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Review

Toxicity of mercury: Molecular evidence

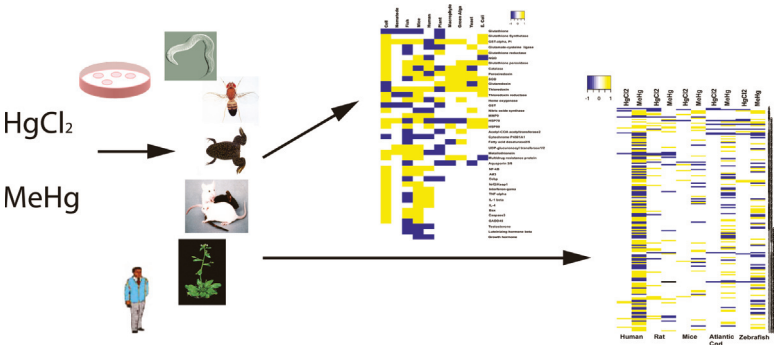
Lixin Yang [a, b, *], Yuanyuan Zhang [a], Feifei Wang [a], Zidie Luo [a], Shaojuan Guo [a], Uwe Strähle [c]

[a] State Key Laboratory of Environmental Criteria and Risk Assessment, Chinese Research Academy of Environmental Sciences, 100012, Beijing, China
[b] Center for Global Health, School of Public Health, Nanjing Medical University, 211166, Nanjing, China
[c] Toxicology and Genetics, Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, 76344, Eggenstein-Leopoldshafen, Germany

HIGHLIGHTS

- Mercury is ubiquitous in the environment and is teratogenic and neurotoxicant.
- Mercury induced cell death mainly involving in ROS production.
- Mercury exposure induced genes involving in many biochemical processes.
- In comparison to $HgCl_2$, methylmercury exposure induces much more genes.
- Knowledge gaps remain for the full understanding of the mercurial toxicity

GRAPHICAL ABSTRACT



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ABSTRACT

Minamata disease in Japan and the large-scale poisoning by methylmercury (MeHg) in Iraq caused wide public concerns about the risk emanating from mercury for human health. Nowadays, it is widely known that all forms of mercury induce toxic effects in mammals, and increasing evidence supports the concern that environmentally relevant levels of MeHg could impact normal biological functions in wildlife. The information of mechanism involved in mercurial toxicity is growing but knowledge gaps still exist between the adverse effects and mechanisms of action, especially at the molecular level. A body of data obtained from experimental studies on mechanisms of mercurial toxicity *in vivo* and *in vitro* points to that disruption of the antioxidant system may play an important role in the mercurial toxic effects. Moreover, the accumulating evidence indicates that signaling transduction, protein or/and enzyme activity, and gene regulation are involving in mediating toxic and adaptive response to mercury exposure. We conducted here a comprehensive review of mercurial toxic effects on wildlife and human, in particular synthesized key findings of molecular pathways involved in mercurial toxicity from the cells to human. We discuss the molecular evidence related mercurial toxicity to the adverse effects, with particular emphasis on the gene regulation. The further studies relying on Omic analysis connected to adverse effects and modes of action of mercury will aid in the evaluation and validation of causative relationship between health outcomes and gene expression.

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* Corresponding author. State Key Laboratory of Environmental Criteria and Risk Assessment, Chinese Research Academy of Environmental Sciences, 100012, Beijing, China.
E-mail address: yanglx@craes.org.cn (L. Yang).

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Abbreviation

AChE	acethylcholine esterase
CAT	catalase
GCL	glutamate-cysteine ligase
Gpx	glutathione peroxidase
GR	glutathione reductase
Grx	glutaredoxin
GSH	glutathione
GSSH	glutathione disulfide
GSTs	glutathione S-transferases
HO	heme oxygenase
IL	interleukin
MAO	monoamine oxidase
MRP	multidrug resistance associated proteins
MT	metallothioneins
NF-kB	nuclear factor kappa B
NQO	NAD(P)H dehydrogenase quinone
nNOS	neuronal nitric oxide synthase
SOD	superoxide dismutase
TNF-α	tumor necrosis factor α
Trx	thioredoxin
TrxR	thioredoxin reductase

