hg accumulation and pathological differences in the kidneys of males and females (Fowler, 1972). The renal effects described seem to be related to sex-hormone levels and a probable interaction of these hormones with kidney function.

Kidney function

Sex differences in kidney function may explain some of the differential responses between male and female rodents following Hg exposure. Membrane transport of individual organic and inorganic anions and cations are regulated differently in the kidneys of males and females (for review, see Morris et al., 2003). Sex differences in renal clearance and re-uptake of many compounds may be under hormonal control. For example, the multi-specific transport proteins known as the organic anion transporting polypeptide family are responsible for the secretion and reabsorption of anions in the kidney, and seem to contribute to sex differences in the kidney. Organic anion transporting polypeptide mRNA concentrations are under the control of androgen, and have higher expression in the kidney of male rats than females, thus leading to sex differences in anion absorption and secretion from the kidney. Furthermore, a clear role for sex hormones in renal tubular transport of compounds such as thiosulfates, amino acids, and certain pharmaceuticals has been demonstrated through experiments using castrated and ovariectomized rats (Morris et al., 2003).

Both MeHg and inorganic Hg have a high affinity for sulfhydryl groups. Glutathione (GSH), a tripeptide, is an enzyme and major antioxidant that is well known for its sulfhydryl groups. In a study by Hirayama and colleagues (1987), the rate of GSH metabolism in mice was significantly slower in males than in females, and the authors suggest

that this could account for the greater excretion and accumulation of Hg in the male kidney (Hirayama and Yasutake, 1986). Hirayama et al. (1987) demonstrated that male mice (C57BL/6N) accumulate higher Hg levels in the kidney, but lower levels in the brain, liver, and plasma, than females following MeHg exposure. This accumulation trend in the kidneys was reversed when males were castrated, leading to female-like accumulation of MeHg in the liver and kidney (but not the brain). The male phenotype was then restored through testosterone-proprionate treatments. Male and female control mice treated with testosterone proprionate had increased urinary Hg excretion, and the females accumulated greater concentrations of Hg in the kidneys than females that were not injected with testosterone proprionate. Male mice treated with MeHg and estradiol benzoate had decreased accumulation of Hg in the kidneys, while hepatic levels increased. Ovariectomized females showed a small decrease in the amount of Hg excreted in the urine. The authors demonstrated that sex hormones have a clear effect on MeHg accumulation in the kidney, and they suggested that this difference is ultimately due to sex-linked differences in GSH metabolism in the kidney and liver.

Yasutake and colleagues (1990) also demonstrated sex-hormone-linked differences specific to renal Hg accumulation and clearance. They showed that male mice (C57BL/6N) had faster renal uptake of MeHg and a slower decrease in renal Hg than females. The authors used creatinine and phenolsufonphthalein as markers for kidney function and noted that MeHg exposure led to a decrease in phenolsulfonphthalein excretion and an increase in plasma creatinine levels in males compared with females. These phenotypes were reversed by male castration or female ovariectomy, and could then be restored by injection of testosterone proprionate or estradiol benzoate to males and females respectively (Yasutake et al., 1990).

Tanaka and colleagues (1992) further explain the sex difference observed in renal kidney uptake through a testosterone-mediated difference in gamma-glutamyltranspeptidase (γ-GTP) activity that appears in male ICR mice after 4 weeks of age, or around puberty. At this age, renal MeHg uptake and γ-GTP activity increase in males, while the levels in females remain constant. The authors demonstrated that $HgCl_2$ also undergoes renal uptake in male mice by the same mechanism (Tanaka et al., 1990). Both organic and inorganic Hg form complexes with GSH in different tissues throughout the body, which helps to explain the renal uptake mechanism described by Tanaka et al. (1991).

The liver contains very high levels of GSH, and serves as a major source of GSH and its S-conjugates which are attached to xenobiotics (such as Hg) in the plasma and bile. These complexes are preferentially taken up by the kidney from the plasma and are extracellularly hydrolyzed by γ-GTP and dipeptidases, resulting in their constituent amino acids and rapid absorption of the xenobiotic into the kidney (Naganuma et al., 1988). Inhibitors of γ-GTP prevented accumulation of Hg in the kidney (Tanaka et al., 1990), and depletion of hepatic GSH using 1,2-dichloro-4-nitrobenzene also prevented renal uptake of Hg (Naganuma et al., 1988). Therefore, by measuring γ-GTP activity, Tanaka and colleagues (1992) were able to demonstrate sexual differences and a correlation with renal Hg uptake at certain ages (specifically around puberty). The authors were further able to link this difference to androgens by castrating male mice, thus inhibiting γ-GTP activity and preventing any sexual differences in renal Hg uptake. Testosterone injections could both restore the male phenotype in castrated mice and induce female mice to increase both γ-GTP activity and renal Hg uptake (Tanaka et al., 1992).

Sex-hormone-mediated differences in renal MeHg accumulation are described by both Tanaka et al. (1991) and Hirayama et al. (1987). However, excretion of Hg in the urine was not always observed to be greater in males across species or strains. Thomas and colleagues (1986, 1987, 1997) saw sex differences in Hg excretion in the feces and urine of Long Evans rats after exposure to MeHg, with females excreting both organic and inorganic Hg at a higher rate and accumulating more Hg in the kidney than males, contrary to studies in mice by Hirayama et al. (1987). On the other hand, renal Hg accumulation does seem to be consistently greater in males across species and strains (Table 1; Tanaka et al., 1991). A comparison of mouse strains by Tanaka et al. (1991) revealed that renal uptake of Hg was greater in males of three tested strains, but γ-GTP activity was only demonstrably greater in males of two of those strains.

To further explore strain differences, urinary Hg excretion in two strains of male mice was compared, and the differences observed were accounted for by greater urinary concentrations of GSH in the strain that excreted more urinary Hg. In this study, the increased excretion of GSH was correlated with a lower urinary γ-GTP activity (Mulder and Kostyniak, 1985). The relationship between Hg, GSH, and γ-GTP activity could explain why inconsistencies exist in the literature on male and female Hg excretion rates and volumes. More studies will elucidate how sex differences in Hg uptake and excretion occur. Sex-hormone-dependent differences between males and females in response to Hg exposure seem to be common amongst rodent species, but other species and taxa need to be studied for similar patterns between the sexes.

A handful of studies on mice, rats, and humans showed greater accumulation of Hg in the female kidney and/or greater urinary excretion of Hg by females rather than males (Barregard et al., 1999; Lie et al., 1982; Magos et al., 1981; Thomas et al., 1986, 1987; Yasutake and Hirayama, 1988). These studies may have observed divergent results from those described above because of strain and species dependent differences, and/or exposure times and the form of Hg used in the experiment. Sex differences are also likely to change throughout life since hormone levels, Hg toxicity, and Hg retention in young animals differs from those of adult animals (Doherty et al., 1978; Silva et al., 2005).

As mentioned earlier, researchers studying Japanese cranes (Teraoka et al., 2007) observed sex differences in Hg accumulation in cranes found dead in the field. Adult cranes

demonstrated a greater accumulation of Hg in the males in both the liver and the kidney. However, juvenile females had greater accumulation of Hg in the kidney and juvenile males had a greater accumulation of Hg in the liver. Subadults showed similar accumulation trends between the sexes in the liver and kidney. Muscle tissues were also examined, and though differences were small, males always accumulated greater levels of Hg than females. The authors have not explored the mechanisms by which sex differences in Hg accumulation might occur in Japanese cranes.

Neuronal outcomes

Pamphlett and colleagues (1997) observed greater concentrations of Hg in the motor neurons of female mice than in male mice, and suggested that the greater brain and neuronal accumulation of Hg in females could be due to the smaller concentrations of Hg amassing in the kidney, and thus a greater amount of Hg available for incorporation into the motor neurons. Pamphlett and colleagues (1997) noted that inorganic Hg is known to be taken up selectively by motor neurons, but only three of the accumulation studies listed in Table 1 used $HgCl_2$ (Nielsen and Andersen, 1989, 1990; Pamphlett et al., 1997). These studies all found that more Hg accumulated in the neurons or brains of females and in the kidneys of males. Nielsen and Andersen (1990, 1989) showed a higher brain deposition of $HgCl_2$ in female Bom:NMRI mice when compared with males 14 days following an oral dose. Studies that used MeHg were greater in number but less consistent in demonstrating male versus female differences in Hg accumulation (Magos et al., 1981; Thomas et al., 1986; Yasutake and Hirayama, 1988). Discrepancies could be due to differences in species, and times and routes of exposure. In both the lab and the field, the concentration of Hg exposure influences sex differences. In some studies, low doses lead to sex effects that disappear or even reverse at higher doses (Inouye et al., 1986; Newland and Reile, 1999).

Differences between males and females in neurological outcomes are not accounted for by the greater accumulation of Hg in the brain of female rodents, or by the greater accumulation of $HgCl_2$ in the motor neurons of female mice (Pamphlett et al., 1997). Sager and colleagues (1983, 1984) found that BALB/c male mice had reduced numbers of cells in the molecular and internal granular layer of the cerebellum when compared with female mice, which could explain why motor-coordination deficits and neurological symptoms are generally more severe in male mice, rats, and monkeys (Gilbert et al., 1996; Gimenez-Llort et al., 2001; Grandjean et al., 1998; McKeown-Eyssen et al., 1983; Rossi et al., 1997; Tamashiro et al., 1986; Vorhees, 1985). Although the trend suggests that males may be more sensitive to Hg with respect to neurological reflexes and coordination, Magos et al. (1981) found that female Porton–Wistar rats developed more severe coordination problems and had more cell damage in the granular layer of the cerebellum than males. Also, Goulet et al. (2003) found that female mice (C57BL/6) demonstrated deficiencies in working memory and horizontal exploration after exposure to MeHg. Bhatnagar et al., (1982) showed that MeHg exposure led to more severe leg paralysis and convulsions in female Pekin ducks, but less severe neurological problems began earlier in male ducks. Furthermore, Inouye and colleagues (1985) found that female MeHg-exposed mice (C3H/HeN) had smaller brains at 10–12 weeks of age when they were exposed on gestational day 13 or 14. These papers emphasize the need for more research into the conditions of exposure that lead to specific differences between male and female animals but that the general trend in neuronal outcomes shows females accumulate more Hg in the brain and motor neurons than males and develop more severe coordination problems than males following Hg exposure.

Hormone-linked immune effects

Silva et al. (2005) demonstrated that $HgCl_2$ has a sex-specific immunotoxic effect on cytokine production by thymocytes, lymph node cells, and splenocytes in BALB/c mice. These effects were caused by *in utero* exposure to $HgCl_2$ but were not observed until adulthood. In this experiment, Hg had an inhibitory effect in females, whereas in males it had a stimulatory effect, when cytokine production was measured at 60 days. Normal cytokine production in 60-day-old male and female mice is already sexually dimorphic, and it is speculated that immune sexual dimorphism is acquired at puberty with the onset of gonadal hormone production. Silva et al. (2005) speculate that Hg could interact with sex hormones during critical prenatal developmental periods when maternal estrogen influences the development of the brain and reproductive tract. It has also been suggested that $HgCl_2$ behaves as an estrogen in both estrogen-receptor-binding assays and MCF-7-cell-proliferation assays (Martin et al., 2003). Hg as an estrogen is discussed in greater depth in the female fertility section, but it is valuable to note that estrogens are important for development. During immune development, estrogen plays a role in both thymic development and atrophy of the thymus during puberty. Therefore, exposure to Hg early in life could alter immune-system development by altering the estrogenic effects on the development of the thymus. This change could alter the future function of the immune system and cytokine production in the adult mouse (Silva et al., 2005). Other sex differences in the immune system have been described in the literature, but will not be discussed because their links to sex hormones are not explicitly addressed (Hultman and Nielsen, 2001; Nielsen and Hultman, 2002).

Sex ratios and survival in fetuses and adults

Hg exposure has been shown to alter the sex ratios of offspring, which can have long-lasting effects on the stability and overall reproductive health of populations. Hg exposures resulted in increased mortality in male fish (*Fundulus heteroclitus*, or mummichog), but not in female fish, probably because of neurological effects (Matta et al., 2001). This same study also observed a decrease in the number of female offspring with maternal exposure to moderate concentrations of MeHg and an increase in the numbers of female offspring with maternal exposure to high concentrations. Vorhees (1985) found

a decreased male-to-female birth ratio in Sprague–Dawley rats exposed to MeHg. In addition, one study on human sex ratios following the Minamata disaster reported that male births decreased relative to the historical background and male fetuses were more often stillborn during the height of the Minamata disaster (Sakamoto et al., 2001). The probability of survival was found to be lower in adult males than females in a study of patients with Minamata disease (Tamashiro et al., 1985), and a study on Sprague–Dawley rats found that the males were significantly less likely to survive after a 26-day exposure to MeHg starting at 7 weeks of age (Tamashiro et al., 1986). It is evident that these effects are seen across species (e.g. fish, rats, and humans), but they certainly seem to be concentration-dependent.

Other sex differences

A variety of other differences between males and females in response to Hg exposure have been demonstrated in different species. For example, human males often have greater accumulation of Hg in the hair than females; however, this may be because of greater fish consumption per weight in men than in women (Mahaffey and Mergler, 1998; Shimomura et al., 1980; Wakisaka et al., 1990; Yasutake et al., 2003). In one study, hair Hg accumulation was only greater in teenage and adult males, but not younger children, and the authors suggested that endocrine factors such as hormone concentrations vary between men and women at puberty and account for this difference (Shimomura et al., 1980).

Vorhees (1985) demonstrated that female Sprague–Dawley rats had delayed vaginal patency after exposure to MeHg, indicating an effect of MeHg on pubertal onset. Tamashiro and colleagues (1986) demonstrated a link between Hg exposure, sex, and blood pressure, showing that exposed female rats (SHR/NCrj) had higher blood pressure during the 3rd and 5th weeks of a 7-week exposure period than control and exposed male rats. Male rats that survived MeHg exposure had reduced blood pressure compared with controls during the 4th week of a 7-week exposure period. This study may relate the cardiac effects of Hg exposure to hormone levels and sex, but further research is needed to make any such link.

Wildlife evidence

In wildlife species, the data available represent different field conditions, sites, exposure scenarios, and stages or ages of individuals. Thus, a wide range of observations exist in the literature, even for the same species. Sex differences in Hg accumulation among species studied in the field do show some trends, however. Females in many species of fish often have higher overall concentrations of Hg than males (Hammerschmidt et al., 2002; Nicoletto and Hendricks, 1988). This finding could be attributable to the fact that eggs have low Hg content but are of substantial mass, resulting in rising Hg concentrations in females after spawning (Niimi, 1983), or the fact that females eat more food to support the energy requirements of egg production (Nicoletto and Hendricks, 1988). Male fish often have lower gonad lipid content and a lower gonad-weight-to-body-weight ratio (Hails, 1983), which can affect the Hg content of these tissues.

Similarly, in marine mammal species such as the bottlenose dolphin, MeHg concentrations have been shown to be higher in females than in males (Meador et al., 1999). In other studies, the opposite trend is seen, and male marine mammals accumulate more Hg than females. This could be attributable to differences in the tissues observed, the age of the animals, the exposure conditions, or whether the animals used for the study were stranded, found dead, or line caught. Francis and Bennett (1993, 1994) found that mature male marine mammals have significantly higher concentrations of heavy metals, including Hg, than females at the same sexual-maturity stage. In these studies, it was believed that females transferred heavy metals to infants through the placenta as well as through lactation (Rejinders, 1988), and therefore had lower levels of contaminants, as they were transferred to their offspring. This could explain why female gonads of grayling fish exposed to Hg contained lower concentrations of Hg than most of the other organs and tissues in the same fish (Fjeld et al., 1998). Male sharks may also accumulate more Hg than females—one study showed that there was a trend for higher accumulation of Hg in males of four out of five species of sharks from offshore waters of Brazil, compared with females (Penedo et al., 2002).

Complex patterns of sex differences in Hg accumulation, dependent on life stage, were described earlier in Japanese cranes (Teraoka et al., 2007). Birds of different sexes can have different metabolic pathways that affect Hg mobilization and excretion (Heath and Frederick, 2005). For example, adult female birds can have lower circulating levels of Hg than adult males, probably due to Hg being excreted into eggs (Braune and Gaskin, 1987). Evers et al. (1998) found that male loons in a number of locations all had significantly higher concentrations of Hg in their blood and feathers than female loons. Also, significant differences in Hg concentrations were seen in the primary feathers of adult male and female herring gulls (*Larus argentatus*; Lewis et al., 1993). Hg concentrations in herring gull eggs were positively correlated with liver concentrations which were then correlated with ovary Hg concentrations. It was estimated that female herring gulls could excrete 20% more Hg via eggs than could be excreted by adult male gulls (Lewis et al., 1993). However, some studies have been hesitant to attribute all sex-specific differences in Hg accumulation to females off-loading into their eggs (Heath and Frederick, 2005; Monteiro and Furness, 2001). Some species, such as black ducks, showed no differences in Hg tissue levels between sexes (Finley and Stendell, 1978). Monteiro-Neto et al. (2003) found that sex-related differences for Hg concentrations were not significant in the dolphin *Sotalia fluviatilis.* Also, sex was shown not to influence cortisol response in yellow perch following exposure to Hg (Hontela et al., 1995).