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1. Introduction

Mercury is ubiquitous in the environment and exists in three forms: elemental, inorganic and organic mercury. All forms of mercury induce toxic effects in mammalian species (Clarkson et al., 2003; WHO, 2007). Each form of mercury has an unique toxicological profile, and differs in the mechamisms of transport and disposition in the body, and metabolic fate (ATSDR, 1999; Patrick, 2002; Clarkson et al., 2007). Although mercury is released from both natural and anthropogenic sources, studies indicate that mercury contamination of the environment is the result of human activities. For example, mercury levels of surface waters have tripled since the industrial revolution. Concentrations of mercury in Arctic marine animals today are about 10–12 times higher than in preindustiral times (prior to about 1800) (Braune et al., 2005; Lamborg et al., 2014). Observations support that a significant fraction of the seafood consumers around the world dose have unacceptably high whole-blood concentrations of mercury, particularly populations are living near small-scale gold mining with diets dependent on local freshwater fish, and populations consumed

marine mammals in Arctic regions (McKelvey et al., 2007) (Sheehan et al., 2014). Furthermore, there are between 316,588 and 637,233 children borned each year in United States with blood mercury level >5.8 μg/L, a level considered by the USEPA causing an increased risk of adverse health effects to babies (Hightower et al., 2006). Similar to USA, it is estimated that about 200,000 births every year in the European Union exceed a higher limit of 2.5 μg/g of hair-Hg concentration proposed by the WHO (Bellanger et al., 2013).

Humans are exposed to elemental Hg from dental amalgam restorations and artisanal gold mining. A decrease of nearly 10-fold in the urinary Hg values between 1975 and 2012 is observed through a biomonitoring programme among dental professionals (Goodrich et al., 2016). However, exposure to elemental Hg in artisanal gold mining areas leads to high concentrations of Hg in human blood, urine and hair, causing neurological symptoms (Steckling et al., 2014). The vaporized elemental Hg is inhaled and absorbed into the blood and easily crosses the blood-brain barrier. With time, gaseous Hg^0 is oxidized to ionic Hg^{2+} intracellularly, which accumulates in the kidney and is retained in brain causing damage there (Ha et al., 2017). Of note, many of these neurological symptoms related to Hg^0 exposure are more closely associated with organic than inorganic mercury (Bose-O'Reilly et al., 2017). It is estimated that up to 10–15 million miners, mainly in developing countries are affected by chronic Hg intoxication (Ha et al., 2017), however this is no longer a big issue in developed countries. Humans are exposed to inorganic mercury through the diet with less than 10% of inorganic Hg absorbed. In addition, it is nearly disappeared since consumer products containing mercury salts has been banned (Bose-O'Reilly et al., 2010). MeHg accumulates in fish and shellfish and has the highest bioavailability compared to the other forms. Nonoccuptional human and wildlife exposures to MeHg predominately occur by the consumption of MeHg contaminated fish and seafood (Driscoll et al., 2013). It has been estimated that 70–80% of total mercury in the human blood is in the form of MeHg (Mortensen et al., 2014). Furthermore, evidences support that MeHg is more toxic than inorganic Hg (McElwee and Freedman, 2011). Numerous studies support that exposure of animals to MeHg at high concentration can cause a variety of disorders, including impaired growth and development, reduced reproductive success, induced liver and kidney damage, and immunomodulation (Sweet and Zelikoff, 2001; Wiener et al., 2003). While, clinical signs of sensory disturbance, visual field constriction, deafness, ataxia, and dysarthria are well correlated with Minamata disease (see (Grandjean and Herz, 2011). Several lines of evidence support that increasingly subtle but important biological effects including behavioral, neurochemical, hormonal, immunological, and reproductive changes are associated with exposure of fish and wildlife to environmentally relevant MeHg (Crump and Trudeau, 2009; Tan et al., 2009; Sandheinrich and Wiener, 2011; Scheuhammer et al., 2012; Batchelar et al., 2013), however the extent of risk to the general population from long-term but environmentally relevant concentrations exposure to mercury remains an area of continuing debate (Grandjean et al., 1997; Davidson et al., 1998).