Certain biomarkers were explored for differences between the sexes. Dietary MeHg inhibited fathead-minnow gonadal development in females but not in males

(Drevnick and Sandheinrich, 2003). MeHg exposure significantly reduced the gonadosomatic index (GSI), a measure of gonad weight relative to total body weight, in female but not male fathead minnows (Drevnick and Sandheinrich, 2003; Hammerschmidt et al., 2002), male but not female walleye fish (Friedmann et al., 1996), and in both female and male catfish (Kirubagaran and Joy, 1988a, 1992).

Summary

The trend for females to accumulate more Hg in the brain and that males accumulate more Hg in the kidneys was fairly consistent amongst the studies. Considering the differences in species, strains, and exposure windows, the established trends show a convincing pattern (Table 1). The behavioral and neurological data, although difficult to compare across studies because of the different parameters measured, show a potential trend for males to have more neurological abnormalities and, whether related or not, potential behavioral problems. Finally, decreases in the number of male births following Hg exposure often alters sex ratios in fish offspring, and the same effect can be seen in humans after high-dose exposures. It is not clear if sex-ratio differences in fish and humans occur by the same mechanism, nor is it clear if this is a widespread phenomenon across species that simply has not been thoroughly researched.

The effects summarized were obtained through a specific literature review of sex differences involving the endocrine system. Many papers exist that do not address sex differences in the areas discussed, either because they were not observed or because those authors did not focus on comparisons of the endpoints between males and females. Because the number of papers on each of the endpoints discussed is so huge, we emphasize that for practical reasons we focused on literature that described observed sex differences.

It is clear that sex differences linked to Hg exposure do exist. Some of these differences are well established, with hormonal links and mechanistic studies that must be expanded to other species and taxa, while others are apparent trends that need more in-depth study in order to understand the conditions that cause the sex differences. We were able to identify potential sex-linked mechanisms that might lead to differences in effects of Hg on the two sexes and potential links to the endocrine system. We also were able to observe general patterns in some of the sex differences across species and taxa to speculate on mechanisms involved, which are evolutionarily conserved. While it is much clearer to study the mechanisms and repeatability of a sex-difference phenomenon in a laboratory setting, it is also important that results from these lab studies further enhance the data that are obtained from epidemiological. The evidence that sex differences linked to Hg exposure do exist strongly indicates that Hg has specific effects on the endocrine system and these effects may be linked to sex steroids as well as other hormones.

Reproductive success

Hg can decrease overall reproductive success by altering gametogenesis and gonadal development in parents or by reducing hatching success of eggs and the survival of embryos (Frederick et al., 1997, 1996; Gerhard et al., 1998; Hammerschmidt et al., 2002; Kirubagaran and Joy, 1988a; Koos and Longo, 1976; Latif et al., 2001; National Research Council, 2000; Schuurs, 1999; Wester and Canton, 1992). Some of these effects are shown in the parents, while others are revealed in the subsequent generations. Hg has also been shown to adversely affect fertilization in many species and, therefore, to limit propagation of individual species by decreasing overall reproductive potential.

Reduced fecundity and fertility following exposure to Hg are often measures of reproductive success that can be observed in a number of species, including fish and humans (Drevnick and Sandheinrich, 2003; National Research Council, 2000; Olsen, 1984; Schuurs, 1999). Reproductive success is also one of the most sensitive endpoints of MeHg toxicity in birds, which has been demonstrated with altered behavior, impaired egg-laying and reduced breeding, hatching, and nestling success (Barr, 1986; Fournier et al., 2002; Heinz, 1979; Janssens et al., 2003; Nocera and Taylor, 1998; Scheuhammer, 1988; Scheuhammer and Blancher, 1994; Thompson, 1996). In mammals, reproductive toxicity is often detected by reduced libido, low fertility, menstruation abnormalities, problems with sperm production and function, mutations to germ cells, damage to the developing fetus, or postnatal developmental problems.

The 'estrogenic' properties of mercurials may help to explain their reproductive effects described below in both males and females. In vertebrates, the reproductive tract functions through the hypothalamic–pituitary–gonadal (HPG) axis, which requires interplay between the hypothalamus, pituitary gland, and gonads to successfully produce sex steroids and signal production of functional spermatozoa and oocytes (Figure 1A). Long-term and short-term exposure to Hg vapor in rats leads to deposits in the arcuate nucleus and median eminence of the hypothalamus, suggesting that hypothalamic alterations may affect the HPG axis and lead to the decreases in serum testosterone that are often seen after Hg exposure (Ernst et al., 1993). Endocrine-mediated reproductive indices and biomarkers of Hg exposure will be discussed further below as they pertain to each sex.

Sex hormones and other reproductive indices are often used as biomarkers of effects on the reproductive system. They can be measured across species and are important in establishing relationships to population-level effects following exposure to Hg. Some reproductive biomarkers that have been shown to be affected by Hg exposure include circulating levels of sex hormones such as T2 and E2, sex ratios, the expression of secondary sex characteristics, conception rates, formation of functional gametes (e.g. abnormal sperm), cyclicity of female mammals, and altered GSI

in fish (Drevnick and Sandheinrich, 2003; Matta et al., 2001).

The following two sections review the literature, using the search strategy described in the introduction, concentrating on studies that looked at the effects of mercurial species on the reproductive system, specifically with respect to the endocrine system. Organ systems of particular interest included the ovaries, testes, and the other components of the HPG axis (Figure 1A). Because many studies looked at the effects of both inorganic mercury and MeHg in the same study, and field studies often observed total Hg, we will not separate the sections according to mercurial species. Rather, we discuss the effects of both types of Hg when used in the same study so that comparisons can be made. The following two sections address male and female reproduction and the specific reproductive organs or systems that were identified as particularly sensitive to Hg in our literature searches.

Male reproductive success

Endocrine defects caused by Hg are suggested by studies that show diminished sexual activity and reproductive ability in humans, other mammals, fish, and birds exposed to MeHg (Drevnick and Sandheinrich, 2003; Fournier et al., 2002; Khera, 1973; McFarland and Reigel, 1978; Stoewsand et al., 1971). Research on Hg exposure in many different animals indicates that Hg has a strong effect on the male reproductive system. The mechanisms of toxicity are not completely known, but could include multiple discrete events that lead to the overall toxic effects. For example, sites of disruption in the male reproductive system probably include steroidogenesis, spermatogenesis, sperm function and morphology, and accumulation of Hg in male reproductive organs that causes pathological changes as well as altered HPG-axis feedback mechanisms. It is not clear if disruption of the different endpoints is a direct or indirect effect of Hg exposure, since disruption of one event may trigger another (i.e. cytotoxicity to the testes may inhibit testosterone production, which could then result in a decrease in the amount of testosterone available to signal spermatogenesis).

In studying the endocrine effects of Hg exposure, it is important to consider how these effects relate to the well-studied and well-documented neurological effects of Hg exposure. One study that addressed this issue noted that hypertrophy of the Leydig interstitial cells was observed after chronic exposure to MeHg in the treated rats, and the authors pointed out that there were no overt neurological effects observed in the treated rats, suggesting that endocrine effects may be observed at lower doses or before onset of the extensively studied neurological symptoms (Burton and Meikle, 1980). The possible mechanisms of action and effects of inorganic and organic Hg on the male reproductive system are discussed below.

A body of research exists that focuses on determining whether Hg-induced fertility problems in males are caused by a block in steroidogenesis and thus HPG axis alterations, or by toxicity to the testes that causes inhibition of spermatogenesis or normal sperm function. While Hg species and exposure times and windows may affect the mechanism of toxicity and the dose needed to produce an effect on the male reproductive tract, many potential mechanisms have come to light and should be further explored in both laboratory animal studies and epizoological and epidemiological studies.

Hg accumulation in the testes

In the previous sections on Hg accumulation and sex differences, it has been demonstrated that specific accumulation occurs in the testes and is probably linked to the reproductive effects that have been demonstrated in males. It is clear that Hg accumulates in both the testes and the spermatozoa, with MeHg showing a greater affinity for the testes than $HgCl_2$ (Ernst et al., 1991a; Lee and Dixon, 1975; McNeil and Bhatnagar, 1985; Schuurs, 1999). In the testes, Hg toxicity can lead to declines in sperm production, as well as altered steroidogenesis. $HgCl_2$ was tested in four different rodent species (rats, mice, guinea pigs, and hamsters) and shown to be toxic to the testes in all of them (Chowdhury and Arora, 1982). Cellular and tissue toxicity as a result of Hg exposure has been observed following exposure to Hg, which can also result in altered testes morphology and weight. Changes to testes and gonadal weight and size have also been associated with Hg exposures in many species including rat, mouse, birds, and fish (Chowdhury et al., 1989; Friedmann et al., 1996; Homma-Takeda et al., 2001; Orisakwe et al., 2001; Ram and Joy, 1988; Rao and Sharma, 2001; Thaxton and Parkhurst, 1973). Both MeHg and $HgCl_2$ cause a decrease in testis weight in both rats and mice (Homma-Takeda et al., 2001; Orisakwe et al., 2001). Male walleye fish treated with dietary MeHg developed suppressed reproductive potential, also as a result of reduced growth and development of testes (Friedmann et al., 1996). Webb et al., (2006) measured total Hg in the gonads of white sturgeon (*Acipenser transmonatus*) from the lower Columbia River and found that immature male sturgeon with increased gonadal Hg concentrations also had decreased GSIs. A decrease in testis weight can also be an effect of testosterone withdrawal and eventual cell death. It is not yet known why Hg shows a preferential affinity and toxicity for the testes. But it is clear that Hg cytotoxicity in the testes is not the only cause for Hg-induced male fertility problems. Other potential modes of action are discussed below.

Steroidogenesis

Burton and Meikle (1980) demonstrated pronounced effects of MeHg on testosterone and corticosteroid production (corticosteroid production discussed in the adrenal system section). In their experiments, treated rats had lower basal testosterone levels than control animals (Table 2). Furthermore, stimulation of the steroidogenesis pathway (Figure 2), using human chorionic gonadotropin, led to testosterone production in the treated rats that was only about 20% of that achieved in the control animals after acute treatment, and threefold less than was achieved in controls after chronic treatment. They also found that mitochondrial conversion of cholesterol to pregnenolone

Table 2. Male and Female Steroidogenesis After Mercury (Hg) Exposure.

Species	Hg type	Altered 3β-HSD activity	Altered progesterone level/activity	Altered testosterone level/activity	Reference
Fish: white sturgeon (*Acipenser transmontanus*)	Total Hg			M	Webb et al. (2006)
Fish: largemouth bass (*Micropterus salmoides*)	Total Hg			M	Friedmann et al. (2002)
Fish: fathead minnow (*Pimphales promelas*)	MeHg			M	Drevnick and Sandheinrich (2003)
Fish: catfish (*Clarias batracus*)	MeHg, MeHg (Emisan-6), $HgCl_2$	MF	F		Kirubagaran and Joy (1988b, 1995)
Fish: snakehead (*Channa punctatus*)	$HgCl_2$	F	F		Mondal et al. (1997)
Mammal: mouse (Swiss strain)	MeHg			M	Rao, (1989)
Mammal: mouse (*Mus musculus*)	$HgCl_2$			M	Rao and Sharma (2001), Sharma et al. (1996)
Mammal: rat (Sprague–Dawley)	MeHg Hg^o		F	M	Burton and Meikle (1980), Davis et al. (2001)
Mammal: rat (Albino)	$HgCl_2$	M			Chowdhury et al. (1985), Vachhrajani and Chowdhury (1990)
	MeHg	M		M	
Mammal: rat (Wistar)	MeHg			M	Homma-Takeda et al. (2001)
Mammal: hamster (*Mesocricetus auratus*)	$HgCl_2$		F		Lamperti and Printz (1973)
Mammal: harp seal (*Pagophilus groenlandicus*)	MeHg		F		Freeman et al. (1975)

The gender of the animals where a response was measured and/or observed is indicated by a M (male) or F (female).

was inhibited in testicular tissue following MeHg exposure, and this could inhibit steroidogenesis. Similarly, MeHg has been shown to suppress testosterone levels in male fathead minnows (Table 2; Drevnick and Sandheinrich, 2003). A study with white sturgeon (*A. transmonatus*) conducted on the Columbia River found a significant negative correlation between plasma levels of testosterone and 11-ketotestosterone muscle Hg concentrations (Webb et al., 2006).

Kirubagaran and Joy (1988b) showed that Leydig cells in the testes of the catfish (*Clarias batrachus*) had reduced activity of 3β-hydroxy-Δ^5-steroid dehydrogenase (3β-HSD; Table 2), an enzyme in the steroidogenesis pathway involved in the conversion of dehyroepiandrosterone to testosterone (Figure 2), following exposure to $HgCl_2$, MeHg and emisan 6 (an organic mercurial fungicide). The testes of treated male snakehead fish (*Channa punctatus*) contained small numbers of sperm with inactive and atrophied Leydig cells following exposure to both inorganic mercury and MeHg (Ram and Joy, 1988). Both $HgCl_2$ and MeHg were also shown to inhibit the activity of 3β-HSD in the rat, leading to a significant decrease in serum testosterone levels and structural malformations in the Leydig cells after 90 days of exposure (Table 2; Chowdhury et al., 1985; Vachhrajani and Chowdhury, 1990). Inhibition of 3β-HSD resulted in impairment of both testicular functions and steroidogenesis (Kirubagaran and Joy, 1988a). Inhibition of 3β-HSD by both organic and inorganic Hg in fish and rats demonstrates an effect of Hg that crosses species (Table 2). The mechanism involved seems to be highly conserved across fish and mammals. Further research is needed to reveal if both organic and inorganic Hg can inhibit 3β-HSD in the testes of other species.

A separate study by McVey and colleagues (2007) observed no effects on 3β-HSD following MeHg exposure when administered orally to rats with different protein or lipid diets. The authors acknowledge that this result could differ from that of other studies because the route of administration (oral versus intraperitoneal) and the period of dosing did not allow for significant accumulation of MeHg in the rats in order to see effects on 3β-HSD. However, the authors demonstrated that different lipid diets can change the effects of MeHg on male rat steroidogenesis. In this study, different protein (casein, fishmeal, or whey-based) or lipid (soybean-oil, docosahexaenoic-acid, seal-oil, fish-oil, or lard-based) diets were administered, and serum testosterone and steroidogenic enzyme activity (3β-HSD, 17-hydoxylase/C-17,20 lyase [17-OHase/C-17, 20-lyase], and 17β-hydroxysteroid dehydrogenase [17β-HSD]) was measured following Hg exposure. Briefly, none of the protein or lipid diets altered 3β-HSD or 17β-HSD levels; there was a decrease in 17-OH levels with casein, whey, and docosahexaenoic-acid diets at the highest concentrations of MeHg; there was a decrease in C17,20-lyase levels with all protein diets; and 17β-HSD levels increased with the docosahexaenoic-acid, fish-oil, and lard diets at different doses of MeHg. The fishmeal protein, but not the oil, diet had a protective effect on enzyme activities and serum testosterone levels. This study clearly demonstrates that consideration of diet in understanding how Hg may alter endocrine function is very important.

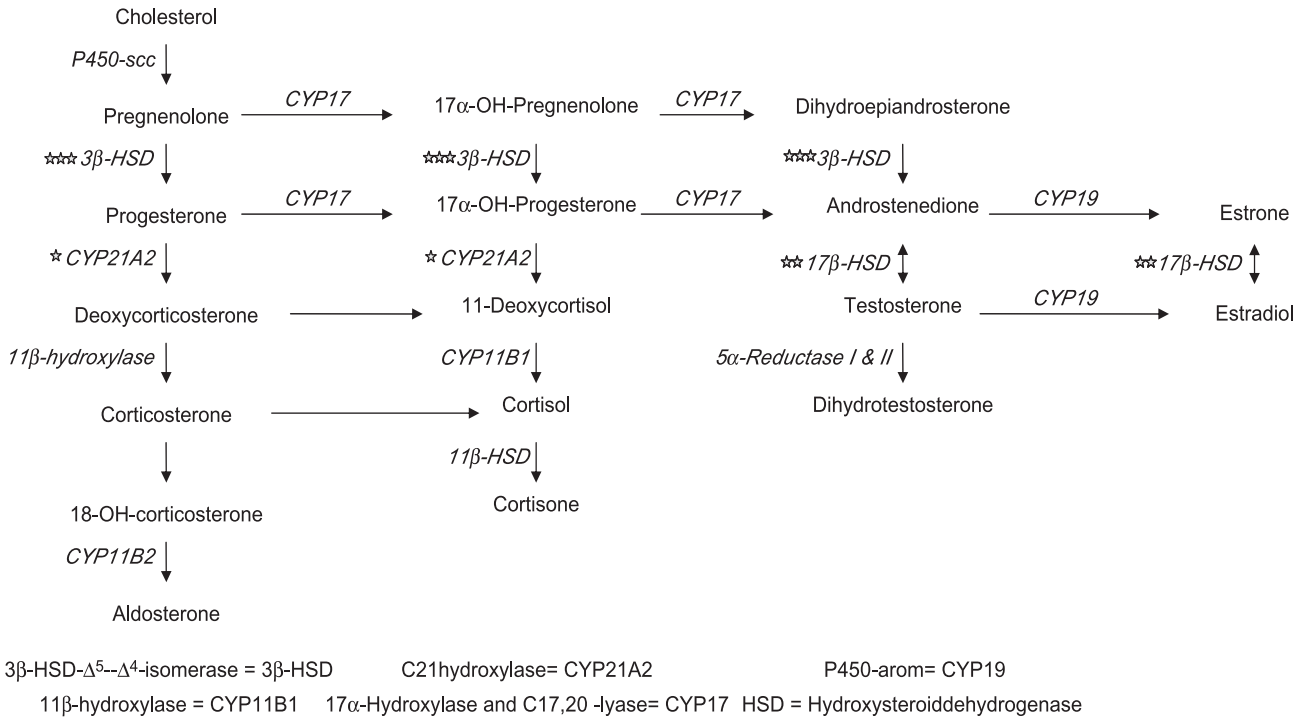

Figure 2. Major mammalian steroidogenic pathways. Key enzymes are shown near arrows. Not all enzymes or steroids are shown. Stars demonstrate examples of specific points in the steroidogenesis where mercury (Hg) has been shown to interfere with normal progression of the steroidogenesis pathway.