In the past two decads, extensive studies have extended dramatically our knowledge in the molecular mechanisms of acute mercury poisoning to wildlife and human health ((Grandjean and Herz, 2011) and herein). We now know that the interactions with sulfhydryl groups, the induction of oxidative stress, and disruption of calcium ion homeostasis are the major and critical mechanisms related to mercurial toxicity, however many aspects are still far from being understood satisfactorily. For example, we still do not understand how MeHg can impact on health outcomes such as adverse effects on fetal growth, neurological function, the cardiovascular system, and immune function in both adults and children. In this review, we summarized what we currently know about the mechanism of action of mercurial toxicity. We then examined the following questions: 1) what are the key issues of toxic effects linked to mercury exposure? 2) what important gaps exist in the current knowledges of mechanisms? Finally, we discuss the challenges in establishing the causative relationship between adverse effects and gene regulation linked to mercurial toxicity.

2. Mercury in the environment

It is estimated that the global release of mercury from natural, anthropogenic sources and reemission from past activities is 6000–11000 tons/yr (Swartzendruber, 2012). In particular, anthropogenic sources are believed to emit approximately up to 80% of the annual emission to the environment (Selin et al., 2008; Pirrone et al., 2010) (Sunderland et al., 2008). The total mercury (THg) in surface water of Antarctic lakes and glacial streams is 2.2–9.5 pM in general (Ullrich et al., 2001). The general background levels of THg in rivers, lakes, and sea sediments are 50 μg/kg, 100–300 μg/kg, and 24–400 μg/kg, respectively (Craig, 1986; Asmund and Nielsen, 2000). Whereas sediments in urban, industrial or mineralized areas can contain up to 100 mg/kg THg and up to 100 μg/kg MeHg (Craig, 1986). Globally, the inventory of mercury in surface soils far exceeds that in the aquatic and atmoshperic compartment. The levels of mercury in non contaminated soil worldwide are in a range of 10–50 μg/kg (Giorgio et al., 1999; Pablo Higueras et al., 2015). However the values above 230–240 μg/kg were found in the most important mercury mining area (Pablo Higueras et al., 2015). The average of total gaseous mercury in northern Europe is 1.98 ng/m^3, whereas particulate mercury and reactive gaseous mercury is 56 and 22 pg/m^3, respectively (Munthe et al., 2001; Hedgecock, 2011). Mercury concentrations in air can reach to 290 ng/m^3 in the region of mercury mine (Zadnik and Pompe-Kirn, 2007). Mercury is mobilizing in the atmosphere, land and the oceans. The gaseous Hg and particulate bound ionic Hg can be transported through atmosphere, whereas land and oceans play a role to redistribute Hg in ecosystem.

In the ecosystem, inorganic mercury is rapidly transformed into MeHg, which then accumulates in the food chain (Jensen and Jernelov, 1969; Compeau and Bartha, 1985; Ullrich et al., 2001). Phytoplankton generally concentrates MeHg 10^4-10^5 above the surrounding waters (Watras et al., 1998; Pickhardt and Fisher, 2007). The estimated MeHg concentrations in phytoplankton and marine zooplankton are in the range of 1.0–6.5 μg/kg (Kim et al., 2004; Luengen and Russell Flegal, 2009) and 0.5–200 μg/kg (Campbell et al., 2005; Hammerschmidt and Fitzgerald, 2006). The averaged THg concentrations in oysters, clams, squid, octopus, scallops and crabs consumed in the United States range from 0.01 to 0.12 mg/kg wet weight (ww) (USFDA, 2006). Mercury concentrations in 13 species of freshwater fish from northeast North America range from 0.19 mg/kg (white sucker, *Catostomus commersoni*) to 0.98 mg/kg ww (muskellunge, *Esox masquinongy*) (Kamman et al., 2005). The averaged concentrations of THg in the muscle of 7 species of Arctic seabirds range from 0.05 mg/kg ww in the black guillemot (*Cepphus grylle*) to 0.8 mg/kg ww in the glaucous-winged gull (*Larus hyperboreus*) (Borga et al., 2006). The averaged concentrations of THg range from 0.41 to 2.32 mg/kg dry weight (dw) in sea mammals (Atwell et al., 1998). Overall, due to its accumulation in the food chain, concentrations of THg increased from invertebrates (clams and zooplankton) to mid-trophic position fishes and seals to the top predator. Since the environmental risk has increased with MeHg exposure and the release of Hg to the environment from anthropogenic sources, mercury still poses a risk to wildlife.