Other testicular enzymes associated with steroid and sperm production were measured and include succinate-dehydrogenase and acid-phosphatase activity, which was inhibited in rats and mice exposed to MeHg and $HgCl_2$ (Chowdhury et al., 1989; Sharma et al., 1996). Also, ATPase, sialic acid and protein production were reduced in the epididymis of mice exposed to $HgCl_2$ (Sharma et al., 1996). Furthermore, cholesterol accumulated in the testes and fructose was reduced in the seminal vesicles of mice exposed to MeHg, indicating a failure in the steroidogenesis pathway to convert cholesterol to androgens (Rao, 1989). Through the same mechanism, impairment of testicular lipid metabolism by Hg might result inhibited steroidogenesis and spermatogenesis in catfish (Kirubagaran and Joy, 1992).

Spermatogenesis

Declines in fertility could be a secondary result of altered steroidogenesis in the testes as discussed above, or could result from a direct effect on sperm production or function (Figure 3). Hg decreases fertility and alters spermatogenesis in multiple species, including rodents and birds (Lee and Dixon, 1975; McNeil and Bhatnagar, 1985; Thaxton and Parkhurst, 1973). Sperm synthesis in the seminiferous epithelium is triggered by testosterone release from the Leydig cells, and is supported by the Sertoli cells (Figure 3A). The overall integrity of Sertoli and Leydig cells after Hg exposure has been assessed in a number of organisms, including rats, mice, and fish (Chowdhury and Arora, 1982; Ernst et al., 1991a, 1991b; Rao, 1989). Hypertrophy of interstitial Leydig cells was seen in rats that were chronically exposed to Hg (Burton and Meikle, 1980). Leydig cells in snakehead fish showed atrophy and were inactive following exposure to both inorganic Hg and MeHg (Ram and Joy, 1988). Pekin ducks treated with MeHg had decreased numbers of Leydig cells and Sertoli cells that were no longer intact (McNeil and Bhatnagar, 1985). It can be difficult to compare cellular testicular responses to Hg across species. The effects of Hg are more easily comparable at the functional level. Similar responses related to testes function, specifically sperm production (Table 3), have been observed across species following exposure to Hg.

Hg exposure may alter male reproduction through effects on spermatogenesis and thus sperm function and morphology (Table 3; reviewed by Schuurs, 1999). In mammals, spermatogenesis takes place within the seminiferous tubules. Within these tubules, cells go through a series of developmental steps, including mitosis, meiosis, and cellular differentiation (Figure 3A). Eventually, germ cells called spermatogonia develop, which then proliferate to become spermatocytes. After two meiotic divisions, the spermatocytes become haploid spermatids. In the final phase of development, the spermatids morph into highly differentiated germ cells called the spermatozoa. This developmental process takes place in 14 stages in the seminiferous tubules (for a diagram, see Homma-Takeda et al., 2001). Kirubagaran and Joy (1992) showed that, when spermatogenesis is impaired in catfish (*Clarias batrachus*) as a result of Hg exposure, the transformation of spermatids into spermatozoa is inhibited. Lee and Dixon (1975) demonstrated that MeHg, and to a lesser extent $HgCl_2$, inhibited DNA, RNA, and protein synthesis at different

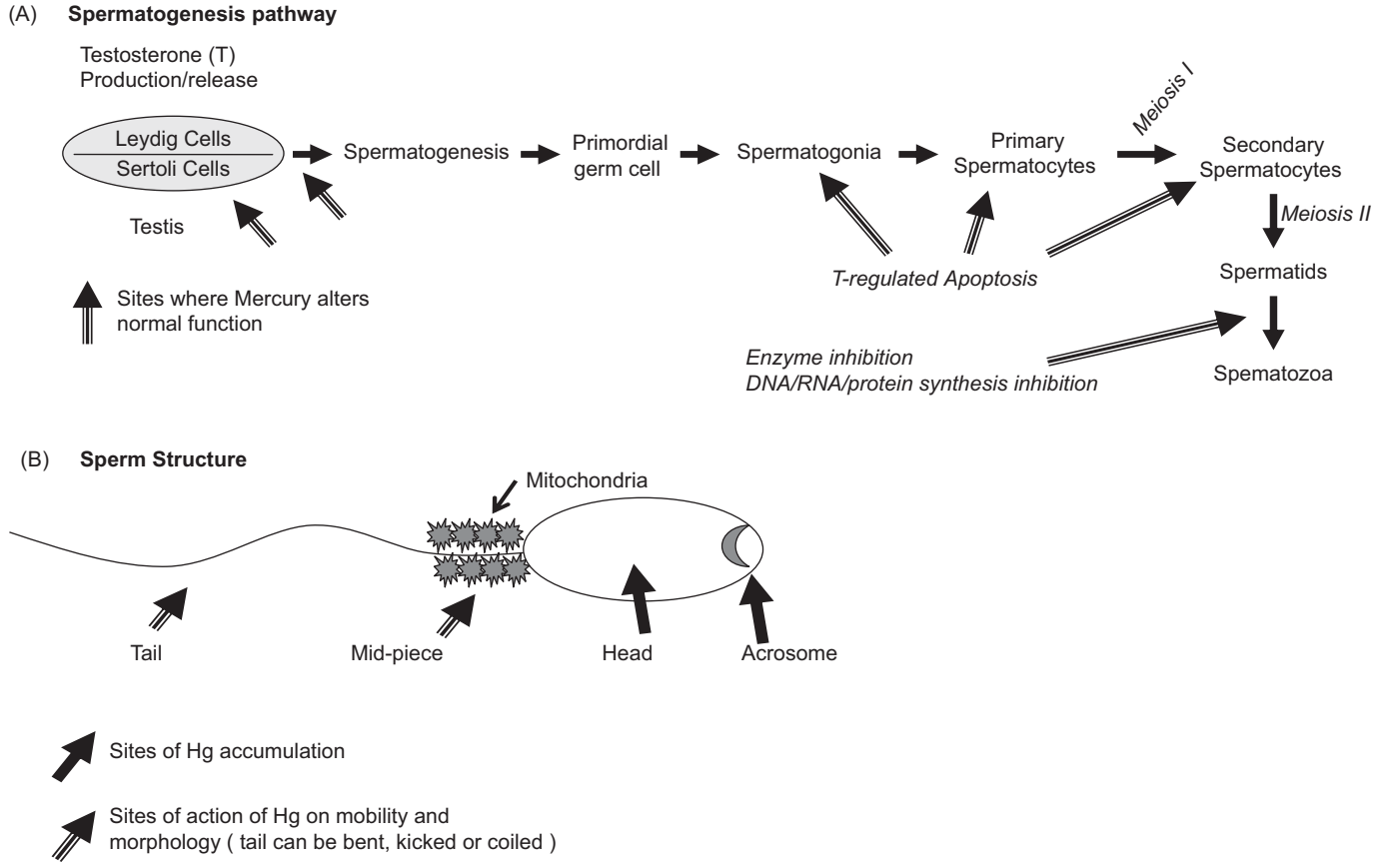

Figure 3. Spermatogenesis pathway. (A) Generalized scheme of the spermatogenesis pathway with arrows that depict where Hg types have been shown to interfere with normal progression of sperm production. (B) The structure of a sperm. Solid arrows indicate where Hg has been shown to accumulate; open arrows specify where Hg has been shown to interfere with normal sperm morphology and motility.

stages of spermatozoa development (pre-meiotic and post-meiotic). They also demonstrated that the effects of Hg during spermatozoa development were reflected in the decreased fertility of mice for up to about 50 days following a one-time exposure to either form of Hg. These timeframes of infertility directly reflect the timeframes of DNA, RNA, and protein inhibition by the two Hg compounds (Lee and Dixon, 1975).

Many of the enzymes mentioned earlier are linked to decreased steroidogenesis, and also affect spermatogenesis (Chowdhury et al., 1989; Sharma et al., 1996). For example, succinate-dehydrogenase and acid-phosphatase activity is localized in post-meiotic spermatogenic cells. Inhibition of succinate dehydrogenase in the testicular tissue of exposed animals may indicate a general decline in mitochondrial efficiency during sperm development (Chowdhury et al., 1989). This enzyme also plays an important role in the initiation of sperm motility (Sharma et al., 1996). Acid phosphatase is associated with lysosomal function. Thus, impairment of this enzyme could cause problems with testosterone translocation, which is also associated with lysosome function and sperm production (Chowdhury et al., 1989).

A natural process of programmed cell death (apoptosis) is involved in sperm development. Spontaneous germ-cell apoptosis takes place primarily in spermatogonia and spermatocytes in Stage I–IV, IX–XI, and XII–XIV tubules. After testosterone production stops or is experimentally withdrawn, spermatocyte and spermatid apoptosis is observed in Stage VII–VIII and IX tubules. When testosterone is present, it is known to act preferentially in Stage VII–VIII seminiferous tubules, and is believed to play a critical role in conversion of spermatids from step 7 to 8. Homma-Takeda et al. (2001) and Vachhrajani et al. (1992) have demonstrated that MeHg exposure induced selective germ-cell apoptosis in spermatocytes and spermatids in Stage VII–VIII and IX–XI tubules. Additional cell loss was also observed in Stage I and XII–XIV tubules in elongated spermatids and meiotic spermatocytes (Homma-Takeda et al., 2001; Vachhrajani et al., 1992). MeHg exposure also led to a marked decline in plasma testosterone levels. Homma-Takeda and colleagues (2001) suggest that the decline in testosterone may signal the stage-and-germ-cell-specific apoptosis observed in their rats during MeHg exposure (Figure 3A). Vachhrajani et al. (1992) note that MeHg toxicity to spermatocytes occurred at later stages, and propose that this toxicity is probably mediated by a stage-specific loss of Sertoli-cell support function, but the potential mechanisms were not uncovered. Apoptosis within the testes could also be due to the toxicity of Hg on the germ cells or seminiferous epithelium itself. Cell death to spermatocytes and declines in sperm number were described by Orisakwe et al. (2001). However, since the pattern of cell death in Hg-exposed rats matches what normally follows when testosterone production decreases

Table 3. Performance of Various Species on Parameters of Sperm Success After Mercury (Hg) Exposure.

Species	Hg type	Decreased sperm numbers	Altered sperm morphology	Altered sperm motility	Reference
Fish: snakehead (*Channa punctatus*)	$HgCl_2$	X	X	–	Ram and Joy (1988), Ram and Sathyanesan (1983)
	MeEHgCl (emisan)	X	–	–	
Fish: guppy (*Poecilia reticulate*)	MeHg	X	–	–	Wester and Canton (1992)
Fish: african catfish (*Clarias gariepinus*)	$HgCl_2$	–	–	X	Rurangwa et al. (1998)
Bird: Japanese quail (*Coturnix coturnix*)	$HgCl_2$	X	–	–	Thaxton and Parkhurst (1973)
Bird: fowl (Shaver Starcross line 579)	$HgCl_2$	X	X	X	Maretta et al. (1995)
Mammal: mouse (CD-1)	$HgCl_2$	X	–	–	Orisakwe et al. (2001)
Mammal: mouse (*Mus musculus*)	$HgCl_2$	X	X		Sharma et al. (1996)
Mammal: rat (Donryu)	MeHg	X	–	–	Sakai (1972)
Mammal: rat (Charles Foster)	$HgCl_2$MeHg	X	X	X	Chowdhury et al. (1989), Vachhrajani et al. (1992)
Mammal: rat (Wistar strain)	MeHg	X	–	–	Homma-Takeda et al. (2001)
Mammal: Florida panther (*Felis concolor coryi*)		X	X	–	Facemire et al. (1995)
Mammal: monkey (*Macaca fasicularis*)	MeHg	X	X	X	Mohamed et al. (1986a, 1986b, 1987)
Mammal: human	Hg	X	–	X	Choy et al. (2002a), Ernst et al. (1991b, 1991a), Ernst and Lauritsen (1991), Keck et al. (1993), Popescu (1978)
	MeHg	X	X	X	
	$HgCl_2$	–		X	
	Total Hg		X	X	

(i.e. programmed cell death, rather than necrotic cell death) and spermatogenesis diminishes, it seems that Hg cytotoxicity is not the main mechanism for sperm decreases in Hg exposed animals. Sakai (1972) describes that spermatogenesis declines are not solely due to MeHg toxicity to the testes, but to inhibition of early DNA-synthesis that is necessary for spermatogenesis.

Sperm function

It has long been known that Hg is toxic to sperm. Hg toxicity affects sperm morphology, motility, and concentration. In fact, organic phenyl mercuric acetate was once used as a spermicide in contraceptives (Baker et al., 1939). Accumulation of Hg chloride in human spermatozoa was observed in the acrosomal tip, the head, and the mitochondria and filaments of the mid-piece (Ernst et al., 1991b; Figure 3B). It caused decreased motility and oxygen consumption in ram spermatozoa that were exposed to 203Hg *in vitro* (Alabi et al., 1985). In Pekin ducks, MeHg caused degenerative changes in primary spermatocytes (McNeil and Bhatnagar, 1985). The authors surmised that germ-cell meiosis was disrupted during spermatogenesis because of Hg's effects on microtubules during cell division (Figure 3A).

MeHg was demonstrated to inhibit sperm movement by interfering with microtubule assembly (Table 3; Vogel et al., 1985). Two potential molecular pathways for MeHg to affect sperm motility are by decreasing mitochondrial energy production in the sperm tail and chemo-mechanical energy transduction by the dynein/microtubule sliding assembly (Figure 3B). Microtubules are responsible for the movement of the sperm tail, providing a mechanism by which both organic and inorganic Hg may alter sperm mobility and quantity in laboratory as well as in clinical human studies (for examples, see Choy et al., 2002a, 2002b; Dickman et al., 1998; Leung et al., 2001; Mohamed et al., 1986a). Mohamed et al. (1986b) demonstrated that MeHg caused a significant decrease in sperm swimming speed *in vitro* in a dose-dependent manner. It was observed that spermatozoa exposed to MeHg developed a side-to-side movement and bent, kinked, or coiled tails (Mohamed et al., 1986a, 1986b). An *in vitro* study of spermatozoa from male monkeys indicates that as sperm motility decreases, oxygen consumption increases. Using an inhibitor of the mitochondrial electron transport chain and an uncoupler of oxidative phosphorylation to inhibit this increase in oxygen consumption, Mohamed et al. (1986a) demonstrated that the effects of MeHg on sperm motility are not due to inhibition of mitochondrial energy production. Rather, the authors suggest that MeHg probably interferes with the dynein ATPase/microtubule assembly to alter sperm motility. Since Hg has an affinity for sulfhydryl groups, it is not surprising that it acts on the sulfhydryl groups in the microtubule assembly. Interestingly, exposure to other chemicals that interfere with microtubule assembly via sulfhydryl groups leads to similar morphological abnormalities in sperm tails (Mohamed et al., 1987), and MeHg affects other microtubules in the neuronal system affecting neuronal axoplasmic transport, neuronal migration, and cell division (Mohamed et al., 1986a). Mohamed and colleagues (1987) were the first to demonstrate the effects of MeHg on sperm morphology and motility. They state that it is logical to expect that defects in both of these

parameters will lead to fertility problems, and suggest that semen abnormalities could one day be used to monitor health effects from occupational exposure to MeHg.

Sperm success and reproduction

Primate and rodent data show similarities regarding sperm effects. It is often difficult to compare rodent laboratory data and human clinical data. In rodents, sperm are collected after necropsy from the epididymis, while in humans and primates, the sperm are collected from semen samples. The epididymal sperm in rodents are generally more motile than human sperm. Numbers of collected sperm are also much more regular between collections in controlled rodent studies with inbred strains. Despite these species differences, the similarities of data from laboratory animals and the human clinical experience are indicative of how human populations may respond to Hg exposure. This is an area where laboratory data and human epidemiological data will advance one another, leading scientists and clinicians to understand the mechanisms of action of Hg in the male reproductive system and the range of effects that are possible in humans on a population scale. Similar comparisons should be made for wildlife, although major challenges exist in this area for extrapolation between species.

A series of studies from Hong Kong demonstrates that men with fertility problems have significantly higher blood, hair, or semen Hg levels than fertile men have (Choy et al., 2002a, 2002b; Dickman et al., 1998; Leung et al., 2001). Choy et al. (2002b) compared the whole-blood Hg levels of fertile versus infertile couples, and recorded the seafood consumption of each study participant. A positive correlation between blood Hg concentration and seafood consumption was found. This study also demonstrated that a significant number of infertile males (as defined by abnormalities in semen quality or quantity) had exceptionally high blood Hg concentrations, and the association between blood Hg concentrations and infertility was statistically significant. Choy and colleagues (2002a) also demonstrated that semen Hg concentration was correlated with abnormalities in sperm morphology and motility, and that semen Hg may be a better biomarker than blood Hg concentration for Hg toxicity to human sperm. Another study determined that all parameters of semen analysis were reduced (concentration, percentage normal morphology, percentage motile, curvilinear velocity, straight-line velocity, amplitude of lateral head displacement), although non-significantly (Leung et al., 2001). Although this study determined that the percentage of motile sperm and the concentration of sperm were not correlated with Hg concentrations in the blood or sperm, seminal fluid Hg concentrations were correlated with abnormal sperm morphology and motion. The morphology of the sperm was especially abnormal in the head and midpiece, which agrees with the animal studies described above (Table 3; Ernst and Lauritsen, 1991; Mohamed et al., 1986a; Mohamed et al., 1986b). Sperm lost their forward progression and became more erratic in motion when Hg concentrations were higher (Choy et al., 2002b). Finally, Dickman and colleagues (1998) measured hair Hg concentrations in fertile and infertile males and showed that Hg levels were significantly higher in infertile males, but the study size was too small to make any definitive links between hair Hg concentrations and altered spermatogenesis.

Large studies on humans who were poisoned with high concentrations of Hg have often focused on neurological endpoints and reproductive outcomes without examining the endocrine system directly (e.g. hormone levels, hypothalamic–pituitary–testicular accumulation, sperm effects, loss of interest in sexual activity, comparisons between males and females). The first study to demonstrate that an exposed human had a testicular accumulation of Hg was a small, single-subject study involving one infertile man who worked in a choloralkali-electrophoresis plant (Keck et al., 1993). This individual had an abnormal sperm count, abnormal sperm motility and morphology, an elevated serum follicle-stimulating-hormone (FSH) level, and high blood, hair, and urinary Hg concentrations (Keck et al., 1993). The study was too small to draw any conclusions on the effects of Hg on male reproduction, but it suggests that more work in this area will help to determine if Hg contributes to male infertility.

Estrogen-receptor activity

Activation of the estrogen receptor (ER) signals important events in both male and female vertebrates. The presence of estrogen in the male mammalian system at particular life stages is required for normal fertility and reproductive function. Estrogen is produced in the male brain and testis in considerable quantities, and is detected in the semen of many species. Similarly both ER forms can be found in the male reproductive organs.

Both the Sertoli and Leydig cells of the testes produce estrogen as do the male germ cells and spermatozoa (Hess, 2000). Estrogen receptors α (ERα) and β (ERβ) are present in the rodent and human prostates and seem to be regulated by estrogen (Prins et al., 2006). However, although estrogen is known to play a physiologic role in prostate development in rodents, its function is not well understood and its role in humans is still unknown (Prins et al., 2006). Estrogen and its receptors are both present in the male epididymal tract, and research into how estrogen regulates reproduction in male mammalian systems via ER pathways is ongoing. ERα expression in the male rodent reproductive tract has been shown to be 3.5 times higher than in the female reproductive tract (Hess et al., 1997a). When ERα function is blocked in the male mouse through receptor knockout experiments, the mice are infertile, while the ERβ-knockout mice remain fertile (for review, see Hess, 2000), indicating that ERα has a larger role in male reproductive function. Research on estrogen function in male reproduction indicates that estrogen may regulate the reabsorption of fluid in the efferent ductules of the male mouse, thus concentrating the sperm and signaling normal maturation of the sperm in the epididymis (Hess et al., 1997b). Inorganic and organic Hg have been shown to bind to the ER and block normal receptor activation and

function. The studies that demonstrate this are discussed in detail below, in the section on female reproduction. However, it is important to note here that estrogen plays an important role in the male reproductive tract, and disruption of this hormone activity by Hg could influence and enhance many of the reproductive effects of Hg reviewed in this paper.

Transgenerational effects

Transgenerational effects, as defined in this review, are "carried across generations as a consequence of events that happen during the lifetime of the previous generation" (Nice et al., 2003). Many papers related to this topic exist, and it could certainly be the topic of another, separate review. However, we attempted to focus on specific endocrine-related transgenerational effects in both the male and female sections.

One large study on men exposed to elemental Hg for at least 4 months in an occupational setting found no associations between Hg exposure and decreased fertility (Alcser et al., 1989). Although the exposed group had a higher rate of miscarriages, it was not clear if this was due to Hg exposure or to a previous history of miscarriage in the women involved (Alcser et al., 1989).

Cordier et al. (1991) found that spontaneous abortions were more frequent with increasing concentrations of Hg in the father's urine measured prior to pregnancy, indicating that Hg could act directly on the father's reproductive system, and indirectly on the mother or embryo. It is also possible that Hg from the father's clothing is transferred to the mother in the home (Cordier et al., 1991). However, another study found no correlation between fertility rates and the Hg concentrations in the father's urine and ejaculate (Hanf et al., 1996).

Editorial comments on the papers by Alcser et al. (1989) and Cordier et al. (1991) debate their statistical analyses and what they mean regarding fertility and Hg exposures (Magos, 1993; Savitz et al., 1995). While a discussion about the statistical methods used in these papers are beyond the scope of this review, we agree with Savitz et al. (1994, 1995) when they say that these papers suggest associations between paternal Hg exposure and spontaneous abortion that must be further explored. Few studies examined fertility and chronic exposure to low levels of Hg. Most men and women do not know their Hg levels, so fertility assessment does not always involve measurement of blood Hg levels. Furthermore, it is unclear how low levels of Hg (those below what are well studied through high accidental exposures) has subtle but critical effects on the endocrine system, fertility, and development. More human studies that focus on the endocrine system are necessary in order to determine exactly how and when Hg exposure in human men could affect fertility. Furthermore, studies on wildlife species that transfer Hg across generations through the male population have not been well documented. However, recent studies on sperm function and exposure to certain pesticides during male development *in utero* have indicated that there may be lasting changes that take place epigenetically through changes in methylation patterns on germ-cell DNA (Anway and Skinner, 2006). To our knowledge, this has not been explored for Hg in any species, so future research in this area could be very interesting.

Summary

Hg has a specific affinity for the testes, which may lead to multiple effects at the molecular and cellular levels, ultimately altering normal reproductive function in the male. As was discussed, Hg can affect multiple points in the steroidogenesis pathway, inhibiting enzymes important for hormone synthesis (Figure 2). Hg can also affect the production of sperm at multiple points in the spermatogenesis pathway through testosterone-regulated apoptosis of spermatogonia and spermatocytes, and inhibition of enzymes important in the progression of spermatids to spermatozoa (Figure 3A). Hg also has significant effects on sperm function and morphology through accumulation, cytotoxicity, and inhibition of mitochondria and microtubule function (Figure 3B). Because Hg can activate ERs, it will be important to further explore the possible ER-regulated mechanisms of toxicity of Hg in the male reproductive tract. Finally, human studies have shown that the effects of Hg on the male reproductive tract can be transgenerational, but more studies in various species are needed to better understand when and how Hg affects the offspring of exposed parents. The studies above represent the information available in the literature from laboratory-based experiments to field and epidemiology studies across multiple species. More research will help to link these different types of studies for a greater understanding of the effects of Hg on the male reproductive tract.

Female reproductive success

Female organisms exposed to all forms of Hg in experimental systems show a variety of reproductive problems: menstrual-cycle abnormalities; inhibition of ovulation; infertility; spontaneous abortions; stillbirths; congenital malformations; and behavioral alterations in offspring (for review, see Schuurs, 1999). Hg's effects on reproduction have been known in humans since at least the late 1400s, when inorganic mercurial salts and organomercurials were used to induce abortions. Some were even used in contraceptive vaginal jellies (Schuurs, 1999). Although reproductive problems clearly result from Hg exposures, the doses and exposure times or windows that lead to reproductive problems have not necessarily been established. The consequences of exposure are especially difficult to establish for human and wildlife populations, where the range of sensitivities among any given population is not easily determined.

The specific affinity that Hg has for the endocrine system, including the hypothalamus, pituitary gland, and ovaries, affects multiple endpoints in female reproduction. Hg causes morphological changes in the reproductive organs and developmental abnormalities in fertility (Table 4), oocyte production (Table 5), fecundity, and finally development of the embryo, fetus, and newborn. The section below

Table 4. Performance of Various Species on Parameters of Female Fertility Success After Mercury (Hg) Exposure.

Species	Hg Type	Decreased spawning, fertilization, or conception success	Increased abortion or stillbirth rate	Reference
Invertebrate: sea squirt (*Ciona intestinalis*)	$HgCl_2$	X	–	Bellas et al. (2001)
Fish: fathead minnow (*Pimphales promelas*)	$HgCl_2$ MeHg	X	–	Drevnick and Sandheinrich (2003), Hammerschmidt et al. (2002), Snarski and Olson (1982)
Fish: killifish (*Fundulus heteroclitus*)	MeHg	X	–	Matta et al. (2001)
Mammal: mouse (Kud:ddY)	MeHg $HgCl_2$	X	X	Kajiwara and Inouye (1992)
Mammal: monkey (*Macaca fasicularis*)	MeHg	X	X	Burbacher et al. (1984)
Mammal: human	MeHg	X	–	Bakir et al. (1973), Cordier et al. (1991), De Rosis et al. (1985), Rachootin and Olsen (1983), Rowland et al. (1994), Sikorski et al. (1987)
	Hg^o	X	X	

Table 5. Altered Performance on Egg Production Endpoints Across Species.

Species	Hg type	Cycle irregularities	Altered oogenesis or changes to oocytes	Delayed or inhibited ovulation	References
Fish: fathead minnow (*Pimphales promelas*)	$HgCl_2$	–	X	–	Snarski and Olson (1982)
Fish: snakehead (*Channa punctatus*)	MeEHgCl (emisan), MeHg, $HgCl_2$	–	X	–	Dey and Bhattacharya (1989), Ram and Joy (1988)
Fish: catfish (*Clarias batrachus*)	MeEHgCl (emisan), MeHg, $HgCl_2$	–	–	X	Kirubagaran and Joy (1988a)
Fish: catfish (*Heteropneustes fossilis*)	$HgCl_2$	–	X	–	Bano and Hasan (1990)
Fish: mosquitofish (*Gambusia holbrooki*)	$HgCl_2$	X	X	–	Tatara et al. (2002)
Amphibian: African clawed frog (*Xenopus laevis*)	$HgCl_2$	–	X	–	Barnes et al. (1999)
Bird: Japanese quail (*Coturnix coturnix*)	$HgCl_2$	–	X	–	Thaxton and Parkhurst (1973)
Bird: white leghorns (domestic fowl)	MeHg	–	X	–	Lundholm (1995)
Mammal: rat (Sprague–Dawley)	Hg^o	X	–	–	Davis et al. (2001)
Mammal: hamster (*Mesocricetus auratus*)	$HgCl_2$	X	–	X	Lamperti and Printz (1974)
Mammal: hamster (Golden Hamster, females)	MeHg, $HgCl_2$	–	–	X	Watanabe et al. (1982)
Mammal: human	Hg^o	X	–	–	De Rosis et al. (1985), Rowland et al. (1994), Sikorski et al. (1987)

describes various effects and potential modes of action for Hg and its actions in the female reproductive system.

Morphological alterations

Morphological alterations resulting from Hg exposure can seriously affect the overall reproductive fitness and success of an organism and population. Female fish have shown decreases in gonad size and weight following exposure to both inorganic Hg and MeHg (Dey and Bhattacharya, 1989; Drevnick and Sandheinrich, 2003; Friedmann et al., 1996; Ram and Joy, 1988). Changes in the morphology of female reproductive tissues and organs across species include gonadal development and weight and follicular maturation. Watanabe and colleagues (1982) observed that $HgCl_2$ exposure inhibited ovulation, but this could not be explained by an increased frequency of chromosome aberrations in hamster metaphase II oocytes, an effect that was observed only during *in vitro* experiments in mouse oocytes by Jagiello and Lin (Jagiello and Lin, 1973). The differences in effects on ovulation between MeHg and inorganic-Hg exposure are not easily explained, but Lamperti and Niewenhuis (1976) suggest that $HgCl_2$ may have more potent effects on the HPG

(ovarian) axis than MeHg has. This is a possible explanation for why $HgCl_2$ inhibits ovulation despite a relatively low level of ovarian accumulation compared with MeHg, which does not delay or affect ovulation (Table 5).

Ovulation and egg production

Hg exposure can interfere with the production of estrogen in females, resulting in reduced numbers, size, and quality of eggs produced. Several studies have demonstrated that ovary development, egg production, and menstrual cycles can be severely altered in females following exposure to Hg (Table 5). Ovary development in the snakehead fish was arrested and ovaries were devoid of vitellogenic oocytes (i.e. oocytes containing egg-yolk protein, discussed further in the next subsection) following exposure to Hg (Ram and Joy, 1988). Eggs from MeHg-treated domestic fowl were reduced in number and size, had a rough surface, indentations, and thinner shells (Lundholm, 1995). Both the hamster and rat experienced abnormalities in corpora-lutea morphology and had lengthened estrous cycles, even with exposure to different forms of Hg (Table 5; Davis et al., 2001; Lamperti and Printz, 1973, 1974). Very small changes in estrous cyclicity and corpora lutea may indicate alterations to the hypothalamic-axis feedback systems, although the plasma hormone concentrations and ability to maintain a pregnancy may not be affected.

Menstrual-cycle abnormalities associated with Hg exposure in humans have been documented in a group of papers, largely from Eastern Europe (Table 5). They demonstrate that exposure to Hg vapor and metallic Hg lead to menstrual-cycle problems such as painful menstruation and changes in bleeding patterns and cycle durations in women workers from various occupations involving exposure to Hg vapor (reviewed in De Rosis et al., 1985; Rowland et al., 1994; Sikorski et al., 1987). The authors describe how many of these abnormalities are interpreted as indirect consequences of the hypothalamic axis.

HPG axis and steroidogenesis

A series of papers from the 1960s indicated that Hg accumulates in the hypothalamus (Berlin and Ullberg, 1963; Cassano et al., 1966; Kurland et al., 1961; Nordberg and Serenius, 1969). In one study, Hg was shown to be concentrated in the corpora lutea of the ovary, the sinusoids of the pituitary gland, and the arcuate nucleus of the hypothalamus (Lamperti and Printz, 1974). The ovaries and gonads of the harp seal (*Pagophilus groenlandicus*) accumulate high levels of MeHg and show a marked alteration of steroid biosynthesis (Freeman et al., 1975). Webb et al. (2006) found a significant negative correlation between total Hg concentration in the livers of white sturgeon (*A. transmonatus*) in the lower Columbia River and plasma E2 level. MeHg also reduced the capacity of the ovaries to produce sex hormones in fish (Drevnick and Sandheinrich, 2003). Apoptosis was discussed in detail in the above Male Reproductive Success section with regards to sperm development. Apoptosis also could play an important role in females exposed to MeHg. Drevnick et al. (2006) demonstrated that dietary MeHg increases ovarian follicular apoptosis in female fathead minnows. The authors suggest that this increased apoptosis could be a possible mechanism for the impairment of reproduction in female fish via the suppression of E2 in female fish exposed to MeHg.

Lamperti and Printz (1973, 1974) showed that the chelating agent, neutrophil activating protein, was able to reverse the effects of Hg and decrease the amount of Hg that accumulated in all of the tissues they measured. To further support the idea that Hg may "directly affect the responsiveness of the ovary and pituitary gland to hormonal stimulation", Lamperti and Niewenhuis (1976) used membranous whorls as a measure of the capability of Hg to induce ultra-structural changes in the arcuate nucleus neurons of the hypothalamus. The increased number of whorls in the treated hamsters is believed to be a secondary effect of a Hg-induced alteration in ovarian function. FSH levels in the pituitary gland of treated animals were significantly higher than in the pituitary glands of control animals on day 3 of estrous, but the plasma levels of FSH and leutinizing hormone (LH) were comparable in the control and treated animals. Lamperti and Niewenhuis (1976) suggested that Hg can inhibit the release of signaling proteins from the arcuate neurons into the hypophyseal portal system, thus affecting the hypothalamic signals to the pituitary gland and gonads.