3. Mercury exposure

Since the organic mercury compounds have been used as seed disinfectants, mercury poisoning of Swedish wildlife was widespread by the mid-1950s (Borg et al., 1969). Observations repeatedly reported that food is the dominant pathway of MeHg uptake in invertebrates, fish, and terrestrial wildlife (Evers et al., 2005; Hall et al., 1997; Tsui and Wang, 2004), particularly mercury levels are generally highest in fish-eating animals (Wren, 1986a). Indeed, mercury is detected at quantifiable levels (2 μg/kg) in every fish sample collected from all 500 lakes in the United States, and the values of mercury in predators range from 23 μg/kg to 6605 μg/kg (Stahl et al., 2009). Similarly, THg concentrations in 166 different species of fish distributed across 12 countries in Africa range from 5.5 to 1865.0 μg/kg ww (Hanna et al., 2015). Nowadays, consumption of fish and marine seafood is considered to be the primary route of exposure of wildlife and most non-occupational human to mercury (Mahaffey et al., 2004, 2009; Mergler et al., 2007; Sunderland, 2007) (Caldwell et al., 1999).

It is estimated that the consumption of marine fish and shellfish accounts for more than 90% of the population-wide mercury intake in the United States (Sunderland and Mason, 2007). The elevated THg levels in the hair were found in frequent fish consumers (Endo and Haraguchi, 2010) (Mezghani-Chaari et al., 2011). To limit mercury exposure, the Food and Agriculture Organization (FAO) and WHO's Codex Alimentarius have established a dietary limit level guideline of 0.5 mg MeHg/kg for fish and 1 mg MeHg/kg for predatory fish (CODEX, 1995). In addition, recent observations support that contaminated rice maybe another important source associated with MeHg exposure for people who are dependent on rice (Feng et al., 2008; Zhang et al., 2010).

Since the early stages of life are generally more sensitive to mercury, the 1.6 μg MeHg/kg body weight/week, corresponding to 2.2 mg/kg in the hair and a mean blood concentration of 8.6 μg/L MeHg in a 70 kg pregnant woman is considered as the value of provisional tolerable weekly intake (FAO/WHO, 2003). Together, numerous studies have demonstrated that exposure of wildlife and humans to MeHg overwhelmingly occurs by the consumption of contaminated aquatic and terrestrial organisms (Karagas et al., 2012). It is clear that exposure to high-level elemental, inorganic and organic mercury results in severe development and neurological effects depending on the length and dose of exposure. However, chronic exposure to MeHg via seafood intake poses a risk to wildlife and human health. With particularly emphasis on the effects on fetal growth and neurological outcomes in childhood associated with MeHg exposure, significant attention has been directed to the long-term consequences of prenatal exposure to low level MeHg.

4. Behavioral changes and/or health outcomes

Understanding of the process by mercury perturbing biological systems across cells to mammals is crucial for elucidating how exposure to mercury leads to toxicity, we thus summarized the adverse effects from cells to mammals. Several lines of evidence support that high-level inorganic and organic mercury can cause cell apoptosis, embryo or fetal death, and neurological sequelae such as severe cerebral palsy, deafness and visual impairment (Bakir et al., 1973; Harada, 1978, 1995; Harada et al., 2001). Furthermore increasing evidence supports that exposure of wildlife to the environmentally relevant MeHg could lead to adverse effects in behavior, physiology and reproduction (Crump and Trudeau, 2009; Weis, 2009) (see Tables 1 and 2).

4.1. Cells

Neuronal death is a well-known phenomenon of inorganic and organic mercury intoxication. Induction of apoptosis in cerebellar and/or differentiated human neurons is observed at low organic mercury concentrations while at higher concentrations, organic compounds result in necrosis. In contrast to organic mercury, exposure to $HgCl_2$ did not lead to apoptosis in cultured human differentiated neurons (Lohren et al., 2015). However, $HgCl_2$ was demonstrated to increase caspase-3 activity in rat brain (Abdel Moneim, 2015). A more likely explanation is that exposure to organic and inorganic mercury occurs in the brain. Of note, neither MeHg nor $HgCl_2$ do cause apoptosis in human astrocytes (Lohren et al., 2015). The discordant observations of that organic mercury exposures induce apoptosis in rat primary astrocytes and in normal human astrocytes may related to differences in sources of cells and cell type. Several lines of evidence support that organic and inorganic mercury exposure can lead to apoptosis in lymphocyte (Shenker et al., 1997; Guo et al., 1998), myogenic cells (Usuki et al., 2008), microglia (Nishioku et al., 2000), monocytes (InSug et al., 1997), and induce apoptosis and necrosis in murine T and B lymphoma cells (Kim and Sharma, 2003). Exposure of human lymphocytes and monocytes to either inorganic or organic mercury leads to a decrease of responsiveness in terms of proliferative capacity, cytokine production, immunoglobulin secretion (Shenker et al., 1992, 1997, 2000; InSug et al., 1997). In addition, observations indicate that both astrocyte and microglia mediate protective effects against MeHg induced neuronal toxicity (Eskes et al., 2002; Wang et al., 2009; Ni et al., 2010). Moreover, interaction of mercury with the motor protein kinesin has been reported to disturb chromosome distribution, and leads to aneugenicity (Bonacker et al., 2004). Taken evidence together, it is clear that organic and inorganic mercury share some common features in cytotoxicity including induction of apoptosis, disruption of the antioxidant system and increase cytokine release, however the profound differences exist in their mechanisms of toxicity. It is unclear how organic and inorganic mercury cause the differences in mechanism of action.

4.2. Invertebrates

Adverse effects on locomotion, inhibiting growth and feeding, reducing the survival of embryos, decreasing ability to capture active prey, and inducing development anomalies in embryo have been well documented in invertebrates including marine arthropods, worm and Drosophila exposed to mercury. Exposure of worm (*C. elegans*) to MeHg and $HgCl_2$ significantly affects locomotion, inhibits growth and feeding, and induces death (McElwee and Freedman, 2011). Inorganic mercury exposure induces mortality and causes specific segment-defective embryos of horseshoe crab embryos (*Tachyleus tridentatus and Limulus polyphemus*) (Itow et al., 1998b) (Botton, 2000). Furthermore mercury exposure causes larval anomalies in bay mussel (*Mytilus edulis*) and Pacific oyster (*Crassostrea gigas*), and induces mortality in larvae of Dungeness crab (*Cancer magister*) (Martin et al., 1981). Inorganic mercury exposure leads to delay metamorphosis and induces developmental defects in shrimp (*Palaemonetes pugio*) (Kraus et al., 1988). Exposure of *Drosophila* embryos to MeHg leads to delay embryonic development and defect in patterning, positioning and maturation of neurons and glia (Rand et al., 2009). Together, results support that invertebrates, particularly the early life-stage of animals (eggs, embryos and larvae) are more susceptible to mercury exposure, but how mercury cause developmental anommalies in embryos remains largely unknown.

Table 1
Overt effects on cells associated with Hg exposure.