Estrogen has been shown to have a protective effect against MeHg in ovariectomized rats (Oliveira et al., 2006). This effect led to a significant decrease in the level of luteinizing-hormone-releasing hormone in the medial hypothalamus and an increase in Hg accumulation in the anterior pituitary gland and the medial hypothalamus. Estrogen replacement reversed the accumulation of Hg in the anterior pituitary gland and the medial hypothalamus, and decreased the release of luteinizing-hormone-releasing hormone in the medial hypothalamus and of LH in the plasma. Thus, the removal of estrogen from healthy female animals makes them more sensitive to Hg, and this effect can be reversed by estrogen replacement (Oliveira et al., 2006). Hg exposure can induce calcium uptake by cells and lead to increased intracellular calcium concentrations, whereas estrogen and non-genomic ERs may inhibit the Hg-induced intracellular increases in calcium in the pituitary gland and hypothalamus, offering a protective function for estrogen in the HPG axis. Estrogen may also be linked to the increase of the antioxidant glutathione that occurs following Hg exposure, also helping to protect the cells from the toxic action of Hg (Oliveira et al., 2006).

The effects of Hg exposure on the female reproductive system are certainly tied to potential alterations in the hypothalamic–pituitary feedback system with the female gonads. The observations mentioned above demonstrate that the mechanisms by which Hg is toxic in female reproduction are not clear. More research is needed to identify whether cytotoxicity of Hg in the HPG axis is sufficient to cause the reproductive abnormalities observed in many of the described experiments. Many questions remain

unanswered—for example, does Hg interact with estrogen in all species, are specific cell types in the female endocrine system more sensitive to the toxic effects of Hg, or can Hg exposure alter hormone concentrations and hormone actions in specific organs by an unknown mechanism? The affinity that Hg has for this system, coupled with the clear effects of Hg on reproduction, highlights the need for more research on the potential modes of action of Hg in the female endocrine system.

Endocrine regulation of reproduction in many species is controlled by the HPG axis. Because $HgCl_2$ accumulates in the pituitary gland, it may cause cell damage that would alter gonadotropin release and feedback by the pituitary gland to release hormones. $HgCl_2$ specifically accumulates in the arcuate nucleus neurons of the hypothalamus, neurons responsible for helping to synthesize and store follicle-stimulating-hormone-releasing hormone, lutenizing-hormone-releasing hormone, and prolactin-inhibiting factor (or dopamine). Lamperti and Printz (1973, 1974) suggested that other 'releasing' hormones may be altered by $HgCl_2$ accumulation and damage to the arcuate nucleus of the hypothalamus; that is, thyrotropin-releasing hormone (TRH), corticotrophin-releasing hormone, and growth-hormone-releasing hormone. At high concentrations, MeHg exposure can inhibit gonadotropic activity in the pituitary glands of fish (Joy and Kirubagaran, 1989). The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release gonadotropin hormones GTH-1 and GTH-2, which in turn act on the gonads to stimulate steroidogenesis (Greeley, 2002; Figure 1A). It was demonstrated that mercurials inhibit the secretion of GnRH from the nucleus preoptimus, which causes pituitary-gland gonadotrophs to be inactivated and result in impaired gonadal growth in snakehead fish (Ram and Joy, 1988). Ram and Joy (1988) also showed that exposure to mercurials compromised the monoaminergic system, which modulates stimulation and control of gonadotrophs in the pituitary gland.

It has been suggested that Hg exposure causes fluctuations in the progesterone content in the corpora lutea via damage to the luteal-cell membrane. As a result, the cellular metabolism needed for steroid production is unable to function normally (Lamperti and Printz, 1973). Altered progesterone levels have been seen in a range of species, including rat, hamster, harp seal, and catfish, following exposure to Hg (Table 2; Davis et al., 2001; Freeman et al., 1975; Kirubagaran and Joy, 1995; Lamperti and Printz, 1973). Kirubagaran and Joy (1995) observed a decrease in cholesterol in the ovaries of catfish following exposure to both organic and inorganic Hg. Hg-induced inhibition of steroidogenesis results from a reduction in free cholesterol and esterified cholesterol, which are precursors for steroid hormone synthesis. It also causes inhibition of 3β-HSD activity, which is the enzyme that catalyzes the conversion of pregnenolone to progesterone, as shown in the catfish (*Clarias batrachus*) (Kirubagaran and Joy, 1988b). Mondal et al. (1997) observed a high rate of progesterone synthesis and a low rate of conversion to 17β-estradiol in the oocytes of *Channa punctatus* (Mondal et al., 1997). Alterations to estrogen or estradiol levels following Hg exposures have been noted in rats and fish (Davis et al., 2001; Drevnick and Sandheinrich, 2003). Drevnick and Sandheinrich (2003) added support to the study by Mondal et al. (1997), demonstrating that suppressed levels of 17β-estradiol following MeHg exposure were positively correlated with the GSI, a measure of gonad weight relative to body weight. Gonadal maturation and activity, and GSI, have been shown to be significantly inhibited by exposure to mercurials in a variety of fish (Davis et al., 2001; Dey and Bhattacharya, 1989; Drevnick and Sandheinrich, 2003; Joy and Kirubagaran, 1989; Ram and Sathyanesan, 1983, 1986). Mondal et al. (1997) also showed that the accumulation of progesterone was positively correlated with a significant increase in 3β-HSD activity following Hg exposure in *C. punctatus*, which shows that Hg plays a role in its induction in the oocytes at the spawning stage. The binding of Hg to the plasma membrane Na^+/K^+-ATPase mediated the induction of 3β-HSD (Mondal et al., 1997). As discussed in the section on male fertility, 3β-HSD activity is also inhibited in males and leads to decreased testosterone production. This enzyme has dual actions in the steroidogenesis pathway. That Hg inhibits 3β-HSD activity in both male and female animals across several species (Table 2), leading to decreases in testosterone and progesterone levels, respectively, implies that Hg acts by a specific mechanism to inhibit 3β-HSD activity.

Vitellogenin production

Many organisms including fish, amphibians and birds produce vitellogenin, a yolk-precursor protein that is a substrate for developing eggs. This protein is tightly coupled with steroid homeostasis and is one of the most common biomarkers for hormone disruption. Vitellogenin synthesis is controlled by the hypothalamic–pituitary–ovarian axis (Ng and Idler, 1983). Gonadotropins released by the pituitary gland stimulate 17β-estradiol (E2) synthesis in the ovary, which then triggers liver hepatocytes to produce vitellogenin (Nath and Sundararaj, 1981a, 1981b; Van Bohemen et al., 1982; Yaron et al., 1977). When E2 levels increase, vitellogenin production increases as well. Induction of vitellogenin gene expression has been shown to be mediated by the ER (Flouriot et al., 1995). Vitellogenin RNA was suppressed in female fathead minnows (Pimephales promelas) with increasing MeHg dietary exposure; however, there was no significant difference in vitellogenin expression in males at any level of MeHg exposure (Klaper et al., 2006). It is clear that Hg has the capability of influencing the HPG axis as an estrogen, depending on the situation. It is important to keep this in mind while assessing the data in this review.

Estrogen-receptor activity

$HgCl_2$ is a weak estrogen at the ERα, as demonstrated via binding experiments, transcriptional-activation assays with pS2 and the progesterone receptor as the downstream genes, and by an assay in which MCF-7 human breast-cancer cells proliferate in the presence of estrogenic compounds (Choe

et al., 2003; Martin et al., 2003). Results from both the binding and transcriptional-activation assays demonstrate that $HgCl_2$ interacts with the hormone-binding domain of the ER, and in both cases the Hg species blocks estrogen from binding to the ER. Binding experiments using modified recombinant ERα protein constructs demonstrate that $HgCl_2$ activates the ERα receptor through cysteines C381 and C447, histidine H524, and the negatively charged amino acids glutamic acid E523 and aspartic acid D538 (Martin et al., 2003). Martin and colleagues (2003) suggest that Hg and similar metals may bind with high affinity to the amino acid sites listed above in the hormone-binding domain of ERα. Martin et al. (2003) suggest that receptor binding could take place in two possible ways. The first suggested mechanism is a two-step model, in which Hg binds to the receptor-binding domain, leading to a conformational change that causes dissociation of stabilizing proteins from the receptor (for example, heat-shock proteins), and allows the metal to then bind to other amino acids, causing receptor stabilization. The second proposed mechanism is for two Hg molecules to bind to the receptor in such a way that both molecules bound to specific sites would change the receptor's conformation so that it resembles normal hormone binding. These two theories on Hg binding must be further tested, but the authors believe that the first suggested mechanism is the closest to reality, on the basis of data from chromium binding experiments. They surmise that other metals, such as Hg, may bind in a similar way. Regardless of the mechanism, Hg behaves as a weak estrogen in both binding and transcriptional-activation assays (Choe et al., 2003; Martin et al., 2003). When Hg acts as an estrogen, it can potentially result in many of the reproductive effects discussed above for both males and females. As mentioned above, Hg has certainly demonstrated multiple modes of action, including acting via both estrogenic and non-estrogenic mechanisms.

Transgenerational effects

Transgenerational effects, as defined earlier in the 'Male Reproductive Success' Section, are consequences of events that happen during earlier generations (Nice et al., 2003). It is well known that inorganic and organic Hg are transferred from mother to fetus in humans and other animals (Amin-Zaki et al., 1981; Ask et al., 2002; Burger and Gochfeld, 2003; Clarkson et al., 1972; Fournier et al., 2002; Galster, 1976; Hammerschmidt et al., 1999; Johnston et al., 2001; Latif et al., 2001; Lauwerys et al., 1978; McKim et al., 1976; Niimi, 1983; Skerfving, 1988; Stern and Smith, 2003; Vimy et al., 1990). Mammalian mothers transfer Hg to their offspring through placental transfer and, to a lesser extent, lactation (Nielsen and Andersen, 1995; Sakamoto et al., 2002; Skerfving, 1988; Yoshida et al., 1994). Female fish and birds have been shown to transfer Hg to their eggs during oogenesis (Burger, 1994; Dey and Bhattacharya, 1989; Fournier et al., 2002; Lewis et al., 1993; Lewis and Furness, 1993; Monteiro and Furness, 2001; Niimi, 1983; Ram and Sathyanesan, 1986). The diet of the maternal adult during oogenesis, and not adult body burden, is the principal factor in MeHg concentration in fish eggs (Hammerschmidt and Sandheinrich, 2005), and dietary Hg has been shown in lab and field settings to be directly related to egg Hg concentration (Albers et al., 2007).

It is expected that a developing embryo, fetus, neonate, or juvenile will be more sensitive to Hg than an adult (in any species), since the early stages of development include many physiological changes that involve cell division and DNA, RNA, and protein synthesis, as well as hormonal changes. Two recent studies with birds have shown that Hg exposure can result in significantly reduced survival of progeny in the early stages of development. Albers et al. (2007) exposed American kestrels (*F. sparverius*) to MeHg via diet. Exposures resulted in decreased numbers of eggs laid and numbers of nestlings fledged per kestrel pair, failed incubation of eggs, and decreased and delayed hatching. Albers and colleagues (2007) noted that the significant effects on progeny occurred in the first two eggs hatched, and also that MeHg exposure had little effect on the fertility of the eggs. Brasso and Cristol (2007) saw similar effects in tree swallows (*Tachycineta bicolor*). This study was conducted in the Shenandoah River watershed and compared populations of swallows in Hg-contaminated and reference sites. Four reproductive endpoints were affected by Hg exposure: proportion of eggs hatched; proportion of nestlings fledged; proportion of eggs fledged; and number of nestlings produced. Together, these two studies provide good evidence that the overall survival of the juvenile raptor and passerine bird species can be seriously affected by Hg exposure. Another study, however, did not find strong support for an influence of *in ovo* Hg exposure on chick survival in American avocet (*Recurvirostra Americana*) and black-necked stilt (*Himantopus mexicanus*) in the field (Ackerman et al., 2008).

One paper recently did an in-depth analysis of the literature to determine how Hg exposure in the adult human is reflected in the fetus. Stern and Smith (2003), in an assessment of epidemiological data, determined that cord-blood Hg concentration is, on average, 70% higher than that of maternal blood based on matched cord-maternal blood pairs. More than 5% of cord-maternal pairs showed cord blood Hg concentrations 300% greater than their paired maternal blood Hg levels (Stern and Smith, 2003). This indicates that MeHg exposures to the fetus are higher than those of the mother (Stern and Smith, 2003). That maternal transfer takes place is clear, but how this transfer affects the developing organism and, specifically, the developing endocrine system, is largely unknown.

After the disasters of Minamata, Niigata, and Iraq, many infants were born with congenital problems due to *in utero* and lactational exposure to MeHg (Amin-Zaki et al., 1976, 1980, 1981; Amin-Zaki and Majeed, 1974; Harada, 1976, 1978; Takeuchi, 1977). The effects on the Minamata and Niigata infants were surprising, since their mothers displayed no obvious adverse effects from the Hg exposure, and these children did not develop clear neurological symptoms until they reached about 6 months of age. Further study in laboratory settings with a range of organisms explored the effects of transgenerational Hg exposures, demonstrating

embryotoxic effects of MeHg and inorganic Hg, alterations in bone development, and cardiovascular and immunological effects (Bajaj et al., 1993; Heinz and Hoffman, 2003a, 2003b; Kajiwara and Inouye, 1986, 1992; Koos and Longo, 1976; Latif et al., 2001; Sharp and Neff, 1982; Tchounwou et al., 2003). Population effects, such as reduced spawning, fertilization, or conception, embryogenesis, hatching and fledging success, and increased rates of abortion or stillbirths, can result from maternal transfer of Hg in many different organisms (Table 4; Bellas et al., 2001; Birge et al., 1979; Burger and Gochfeld, 1997; Fimreite, 1974; Finley and Stendell, 1978; Heinz, 1976a, 1976b, 1974; Janssens et al., 2003; Khan and Weis, 1987, 1993; Latif et al., 2001; Matta et al., 2001; Snarski and Olson, 1982; Spann et al., 1972; Wright et al., 1974). Developmental effects have also been shown to be the result of maternal transfer of Hg (Burbacher et al., 1984; Fjeld et al., 1998; Heinz, 1976a, 1979; Hoffman and Moore, 1979; McKenney and Costlow, 1982; McKim et al., 1976; Sikorski et al., 1987; Snarski and Olson, 1982). However, it is unclear whether these reproductive and developmental effects are the direct (e.g. via receptor binding) or indirect (e.g. via decreased fitness resulting in increased developmental delays) result of endocrine disruption. More research is certainly needed on Hg types and their link to the endocrine system, particularly following transgenerational exposures, since the developing organism is expected to be more sensitive than the adult.

Summary

Hg can affect the female reproductive system and HPG axis in numerous ways, through estrogenic and other pathways. Although all the specific mechanisms by which Hg is toxic in female reproduction are not yet clear, several effects have been consistent across taxa groups, such as changes in estrogen or estradiol levels following exposure to Hg. With a decrease in estrogen production, reductions in the number, size, and quality of eggs produced have been observed. Overall ovary development, egg production, and menstral cycles have also been severely changed following Hg exposure. Hg accumulation has been shown to alter various releasing hormones (i.e. TRH, CRF, and GnRH) and progesterone levels. Hg can also inhibit 3β-HSD activity, as has been observed in males, and the release of signaling proteins, which affects the hypothalamic signals to the pituitary gland and gonads. Exposure to inorganic and organic forms of Hg results in decreased gonad size and weight in fish species. Mammals, fish, and birds are all known to transfer Hg to offspring and this clearly affects the numbers of successful progeny. It is clear that Hg affects female reproduction; however, more research is needed on the potential modes of action of Hg in the female endocrine system.

Thyroid system

The thyroid system is highly conserved amongst the vertebrates (Figure 1B). The mammalian thyroid is generally located close to the pharynx. Most of the thyroid tissue in fish (and some amphibians) is found throughout the connective tissue of the pharyngeal area, but it can also be distributed throughout the body in areas around the eye, ventral aorta, hepatic veins, and anterior kidney. Despite these differences in the location of thyroid tissue, the thyroid system of all vertebrates functions via the hypothalamic–pituitary–thyroid (HPT) axis. The brain signals the hypothalamus to release thyrotropin releasing hormone (TRH), which is delivered to the anterior pituitary gland to stimulate the synthesis and release of or thyroid-stimulating hormone (TSH). TSH, in turn, signals thyroid-hormone production by the thyroid gland, especially thyroxin (T4; Figure 1B). Triiodothyronine (T3), the more active form of thyroid hormone (TH), is produced to a lesser extent in the thyroid, but can be converted to T3 from T4 in peripheral tissues by deiodinases. T4 and a small amount of T3 produced by the thyroid gland are released into the blood and carried by thyroid-hormone-binding proteins (e.g. thyroid binding globulin, transthyretin, or albumin) in the plasma to target tissues. TH can stimulate gene expression in TH-sensitive cells, or it can be metabolized by enzymes in the liver. Furthermore, TH levels in the blood feedback on the HPT axis to signal regulation of TRH and TSH release from the hypothalamus and pituitary gland respectively (Figure 1B).

The thyroid gland is made up of thyroid follicles, which are made up of tightly bound epithelial cells surrounding a space called the colloid. On the surface of the epithelial cells is a sodium-iodide symporter (NIS), which transports iodide into the thyroid gland following stimulation of the thyroid gland by TSH. THs are formed in the colloid, which contains a large reserve of iodine bound to a protein called thyroglobulin. The enzyme thyroid peroxidase (TPO) catalyzes the oxidation of iodide in the colloid, which leads to the iodination of thyroglobulin and the coupling of iodinated tyrosyl residues to form iodothyronine, mostly in the form of T4. The thyroglobulin and the attached T3 or T4 is endocytosed into the apical epithelium, and this endosome fuses with a lysosome in the cytoplasm. Inside the lysosome, the THs are cleaved from thyroglobulin and exocytosed at the basal membrane of the epithelial cell, releasing the contents (T4, T3, and thyroglobulin) into the blood supply (for a general review of the thyroid system, see Zoeller et al., 2007).

Hg accumulation in the HPT axis

As mentioned in the accumulation section, the HPT axis is one of the areas where significant accumulation of Hg occurs at concentrations that can rival the kidneys and liver. In 1974, Kosta and colleagues did a post-mortem study on retired Hg mine workers who were chronically exposed to Hg vapor. Hg concentrations in the mine workers were greatest in the thyroid and pituitary gland, 3–4 times greater than those in the kidney (Kosta et al., 1975). Hg concentrations in these endocrine organs were about 1,000 times higher in the mine workers than in the controls. Falnoga et al. (1999, 2000) observed high concentrations of Hg in the pituitary gland and thyroid of retired mine workers from the same mine almost 30 years later. Elevated levels of Hg were also observed in the residents of the mining town (albeit to a

lesser degree). Nylander (1986) showed that dentists who worked with amalgams accumulated high levels of Hg in the pituitary gland that were 10–70 times higher than in unexposed controls (Nylander and Weiner, 1991). In rodents, both inorganic and organic Hg has a high affinity for the thyroid and pituitary gland relative to other organs (for data and review, see Nishida et al., 1986). These high concentrations of Hg accumulation observed in the pituitary gland and thyroid have led researchers to explore the potential effects of Hg on the thyroid system. Hg in the thyroid gland could alter TH synthesis and release via many different mechanisms, whereas Hg accumulation in the pituitary gland could lead to changes in the feedback mechanisms and signaling pathways that regulate the production of TH.

Thyroid hormone concentration changes

TH levels and associated enzyme activities are clearly altered in several fish and mammalian species following exposure to MeHg, $HgCl_2$, or Hg vapor. The trends in plasma levels of TSH and protein-bound and free T3 and T4 were not always consistent amongst the papers reviewed, probably because of differences in species, strains, ages of the animals, and exposure times and doses. Some trends in the thyroid system in response to Hg exposure exist (Table 6); however, because the thyroid system is so highly regulated by feedback mechanisms, it is possible that changes to the thyroid system could reveal opposite trends in TH concentrations, because the hormone measurements are performed at different time periods in the response to Hg exposure. Circadian rhythms also influence hormone concentrations and this can explain some of the differences in TH levels, especially in field studies, which are less controlled.

The studies reviewed here are summarized in Table 6. Many studies observed that plasma T3, T4, or both decreased after exposure to $HgCl_2$ and MeHg in fish, rats, and mice in the laboratory (Bhattacharya et al., 1989; Goldman and Blackburn, 1979; Kawada et al., 1980; Kirubagaran and Joy, 1994; Mochizuki and Asahara, 1978; Nishida et al., 1986; Sin et al., 1990; Sin and Teh, 1992), and in fish exposed to Hg in the field (Hontela et al., 1995). On the other hand, plasma T3 and T4 levels increased in several reports in many species, including fish, rats, and occupationally exposed humans (Barregard et al., 1994; Bleau et al., 1996; Hontela et al., 1995; Kabuto, 1991). Other studies observed increases in the

Table 6. Changes in Performance on Thyroid System Endpoints in Various Species After Mercury (Hg) Exposure.

Species	Hg type	Altered serum T3 levels	Altered serum T4 levels	Altered T4/T3 ratios	Altered iodine uptake or release	Altered TSH levels	Altered TPO/ IPOD iodide oxidation	Hypertrophy of thyroid follicles	References
Fish: snakehead (*Channa punctatus*)	$HgCl_2$	–	↓	–	–	–	↓	–	Bhattacharya et al. (1989)
Fish: yellow perch (*Perca flavescens*)	Total Hg	↑	↓	–	–	–	–	–	Hontela et al. (1995)
Fish: catfish (*Clarias batrachus*)	MeHg	–	–	–	X	–	–	X	Kirubagaran and Joy (1989, 1994)
	$HgCl_2$	–	–	–	X	–	–	X	
	Total Hg	↓	↓	–	–	–	–	–	
Fish: rainbow trout (*Oncorhynchus mykiss*)	MeHg	↑	↑	–	–	–	–	–	Bleau et al. (1996)
Mammal: mouse (ddY)	MeHg	No effect	↓	–	↓ trend	–	–	X ↑weight at high dose	Kawada et al. (1980), Nishida et al. (1986)
	$HgCl_2$		↓		↓ trend				
Mammal: mouse (Swiss Albino)	$HgCl_2$	↓	↓	–	–	–	–	–	Sin et al. (1990), Sin and Teh (1992)
	HgS	↓							
Mammal: rat (F344)	$HgCl_2$	–	–	–	–	–	–	X	NTP (1993)
Mammal: rat (Sprague–Dawley and Wistar)	$HgCl_2$	No effect	↓	–	↓	–	–	–	Mochizuki and Asahara (1978)
Mammal: rat (Long Evans)	$HgCl_2$	↓	–	–	↓↑ (see text)	–	–	–	Goldman and Blackburn (1979)
Mammal: rat (Wistar)	MeHg	–	–	–	–	↑	–	–	Kabuto (1986)
Mammal: rat (Male Wistar, TPO, TSH) and pig (slaughter house, TPO)	MeHg	–	–	–	–	↓	No effect	–	Nishida et al. (1989)
	$HgCl_2$					No effect	↓	–	
Mammal: rat (Wistar)	MeHg	–	↑	–	–	↑	–	X	Kabuto (1991)
Mammal: pig (slaughter house)	MeHg	–	–	–	–	–	↓Tg iodination	–	Nishida et al. (1990a)
	$HgCl_2$						↓iodide oxidation & Tg iodination		
Mammal: Human	Hg vapor	↓	↑	↑		↓			Barregard et al. (1994), Ellingsen et al. (2000)
Mammal: Human	MeHg	–	–	–	–	–	–	X (neoplasms)	Futatsuka and Eto (1989)

Abbreviations: IPOD, iodide peroxidase; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

ratios of T4 and T3 or in other THs, such as rT3, in humans following occupational exposure to Hg vapor (Barregard et al., 1994; Ellingsen et al., 2000). Three studies monitored serum levels of protein-bound iodine (PBI) as an indicator of TH levels. In catfish, PBI levels decreased with exposure to $HgCl_2$, MeHg, or the fungicide emisan 6 for 45, 90, or 180 days (Kirubagaran and Joy, 1989). Rats exposed for 40 days to $HgCl_2$ had increased PBI concentrations. Finally, rats exposed to $HgCl_2$ for 48 h showed a decrease in PBI levels and a decrease in the ratio of PBI to total serum iodine (Mochizuki and Asahara, 1978). In the same study, thyroid iodine uptake also decreased, as did the thyroid-to-serum iodine ratio. The first of these three studies showed hypertrophy of the thyroid epithelium or an increase in thyroid-gland weight, and both suggest that the thyroid was in a hypertrophic state. Hg has been shown to cause hypertrophy and hyperplasia of thyroid follicles in fish (Kirubagaran and Joy, 1989; Ram and Sathyanesan, 1983, 1984). The regulation of thyroid function and hormone levels is so complex that it is difficult to identify single variables that might explain differences in the apparent responses of the HPT axis to Hg in different studies.

The mechanisms by which both inorganic and organic Hg can lead to decreases in TH levels are not yet clear. Work by Nishida and colleagues (1986) demonstrated in mice, albeit at high concentrations, that MeHg and $HgCl_2$ do not interfere with organification (formation of iodotyrosine) but do inhibit the coupling of iodotyrosines to become iodothyronine, or TH.

TSH was also monitored in several studies that produced equally variable results. In one study, rat serum TSH was increased for up to 7 days following a one-time exposure to MeHg (12 mg/kg), and an increase in TSH was also detectable at 26 h following a high dose of MeHg (16 mg/kg). When rats were given a dose of MeHg (12 mg/kg) and then challenged with TRH, the TSH levels significantly increased over control rats at 30 min. Both prolactin and TSH rapidly recovered following this increase, indicating that Hg does not alter the metabolism of these hormones (Kabuto, 1986). In a separate study by Nishida and colleagues (1989), rats exposed to MeHg for 2 weeks had low serum TSH levels, while rats exposed to $HgCl_2$ had normal TSH levels. The difference in serum TSH levels in response to MeHg and $HgCl_2$ may reflect the difference in Hg species, the dosing regime (once only versus 2 weeks), the dose level, or the period following the exposure when the blood samples were collected. Kabuto (1991) confirmed his previous findings, showing that TSH increases following MeHg exposure. In this study, Hg exposure also led to increases in urinary levels of dopamine, norepinephrine, and epinephrine for up to 50 days following exposure to MeHg, which could indicate that the elevated dopamine level is affecting pituitary-gland function and leading to increases in norepinephrine and epinephrine levels. At day 90, animals had elevated serum TSH and T4 levels, and the thyroid gland was heavier, suggesting that the animals were in a mildly hyperthyroid state.

The patterns observed in TH levels, TSH, and thyroid-gland weight following Hg exposure can indicate whether an animal is in an abnormal thyroid state (for example hyperthyroid, hypothyroid, or hyperthyroxinemic). The thyroid gland was reported to be hypertrophic in fish exposed to $HgCl_2$ or MeHg, but MeHg was more potent in inducing a change in the thyroid gland (Kirubagaran and Joy, 1989). Similarly, in the Kabuto (1991) study described above, it was suggested that the thyroid gland was in a mild hypertrophic state, on the basis of the elevated TSH and T4 plasma levels observed following MeHg exposure. Goldman and Blackburn (1979) also saw an increase in thyroid weight after exposure of female rats to $HgCl_2$, but because no change was detected in TH levels, the rats could not be considered hyperthyroid or hypothyroid. Nishida and colleagues (1989) suggest that, in rats, MeHg induces a hypothyroid state and that $HgCl_2$, on the other hand, inhibits the function of TPO, leading to a hypertrophic state. There is evidence that Hg exposure leads to a slight increase in thyroid follicular-cell carcinomas in rats exposed to high concentrations of $HgCl_2$ (NTP, 1993), and humans with Minamata disease have been shown to have a significantly higher incidence of thyroid-gland neoplasms than patients with other neurodegenerative diseases (Futatsuka and Eto, 1989).

As was mentioned previously, T3 and T4 are essential for maintenance of metabolic homeostasis in vertebrates (Clement, 1985) and have been measured in a number of species exposed to Hg. TH synthesis can be altered in fish following exposure to Hg (Bhattacharya et al., 1989). At sites contaminated with Hg, Hontela and colleagues (1995) discovered that male fish in the Saint Lawrence River had decreased levels of T4 and increased levels of T3. Facemire et al. (1995) suggested that Florida panthers exposed to environmental Hg experience hyperthyroidism. Field studies are difficult to interpret because of confounding factors and exposure differences. More studies are required to determine how Hg affects species in the field.

In humans, the majority of studies on the HPT axis have been on workers exposed to Hg vapor in occupational settings, such as in chloralkalai plants or the dental profession. Some of the earliest epidemiological studies observed no changes in serum levels of TSH, T3, T4, or prolactin in exposed groups (Erfurth et al., 1990; Langworth et al., 1990), and when one exposed group was challenged with TRH, pituitary-gland function remained normal (Erfurth et al., 1990). Both of these studies had very small sample sizes, which could explain why they did not see the effects on the thyroid system that other studies have observed. It is also possible that the exposure time and concentrations in these groups led to compensatory actions in the thyroid system that masked any changes. Another study showed very weak differences between the TSH levels of exposed and unexposed workers that were not strong enough to indicate a relationship between blood Hg levels and serum TSH and prolactin (McGregor and Mason, 1991).

More recent studies on larger groups of subjects have revealed that T3 and T4 levels changed after occupational

exposures to Hg vapor (Barregard et al., 1994; Ellingsen et al., 2000). Both of these studies were on chrloralakai-plant workers. In addition to changes in TH levels, Barregard et al. (1994) observed a decreasing trend in TSH and prolactin, and Ellingsen et al. (2000) showed an increase in reverse T3 (rT3). Ellingsen et al. (2000) suggest that Hg vapor could affect type 1 iodothyronine deiodinase, which prefers rT3 as a substrate. Therefore, if Hg blocks deiodinase function, it would lead to an increase in rT3 levels. The authors suggested that the increase in rT3 level and the T4/T3 ratio was linked to low urinary iodine, which could be a risk factor for workers who may experience increased TH levels during occupational Hg exposures. The T4/T3 ratio increased in both of these papers, and Barregard et al. (1994) showed that this was due to an elevation in T4 levels and an inverse correlation between Hg and T3 levels. Barregard et al. (1994) also suggested that Hg may inhibit 5′deiodinase (the deiodinases that converts T4 to T3), leading to an increase in total T4 and a decrease in total T3 levels.

Other papers discussed below did not examine TH levels, but did demonstrate links to the thyroid system through adverse effects that are linked to the thyroid system. For example, one paper showed that women with hormonal disorders had higher Hg excretions when stimulated with the chelator 2,3-dimercapto-1-propane-sulphonic acid (Gerhard et al., 1998). The same group showed that there was a significant increase in Hg excretion in women with thyroid dysfunction, whether it was hypothyroidism or hyperthyroidism (Gerhard et al., 1998). Perhaps Hg decreases the capability of the thyroid gland to respond to different kinds of stress—and whether the stress leads to increased or decreased thyroid activity, the system is more prone to develop thyroid dysfunction during situations where the body would normally compensate. Gavrilescu and colleagues (1968) demonstrated that occupational exposure to Hg caused 4/10 patients to experience hyperthyroidism. Studies of pregnancy and thyroid function have shown that abnormalities in TH levels are associated with infertility or abnormal pregnancy (for discussion, see Gerhard et al., 1991). Therefore, since the thyroid system seems to be linked to female ovarian function, it may be that the effects of Hg on the thyroid system described above are linked to the effects described in the section of this review on female fertility. It is also prudent to consider the importance of THs to the developing fetus and child. The neurotoxic effects of Hg, coupled with its potential effects on the thyroid system, during pregnancy should be remembered. Furthermore, it is clear that more research is needed on the thyroid system's links to the HPG axis with respect to Hg exposures, and that thyroid endpoints should be included in studies of Hg exposure in humans, as well as in other species.

Although field and occupational exposures to Hg are difficult to interpret, there is evidence to suggest that certain exposure scenarios lead to thyroid abnormalities. Many of the wildlife field studies and human epidemiological studies on the neurotoxicity of Hg may not have focused on thyroid-system effects. More studies are needed that look at thyroid endpoints in order to understand the effects on wildlife and humans during different exposures and time periods.

Possible mechanisms that alter thyroid status

Thyroid peroxidase

TPO, as described earlier, is intimately involved in the production of TH because it oxidizes iodide, catalyzes the iodination of thyroglobulin and helps couple the iodinated tyrosyl residues to form iodothyronine, which becomes either T3 or T4, depending on the number of iodide molecules attached (Zoeller et al., 2007). TPO assays are commonly used to determine whether TPO activity is normal in an organism.

TPO activity was shown to decrease in snakehead fish (*C. punctatus*) after exposure to $HgCl_2$ as measured by iodide peroxidase (also known as TPO) activity or guaiacol (non-iodide) peroxidase activity (Bhattacharya et al., 1989). TPO and lysosomal enzyme activities, such as lysosomal protease, are important to T4 production and have been monitored in a variety of fish species. Disturbances in lysosomal-protease and cytosolic iodide-peroxidase levels and activity may affect T4 production and release (Bhattacharya et al., 1989). Changes to acid-phosphatase activity indicate changes to lysosomal membranes as a result of Hg exposure. By measuring such enzyme activity, it was shown that thyroid activity in *C. punctatus* is altered by Hg exposures. The Hg affects the iodide peroxidase and lysosomal pathways, decreasing T4 production and release (Bhattacharya et al., 1989). In fish, it is believed that guaiacol-peroxidase elevation may help in the detoxification of many pollutants (Bhattacharya et al., 1989).

In rats, TPO is inhibited by $HgCl_2$, but not by MeHg, and Nishida and colleagues (1989) suggested that MeHg induces a different thyroid state (hypothyroid) than $HgCl_2$ (hyperthyroid) because of alternate effects of the two Hg species on the TPO enzyme. Nishida and colleagues (1990a) also showed that, while $HgCl_2$ was the only Hg species that inhibited TPO-mediated oxidation of iodide, both $HgCl_2$ and (to a lesser extent) MeHg inhibited the iodination of thyroglobulin or bovine serum albumin. In an *ex vivo* study in mice, the authors demonstrated that MeHg is present in the thyroid gland after oral administration, and that, therefore, the lack of susceptibility of TPO to MeHg is not due to its absence or degredation in the thyroid gland but rather to an inability to inhibit the enzyme (Nishida et al., 1990b). The authors suggest that MeHg is more hydrophobic than $HgCl_2$ and cannot bind to the hydrophilic active site on TPO, causing a difference in the effect of the two Hg types on TPO. Hg has a high affinity for iodide, and a differential affinity for this element by $HgCl_2$ and MeHg could partially explain the divergent results (Nishida et al., 1990a).

Iodine uptake

Iodine is a key component of TH, and its uptake into the thyroid in its free elemental form (iodide or I^-) regulates the amount of TH that can be produced. Human adults have a large store of iodide in the thyroid gland, and this store can last up to 2–3 months in normal healthy adults. Human fetuses and infants have a much smaller store of iodide in their

thyroid glands, with reserves of 1–2 days. In adult rodents, the stores are also much smaller than in human adults, lasting 2–3 weeks. Rodent and pig studies measured the effects of $HgCl_2$ and MeHg on radio-labeled iodine uptake into the thyroid gland. Most of these studies showed a decline or at least a decreasing trend in iodine uptake into the thyroid following Hg exposure (Kawada et al., 1980; Mochizuki and Asahara, 1978; Nishida et al., 1986). In one study on rats, short-term exposures to $HgCl_2$ (6–40 days) led to an increased iodide-release rate, and an increase in iodide-uptake rate, at 40 days of exposure, coupled with an increase in protein-bound iodide (Goldman and Blackburn, 1979). After a longer time period (3 months), the rats experienced decreases in radio-labeled iodide uptake and release from the thyroid, and these effects were permanent and irreversible when the animals were no longer exposed to $HgCl_2$. Goldman and Blackburn (1979) suggest that these results demonstrate that $HgCl_2$ has a lasting influence on thyroid function. In a separate study by Nishida and colleagues (1986), MeHg and $HgCl_2$ reduced ^{125}I uptake in the thyroid. Because Hg has a high affinity for iodide (Nishida et al, 1989), it could be that Hg blocks iodide uptake at the NIS by binding to it and creating a complex that can no longer pass through the NIS. MeHg and $HgCl_2$ both inhibited Na^+K^+ ATPase in pig thyroids (Kawada et al., 1980), which also influences the Na^+ gradient that NIS function is dependent upon in order to transport I^-. Furthermore, in mice, both Hg compounds caused a significant decline in ^{131}I uptake in this experiment.

Selenoproteins and deiodinases

Selenium (Se) is an essential trace element that is obtained through the diet. In laboratory animals, it has been shown to protect from Hg toxicity (Nishikido et al., 1987). Many of the enzymes in the thyroid and detoxification systems of vertebrates are selenoproteins (for example, the deiodinases, glutathione, and glutathione peroxidase). Hg has a high affinity for Se and the two compounds accumulate at a molar ratio of 1:1 in most vertebrates, leading to the removal of both from biological turnover (Drasch et al., 2000; Falnoga et al., 2000; Kosta et al., 1975; Yoneda and Suzuki, 1997a). Se deficiency may result in an animal being more sensitive to Hg toxicity. It is clear that Hg can be sequestered by selenoproteins like selenoprotein P, which can bind Hg at each of its 10 selenocysteinyl residues to hold Hg in the blood (Yoneda and Suzuki, 1997b). Drasch and colleagues (2000) suggested that Se-deficient animals can have potentially compromised selenoproteins (i.e. selenoproteins that have a lower than normal concentration of incorporated Se molecules). In Se-deficient human populations, which exist in parts of Germany and England, selenoenzymes may begin to decrease with increasing Hg exposure. Drasch et al. (2000) demonstrated that an Se hierarchy exists in the human body to supply the most important tissues with enough Se for essential selenoenzyme function (for example, thyroid tissue). As selenoproteins often exist in the endocrine system, this may explain why there is often a significant accumulation of Hg in certain endocrine tissues.

In the thyroid system, the deiodinases make up 3 isoforms (types 1 through 3) of selenoenzymes that convert THs from one iodinated form to another (T4, T3, rT3, 3,3′-T2), and may be targets for thyroid-system disturbances by Hg. Barregard and colleagues (1994) imply that changes in TH levels in the plasma of workers exposed to Hg vapor may be due to an inhibitory effect of Hg on a 5′deiodinase (type 1 or 2 deiodinase) that converts T4 to T3 in both the thyroid and peripheral tissue. Ellingsen and colleagues (2000) also suggest that Hg-vapor exposure could alter the function of type 1 deiodinase, which deiodinates rT3 at the 5′ position.

In pregnant mice exposed to MeHg on gestational day (GD) 12–14, Hg reduced gluatione-peroxidase activity in the fetal brain and the placenta, and also decreased 5′deiodinase activity (type 3 deiodinase) in the mother. Type 3 deiodinase is involved in transfer of T4 from mother to fetus; thus, decreased type 3 deiodinase activity during pregnancy could limit the amount of T4 available to the fetus (Watanabe et al., 1999). Watanabe et al. (1996b) also found that 5′deiodinase activity was increased in the fetal brain, although there was no change in T3 or T4 levels. They also showed that 5′deiodinase activity was increased in the placenta. These patterns of deiodinase activity suggest that fetal mice may become hypothyroid when exposed to MeHg on GD 12–14, but that by the time they were monitored on GD 17, compensatory actions in the thyroid system led to changes in the activity levels of the deiodinases that reflected the response to an earlier hypothyroid state (Watanabe et al., 1999). Studying deiodinase activity is complicated, because it is intricately tied into the thyroid system's negative feedback loops. More study on TH action—for example, potential deficits in brain development—will reveal the outcome of these subtle and often transient alterations in thyroid-system enzymes and hormones.

It is likely that many of the elements of the thyroid system that are described above are connected in their responses to Hg. However, the research to date does not provide a clear cause-and-effect picture of how Hg alters thyroid-system function or TH action. The literature does point to Hg having the capability to alter the thyroid system in multiple places, including the TPO oxidation and iodination steps, and to the capability of the deiodinases to convert T4 to T3 or rT3 to diiodothyronine. More work is needed to understand the very complicated feedback mechanisms and compensatory activities that make the data so difficult to interpret and compare across studies.

Adrenal system

The adrenal system is well known for regulating stress responses, but is also involved in other auto-regulatory functions, such as helping to control body fluid balance, blood pressure, blood sugar, and other central metabolic functions. Vertebrates have three adrenal tissue types that produce catecholamines (epinephrine and norephinephrine), glucocorticoids, and mineralcorticoids (mineralcorticoid-like hormones). The inner adrenal glands in mammals and homologs in other vertebrates are regulated by the

autonomic nervous system during acute stress by secreting two catecholamine hormones known as epinephrine and norepinehprin (made by chromaffin cells). These medullary adrenal hormones are an important reaction to stress, but this section will focus mainly on the other adrenal tissue type—the adrenal cortex. The adrenal cortex is regulated by the hypothalamo–pituitary–adrenal (HPA) axis (Figure 1C). Much of the research on Hg and its relationship to the adrenal gland concentrates on the HPA axis. The HPA axis regulates the glucocorticoid system (cortisol and corticosterone) and the basic components of the axis are homologous across taxa. These components include signaling hormones and feedback mechanisms that help vertebrates adapt to changes in their environment, and can include stress responses to contaminants like Hg.

In mammals, inputs from the central nervous system either stimulate or inhibit the release of corticotropin-releasing factor (CRF) from the basal hypothalamus. Once released, CRF stimulates cells in the anterior pituitary gland to produce and secrete adrenocorticotropin (ACTH). ACTH then signals the adrenal gland to produce the glucocorticoid hormones—cortisol (also called hyrdrocortisone) is the major glucocorticoid in humans and teleost fish and corticosterone is the major glucocorticoid in rodents, birds, and other species. Cortisol and corticosterone are the main glucocorticoids produced by the adrenal cortex. Adrenal cortisol and corticosterone are eventually released into the plasma, where they can act on the hypothalamus and pituitary gland in a negative-feeback loop that inhibits the production of glucocorticoids. Plasma cortisol and corticosterone levels are also regulated by liver metabolism. The main roles of glucocorticoids are in metabolism (maintaining normal levels of glucose in the blood), immune function (anti-inflammatory and immunosuppressive properties), and fetal development (for example, lung development for the extrauterine environment).

Another role of the adrenal cortex in mammals is to produce mineralcorticoid hormones, which regulate extracellular concentrations of minerals, particularly sodium and potassium. The main mineralcorticoid is aldosterone, which is mainly active in the distal tubule of the kidney to increase sodium and water resorption and excretion of potassium. It also has some activity in the salivary glands, sweat glands, and colon. Aldosterone and cortisol (or corticosterone) have similar affinities for the mineralcorticoid receptor. Aldosterone sensitive cell types in the adrenal cortex are defined by the enzyme 11β-hyroxysteroid's capability to convert cortisol to cortisone, a form of the steroid with a weaker affinity for mineralcorticoid receptors. Therefore, this enzyme activity increases the effectiveness of aldosterone by decreasing its competition with cortisol. Because the conversion of cortisol to cortisone increases the activity of aldosterone it links the mineralcorticoid system to HPA axis function.

The fish adrenal system is similar to the mammalian system in the cell types and hormones that regulate it. In fish, the adrenal gland is made of inter-regnal cells and chromaffin cells. The chromaffin tissue, which is the homolog of the mammalian adrenal medulla, produces catecholamines, and the interregnal tissue, which is the homologue of the mammalian adrenal cortex, produces corticosteroid hormones (Donaldson, 1981). Blood cortisol levels have been used to link specific endocrine dysfunctions to compromised health of fish following exposure to Hg. For instance, an increase in plasma cortisol levels was observed in rainbow trout that was accompanied by a decrease in plasma testosterone levels, resulting in altered reproductive success (Pankhurst and Van Der Kraak, 2000). Cortisol is the major glucocorticosteroid hormone secreted by inter-renal steroidogenic cells (Leblond and Hontela, 1999). It maintains hydromineral balance, alters liver glycogen content, and increases levels of free fatty acids and glucose in the blood (Wendelaar Bonga, 1997). Blood levels of cortisol increase in healthy fish following acute stress or exposure to contaminants (Barton and Iwama, 1991; Schreck, 1990; Thomas, 1990). As in mammals, when the fish brain detects a stressor, the hypothalamus produces CRF, which passes through the hypothalamus to act on the pituitary gland to stimulate ACTH secretion (Wendelaar Bonga, 1997). ACTH binds to a specific receptor on the plasma membrane of steroidogenic cells in the head kidney and stimulates cortisol synthesis through a cAMP-mediated mechanism (Ilan and Yaron, 1980).

A review of the literature on the effects of Hg on the adrenal system showed that this is an area that has had little attention. Most of the research has been on fish species and rodents in laboratory settings. An overall comparison of the literature across taxa reveals a general decrease in cortisol and corticosterone following Hg exposure (Table 7), and several papers explored the mechanism of this decrease by examining specific steps in the steroidogenesis pathway. Another trend observed across taxa was (to a lesser extent) an increase in adrenal hyperplasia or increased adrenal weights. These effects are discussed in detail below.

Adrenal and plasma corticosteroid levels

As mentioned above, fish responses to stress occur via processes in the chromaffin tissue and interregnal tissue (Donaldson, 1981). The latter is part of the hypothalamo–pituitary–inter-renal (HPI) axis in fish, which elevates the blood cortisol level following exposure to Hg (Pickering, 1993). This is usually preceded by an elevation of catecholamines, which stimulates lipolysis, glycogenolysis, and gluconeogenesis (Sheridan, 1986; Vijayan and Moon, 1992). The HPI axis can be impaired with chronic exposure to Hg, which can reduce the fish's capability to respond normally to stress.

Impairment of adrenal function was observed in catfish (*C. batrachus*) following exposure to Hg, as evidenced by significantly decreased plasma cortisol levels and histological changes in the adrenal and ACTH cells (Kirubagaran and Joy, 1991). Similarly, yellow perch (*Perca flavescens*) and northern pike (*Esox lucius*) exposed to total Hg in the wild also showed impaired cortisol response to the acute stress of capture (Hontela et al., 1992; Lockhart et al., 1972). These

Table 7. Changes in Cortisol-Corticosterone Levels After Mercury (Hg) Exposure, According to Species.

Species	Hg type	Change in cortisol–corticosterone levels	Reference
Fish: northern pike (*Esox lucius*)	Total Hg	↓	Hontela et al. (1992), Lockhart et al. (1972)
Fish: catfish (*Clarias batrachus*)	$HgCl_2$ & MeHg	↓	Kirubagaran and Joy (1991)
Fish: yellow perch (*Perca flavescens*)	Total Hg	↓	Hontela et al. (1992, 1995)
Fish: rainbow trout (*Onchorhynchus mykiss*)	$HgCl_2$ & MeHg	↑	Bleau et al. (1996)
		↓	Leblond and Hontela (1999)
Fish: walleye (*Stizostedion vitreum*)	MeHg	↓	Friedmann et al. (1996)
Bird: broiler cockerels (*Gallus domesticus)*	$HgCl_2$	↓	Thaxton et al. (1982, 1975)
Mammal: mice (129/SvSl)	MeHg	↓	Grady et al. (1978)
Mammal: rat (Sprague–Dawley)	MeHg	↓	Burton and Meikle (1980)
	$HgCl_2$		Ng and Liu (1990), Veltman and Maines (1986)
Mammal: rat (Charles Foster)	$HgCl_2$	↓↑	Agrawal and Chansouria (1989)

results suggest physiological endocrine dysfunction results from Hg exposure (Hontela et al., 1995), as cortisol has a regulatory role in reproduction, growth, osmoregulation, and the immune response in fish (Anderson et al., 1991; Donaldson, 1990; Maule et al., 1989). The endocrine effects of Hg in these fish were manifested in impaired cortisol and TH secretion as well as abnormally high liver glycogen stores and smaller gonads in both sexes (Hontela et al., 1995). Although definite mechanisms causing a reduction in blood cortisol levels in fish have not yet been established, contaminants may be interfering with cortisol production through the HPI axis, hormone metabolism rates, and exhaustion of the HPI axis during chronic exposure to Hg (Hontela et al., 1995).

Other studies on fish have also reported a decrease in plasma cortisol levels following exposure to MeHg or $HgCl_2$ (Friedmann et al., 1996; Leblond and Hontela, 1999; Lockhart et al., 1972). Some studies saw no change in cortisol levels during a stress response (Friedmann et al., 2002), while others observed an increase in plasma cortisol after exposure to $HgCl_2$ (Bleau et al., 1996). These observations, which were not in accord with the general trend, may be due to differences in exposure times, species, or field conditions. They may also reflect the point in time when cortisol levels were sampled. If cortisol levels are decreased, they may then trigger reduced negative feedback on the pituitary gland and increased release of pituitary-gland hormones. Thus, Hg exposure could signal an initial decrease in corticosteroids, which would then activate the HPA axis to increase production of corticosteroids (Bleau et al., 1996; Kirubagaran and Joy, 1991). A similar pattern of increased and decreased plasma corticosteroid levels through time was observed in rats by Agrawal and Chansouria (1989) and is discussed below.

Thaxton and colleagues (1975, 1982) also saw decreased adrenal corticosteroids following $HgCl_2$ exposure in broiler cockerels (chickens). Similarly, mice and rats show decreases in plasma corticosterone levels following MeHg and $HgCl_2$ exposure to adult and weanling male rats and isolated rat adrenal cells (Burton and Meikle, 1980; Ng and Liu, 1990; Veltman and Maines, 1986). As with the fish, some studies in rats reported either increases or no change in plasma corticosterone levels with $HgCl_2$ exposure (Agrawal and Chansouria, 1989; Grady et al., 1978). Grady and colleagues (1978) suggest that an impairment of adrenal corticosterone production was likely in MeHg-exposed female rats, but that the data were too variable to observe significance. Perhaps a larger sample size would have revealed a significant impairment due to Hg. Agrawal and Chansouria (1989) suggest that their results showed an increase in plasma corticosterone rather than a decrease because $HgCl_2$ probably acted by different mechanisms to alter plasma corticosterone levels depending on dose, exposure time, and the sampling times for corticosterone following the end of the Hg exposure. For example, in this study, the dose of $HgCl_2$ used led to changes in the plasma corticosterone levels, as did the duration of exposure. The lowest dose of $HgCl_2$ caused an increase in plasma corticosterone levels for up to 120 days. At the higher doses of $HgCl_2$ plasma corticosterone levels first decreased, then increased, and then either decreased again or leveled off at control concentrations (Agrawal and Chansouria, 1989). Adrenal corticosterone levels at all three Hg doses increased for up to 120 days in this experiment, regardless of whether plasma corticosterone was going up or down. These varying results could reflect compensatory mechanisms within the HPA axis and the liver to achieve homeostasis during long-term exposures to $HgCl_2$.

Mechanisms that alter plasma corticosteroid concentrations

Hg can alter plasma corticosteroid concentrations by acting directly on the hypothalamus or pituitary gland to alter the production of corticosteroids through the HPA axis, by means of cytotoxic mechanisms that target the corticosteroid producing cells, or by directly acting on the steroidogenesis pathway.

Kirubagaran and Joy (1990) suggest that changes in monoamine activity in catfish due to multiple species of

Hg may alter neuroendocrine regulation of several pituitary-gland hormones including prolactin, gonadotropin, and melanophore stimulating hormone, thus affecting the release of ACTH and the downstream production of corticosteroids by the adrenal glands. This is supported by research that demonstrates that Hg affects the functional interrelationship between the pituitary gland and its endocrine target organs (Kirubagaran and Joy, 1990). It is also supported by a similar study, by the same authors, in catfish that demonstrates that TH synthesis is also affected by Hg exposure (Kirubagaran and Joy, 1989). Other work on fish has also shown that multiple Hg types interfere with the cells in the pituitary gland that synthesize steroid-controlling hormones (Bleau et al., 1996; Norris et al., 1997, 1999; Thomas and Khan, 1997). The pattern of adrenal-gland weight increase or hyperplasia following exposure to MeHg indicates a feedback mechanism, probably triggered by increased release of ACTH, which leads to increased activity of the adrenal gland and enlargement of the adrenal gland in the rat (Burton and Meikle, 1980)

Ng and Liu (1990) found that $HgCl_2$ exposure led to reduced cell viability in the adrenal glands of rats, which was linked to decreased corticosterone production. The authors explained that, in their study, $HgCl_2$ had a specific toxic mechanism on the adrenal gland as well as the Leydig cells of the testis, and that this was the mechanism by which production of corticosterone and testosterone were decreased. Toxic effects on steroid-synthesizing organs in fish species have also been suggested to reduce steroid titres (Bleau et al., 1996; Kirubagaran and Joy, 1989, 1990).

Several papers explored the steroidogenesis pathway to determine if mercurials are able to directly inhibit enzymes that lead to the production of corticosteroids. Thaxton and colleagues (1975, 1982) found that cholesterol, the precursor to steroid synthesis in the adrenal glands, was decreased in chickens exposed to $HgCl_2$. They also saw an increase in adrenal weight relative to body weight following $HgCl_2$ exposure, and suggest that the weight change is due to a decrease in corticosterone levels, because the weight increase could be partially reversed by administration of corticosterone, the major corticosteroid in birds (Thaxton et al., 1975). Thus, it seems that the decrease in cholesterol may ultimately lead to a decrease in corticosterone. Burton and Meikle (1980) found that the conversion of cholesterol to pregnenolone was impaired in rats exposed to MeHg. Finally, Veltman and Maines (1986) studied the synthesis of corticosterone in rats following exposure to $HgCl_2$, and determined that there was an increase in cytochrome P-450 in the mitochondrial fraction of the adrenal glands, which in turn caused an increase in side-chain cleavage of cholesterol and a sevenfold increase in the rate of production of pregnenolone. On the other hand, the authors found a decrease in cytochrome P-450 activity in the microsomal fraction of the adrenal gland, and thus impaired 21-α-hyrdoxylase activity, the enzyme that converts 17α-hydroxyprogesterone to 11-deoxycortisol (Veltman and Maines, 1986). In this study, $HgCl_2$ led to a 50% reduction in corticosterone production in rats, a 300% increase in plasma dehydroepiandrosterone (the primary rat adrenal androgen), and a 70% increase in plasma progesterone. The authors suggested that these abnormalities in steroid concentrations reflect an Hg-induced defect in steroid biosynthesis by inhibiting cytochrome $P\text{-}450_{c21}$ (the cytochrome P-450 of 21α-hydroxylase) activity (Veltman and Maines, 1986) and blocking the conversion of 17α-hydroxyprogesterone to 11-deoxycortisol and ultimately corticosterone. Cytochrome $P\text{-}450_{c21}$ contains more free cysteine sulfhydryl residues within its active site than any other cytochrome P-450 in the adrenal cortex, thus Hg could bind to sulfhydryl groups in the active site and block 17α-hydroxyprogesterone from binding. As a result, an increase in plasma progesterone could then be observed, since it is not being converted to cortisol by cytochrome $P\text{-}450_{c21}$. A build-up of progesterone would then force the steroidogenesis pathway towards adrenal androgen production, as was seen by Veltman and Maines (1986).

It has been demonstrated that the mercurials are strong and irreversible inhibitors of C-21-hydroxylation, and they convert cytochrome P-450 into the inactive P-420. It has also been suggested that steroids and mercurials interact with the same site of the cytochrome enzymes (for review see Cooper et al., 1968), thus providing a mechanism for Hg to interact directly with an enzyme in the steroidogenesis pathway and so decrease production of the corticosteroids. Furthermore, fluctuations in the levels of ascorbic acid, glutathione, and glutathione reductase are believed to affect 21α-hydroxylase activity (Greenfield et al., 1980). As reviewed in the section on thyroid, glutathione and other selenoproteins are bound by Hg at Se sites. It is possible that mercurial complexes formed with glutathione and glutathione reductase could lead to functional changes in their levels, and thus a decrease in 21α-hydroxylase activity and cortisol and corticosterone production.

Another enzyme in the steroidogenesis pathway that is altered by MeHg is 11β-hydroxy-steroid dehydrogenase, which was increased in the female harp seal after MeHg exposure (Freeman et al., 1975). It is well known that, in mammals, 11β-hydroxysteroid converts cortisol to cortisone and allows aldosterone (the main mineralcorticoid) to bind to the mineralcorticoid receptors and regulate mineral homeostatis in the extracellular fluids of the body. Therefore, an increase in 11β-hydroxy-steroid may result in a higher yield of cortisone in the adrenal incubate of the seal, and a lower level of functional cortisol, leading to a decrease in cortisol levels. However, the role of cortisone in the seal is not known (Freeman et al., 1975), so the conclusions regarding the effects of Hg on the seal adrenal system in this instance are speculative at best.

It is likely that cytotoxicity to the adrenal gland, alterations to the HPA axis, and effects on the steroidogenesis pathway involved in corticosteroid production are all implicated in the response of the adrenal system to Hg exposure. The effects seen in the literature are relatively well conserved across species and taxonomic groups (fish, birds, and rodents) in

the adrenal system's response to Hg. The literature indicates that specific mechanisms, apart from cytotoxicity alone, are responsible for the changes observed in plasma corticosteroid levels following exposure to both organic and inorganic Hg.

Conclusions

"Exposure to mercury has been associated with adverse reproductive effects in fish and wildlife and it has also been labeled an endocrine disrupter." (Colborn et al., 1993).

The literature reviewed in this paper confirms this statement: that Hg has specific endocrine effects within all three hypothalamic–pituitary axes and across humans and wildlife. Endocrine research on the effects of Hg began over 35 years ago, and more research in this area is greatly needed. The authors hope that this comprehensive review on the endocrine actions of Hg will stimulate interest and research in this area.

For the purposes of this paper, it was difficult to compare doses of Hg across all studies because of variations in Hg species, exposure patterns, duration, and the developmental periods in which the exposures took place. Often the conditions of these studies were not comparable to those conducted under laboratory or clinical conditions and did not allow for complete comparisons. For instance, the route of exposure often differed among studies, frequently as a function of the type of study (i.e. laboratory versus field study). Also, duration of exposure and the developmental stage during exposure were major contributors to high variability. Despite these complexities, in the majority of cases where the same species of Hg was studied, the outcomes and results of the studies still demonstrated similarities, including general consistencies in the range of responses.

Chemical forms of Hg

It is well known that the toxicity of Hg is dependent on its chemical form. Elemental Hg ($Hg2^{+}$), MeHg, and $HgCl_2$ are the most common forms used in the empirical studies described throughout this publication. Dietary MeHg contaminates internal organs more rapidly than inorganic Hg (Boudou and Ribeyre, 1985; Spry and Wiener, 1991). Internal, inorganic Hg can result from the demethylation of MeHg, and MeHg can be formed through methylation of inorganic Hg by gut bacteria following ingestion. MeHg is the form of Hg to which humans are most commonly exposed. It has a greater affinity for the skin, gills, and gut of aquatic organisms and, because it is believed to be the most toxic, it is also the most studied. Compared with the number of MeHg studies, relatively few studies have examined the health effects of exposure to elemental or inorganic Hg in animals, especially humans. Although the type of Hg in the studies discussed in this paper was not always analogous, we attempted to compare similar studies where possible.

Conservation across taxonomic groups

Chemical signalling systems, such as the endocrine system, and their corresponding mechanisms are relatively conserved throughout the animal kingdom (McLachlan, 2001). The functionality of the endocrine system is highly conserved across species; this conservation includes the actual hormones themselves (i.e. androgens and estrogens) and certain endocrine axes such as the hypothalamic-pituitary axes. Comparison of the endocrine effects of Hg across taxa clearly demonstrates the conserved nature of the endocrine system. For many vertebrates, the components of the hypothalamic pituitary axes are homologous, while for other species, including the invertebrates, the functional role of the endocrine system is maintained. Although it was difficult to compare studies across similar species, let alone different taxa, similar trends in the effects of Hg on different aspects of the endocrine system were observed. Dosing time and length, as well as sampling times, influenced the results, as the endocrine system is constantly responding to environmental cues and adjusting to them. Because of the regulatory function of the endocrine system, careful interpretation of study comparisons was made, and areas of additional research were evident.

Mechanisms of toxicity

For each aspect of the endocrine system, both direct mechanisms (e.g. direct inhibition of enzymes in steroidogenesis) and indirect effects (e.g. abnormalities in female cyclicity) of Hg were observed. Available data limited our ability to firmly link indirect and direct effects. Nonetheless, there are some proposed common effects and mechanisms.

Accumulation

It is clear that Hg has an affinity for the endocrine system. In several of the reviewed studies, the pituitary gland, thyroid, and testes had accumulated concentrations of Hg that were similar to or not much lower than the levels that accumulated in the kidney or liver. It is not clear why Hg may target the endocrine system, but one reason may be Hg's affinity for Se, and, thus, the selenoproteins. This affinity has specific implications for accumulation in the endocrine system because of the potential abundance of selenoproteins functioning in the endocrine system, including in hormone metabolism.

Accumulation of Hg in the pituitary gland potentially links each of the hypothalamic–pituitary axes (HPA, HPT, and HPG) to endocrine dysfunction. An example of this can be seen in the decrease in cortisol and TH produced in Hg-exposed catfish (Kirubagaran and Joy, 1989, 1990), or in the trend for increased adrenal and thyroid gland weights in response to Hg-related disruption of feedback mechanisms of the hypothalamic–pituitary axes as described in the sections on the adrenal gland and thyroid gland.

Specific cytotoxicity for endocrine tissue

Hg is well known for its general cytotoxic effects, but a review of the literature indicates that it may have specific toxicity to certain endocrine tissues. This could be due to an affinity of Hg for selenoproteins or sulfhydryl groups on enzymes common to steroid-producing cells. Hg seems to have an affinity for specific tissue types within the thyoid gland (Falnoga

et al., 2000; Kosta et al., 1975), the adrenal gland, and the testes (the Leydig cells) in rodents (Ng and Liu, 1990), and a similar phenomenon was observed in fish (Bleau et al., 1996; Kirubagaran and Joy, 1989, 1990). Another example of direct toxicity within the endocrine system is Hg's specific toxicity to sperm, causing abnormalities in numbers, morphology, and motility.

Changes in hormone concentrations

General patterns of hormonal changes across taxa occur within the thyroid, adrenal, and reproductive systems. Hg exposure can lead to changes in hormone concentrations that are abnormal. In the adrenal and thyroid systems, for example, a general Hg-related decrease in glucocorticosteroid and TH levels across taxa (fish, chickens, and rodents) occurred. Variation in these observations may reflect differences across the studies in exposure start time and length, Hg concentration and type, hormone sampling time, and species differences.

Interaction with sex hormones

Clear accumulation, elimination, and toxicity differences were seen between the sexes within the same species. Often these differences could be eliminated by castration or ovariectomy, pointing to sex hormones as the basis for many of Hg's differential effects in males and females. Although the interaction of the sex hormones and Hg cannot be explained for each of the scenarios described in the relevant section, there are undeniably roles for sex hormones in the effects of Hg.

The steroidogenesis pathway

Hg is capable of directly inhibiting enzymes within the steroidogenesis pathway, as well as potentially up-regulating enzymes related to other parts of the pathway. For example, impaired 21-α-hyrdoxylase activity, the enzyme that converts 17α-hydroxyprogesterone to 11-deoxycortisol, was caused by Hg exposure in rats (Veltman and Maines, 1986). Enzyme inhibition in the steroidogenesis pathway may decrease levels of the downstream hormone (e.g. corticosterone), increase levels of the upstream hormones and cholesterol, and increase in other pathways that branch off upstream but share precursor hormones with the affected pathway. A similar story was discussed in the section on the reproductive system, when the enzyme 3β-HSD was shown to be inhibited by both types of Hg in fish and rats, leading to decreases in testosterone production.

The mechanisms of action of Hg listed above were identified as common across the endocrine system. Others described in the review are specific to particular parts of the endocrine system. For example, studies indicate that Hg can bind with a weak affinity to the ER. Many of the mechanisms discussed may also lead to combined effects on the endocrine system, linking one part of the endocrine system to another. Given the effects of Hg across the endocrine system, it is reasonable to consider that the subtle endocrine effects of Hg, which have been largely overlooked in risk paradigms, should be examined at greater depth through additional research and the mining of historical databases.

Research needs

A wide array of information that demonstrated the effects of Hg on the endocrine system was reviewed in this paper. However, there are clearly gaps in the knowledge and areas where an increased focus on Hg's potential endocrine effects may inform public and wildlife health. The most solid endocrine-system information for Hg has been gained through human epidemiological studies and laboratory experiments. Whilst wildlife studies largely formed the basis for much of the initial interest in Hg exposures, there is still a need for additional research into the effects of Hg on wildlife species. Research in the following areas would improve scientific understanding of Hg's interactions with the endocrine system and also improve our assessment of the risks that Hg poses to wildlife and human health:

- increasing basic biological information for many wildlife species;
- understanding how multiple stressors behave in combination with Hg;
- exploring how the sublethal and indirect effects of Hg translate to adverse outcomes;
- developing tools for extrapolation across and between levels of biological organization including individuals to populations; and
- understanding the overall outcome of effects of Hg that occur on multiple organ systems at any given time.

These issues are easily identified as areas where research is needed in the context of Hg and the endocrine system and are applicable to wildlife, domestic animals, and human health. Many of the specific reserach needs identified in this review for both humans and wildlife parallel those described as general research needs for wildlife toxicology in a Wildlife Toxicology workshop held by the Smithsonian Institution in March 2007 (Grim et al., 2007). Advances in the five areas listed above will improve our understanding of how Hg affects the endorcrine systems of multiple species and our ability to extrapolate the effects of Hg from one species to another. Research in these areas will also allow us to understand how laboratory data translate to field observations, and vice versa. By understanding how multiple stressors and chemicals behave in combination with Hg, confounders in field and epidemiological studies will be more easily understood. Scientists must determine the compounds with which Hg is most commonly associated in organisms and the environment, and which may also have similar endocrine effects to Hg.

Many of the effects of Hg on the endocrine system are subtle and less direct than the neurological effects that have been more heavily studied. Understanding how these indirect and sub-lethal effects affect the health of an organism will allow scientists and regulators to evaluate the risks of the short-term toxic effects of Hg versus those that are less direct and less lethal, but equally undesirable. The progression from sub-lethal and indirect effects to apical endpoints such

as reproductive success, mortality, fecundity, and fertility remains to be described. Finally, it is clear that Hg has multiple effects on multiple systems. When an organism is exposed to Hg, there are many possible outcomes, depending on the dose and length of the exposure, the type of Hg, the age and sex of the animal exposed, and the type of exposure. Once an exposure has occurred, Hg may act on multiple parts of the endocrine system as well as the nervous and other systems. Understanding how Hg acts on multiple organ systems at one time in an organism will help scientists predict the adverse outcomes of the many potential exposure scenarios.

Awareness of data from species not typically included in toxicity studies is essential for thorough risk assessments of environmental chemicals. Furthermore, the effects should be examined at the mechanistic, individual, and population levels to gain a better understanding of the effects of Hg mixtures relative to biological organization. Data showing Hg-related effects at different levels of biological organization (e.g. residues, physiology, pathology, behavior) should be collected for research and risk assessments. For example, altered thyroid levels may lead to chronic stress to the system that could make the organism more vulnerable to other insults, such as predators or disease. Finally, identifying population-level effects is a complex process. Most studies are not able to make the connection between laboratory findings and effects observed in wild populations. Species with certain life-history characteristics may be more prone to population effects of Hg. For example, long-lived piscivorous or other predatory animals feeding in aquatic food chains are at greatest risk for high dietary MeHg exposure, accumulation, and toxicity (Scheuhammer et al., 2007). For human epidiemological studies, an effort by the research community to include endocrine endpoints in their analyses could be informative.

By reviewing the literature and conducting comparisons across the components of the endocrine system, it was possible to discern the general patterns of Hg's effects on endocrine function. Areas of focus for future research have been identified and described above. It is clear that Hg is endocrine active, and that many of these effects occur through multiple, yet elegant, modes of action. This review primarily explored the endocrine components of the hypothalamic–pituitary axes. Other components of the endocrine system exist that require a separate review of the literature. For example, a review of the immune system alone would reveal other Hg-related changes in the endocrine system. It is hoped that this review will stimulate discussion and innovative research projects relevant to both wildlife and human health.

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