Cells	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
SAF-1 cell line (derived from the fin of sea bream)	Cells were exposed to mercury for 24 h	MeHg 0.015, 0.049 mM; $HgCl_2$ 0.160, 0.500 mM.		ROS generation; regulation in expression of genes related to cellular protection (metallothionein a), oxidative stress (Hsp70, Prx1, 2, SOD, GR and CAT), apoptosis (Bcl2, Bax).	Morcillo et al. (2016a)
Erythrocytes from sea bream and sea bass	Cells were exposed to mercury for 24 h	MeHg 5–75 μM; $HgCl_2$ 1–10 μM.		Viability of erythrocytes declines in a dose-dependent manner; regulated genes involve in protection, oxidative response and apoptosis, including SOD, CAT, GR, peroxiredoxin, metallothionein a, Hsp70, Hsp90, Bax, Calp.	Morcillo et al. (2016b)
Rat cerebellar granule cells (CGCs)	Cells were treated with MeHg for 1 h	MeHg 0.5–10 μM.		Necrosis and apoptosis; relatively high MeHg concentrations cause the rapid impairment of mitochondrial activity, de-engergization of mitochondria and plasma membrane lysis and cytoskeletal breakdown.	Castoldi et al. (2000)
Primary astrocytes from rat	Cells were exposed to MeHg for 24 h	MeHg 0.3, 1, 3, and 10 μM. LC50 = 40 μM.		Cell death with dose dependent manner; increased mRNA and protein levels of NGF and BDNF.	Takemoto et al. (2015)
SH-SY5Y human neuroblastoma cells		MeHg 0.3, 1, 3, and 10 μM. LC50 = 1.5 μM		Cell death with dose dependent manner, and nearly all the cells died at 10 μM	
Primary rat microglial cells	Cell were exposed to MeHg for 6 h	MeHg 0.1–5 μM.		Decrease in cell viability; causing a rapid increase in ROS generation with concentration and time dependent manner; decrease in the ratio of GSH/GSSG; increase in mRNA levels of HO1, NQO1, xCT.	Ni et al. (2010)
Primary rat astrocyte and microglia				Increase in rate of cell death; leading to rapid ROS generation and GSH depletion; upregulation of Nrf2 and genes downstream of Nrf2 including HO1, NQO1, xCT.	Ni et al. (2011)
Hamster lung fibroblast cells V79, and microtubule assembly in a cell-free system	Cells were exposed to mercury for 18 h	$HgCl_2$ 1–100 μM; $Hg(NO_3)_2$ 1–10 μM. Inhibition of microtubule assembly LC50 is 5.8 μM.		Inhibit the microtubule assembly, microtubule motility. Induce micronuclei and lost integrity of cytoskeleton at 250 μM mercury.	Bonacker et al. (2004)
Rat astrocyte	Cells were exposed to MeHg for 6 h	MeHg 1–10 μM.		Increase in F2-isoprostanes and ROS formation, reduce the inner mitochondrial membrane potential, inhibit the net uptake of glutamine and expression of the mRNA encoding the glutamine transporters, SNAT3/SN1 and ASCT2.	Yin et al. (2007)
Rat cerebrocortical neurons	Cells were exposed to MeHg, inorganic mercury (IHg) for 1–3 days	MeHg and IHg 10 nM, 100 nM, and 1 μM.		Apoptotic process, damage to neuritic extension, and axonal degeneration. Decrease in expression of Tau, Rac1, Cdc24. RhoA was suppressed. MAP2 protein expression was altered.	(Fujimura et al., 2009; Fujimura and Usuki, 2012)
Murine T (EL4) and B (A20) lymphoma cells	Cells were incubated with $HgCl_2$ for 24 h	$HgCl_2$ 0–100 μM.		Induce a mixture of apoptosis and necrosis; increase intracellular calcium; induce ROS and increase in IL-4 and TNFα gene expression.	Kim and Sharma, 2003
Retinal epithelium (RPE) cells from pig eyes and human RPE cell line (D407)	RPE cells were exposed to $HgCl_2$ for 15 min	$HgCl_2$ 0.01–1000 μM. EC50 values of 35 ± 7 μM for D407, 99 ± 7 μM for primary RPE cells.		Induce cytotoxicity; decrease in glutamate uptake; increase in intracellular calcium concentration with concentration-dependent manner.	Toimela and Tahti (2001)
Human neuroblastoma BE(2)-C, HepG cells, retinal neurons and skeletal muscle primary culture from chick.	Cells were exposed to $HgCl_2$ for 5 h.	$HgCl_2$ 1–30 μM.		Inhibit Jak-STAT signaling by both CNTF and IFN-γ dependent; induce oxidative stress only in neuronal cells, but it does not affect signaling in HepG2 and skeletal myotubes.	Monroe and Halvorsen (2006)
Human monocyte and T-cells	Cultured sells were treated with MeHg or $HgCl_2$ for 2–16 h	MeHg 0–5 μM; $HgCl_2$ 0–50 μM.		Induce apoptosis, PARP cleavage; affect mitochondrial structure; generate free radicals; reduce the GSH concentration; cause a significant increase in the presence of cytochrome *c* in the cytosol. Decrease in mitochondrial transmembrane potential; generate ROS; thiol depletion and activating death-signaling pathways in monocyte.	(InSug et al., 1997; Guo et al., 1998; Shenker et al., 2000)
Human hepatoma HepG2 cell line	Cells were treated with $HgCl_2$ for 24 h	$HgCl_2$ 2.5–10 μM.		Significantly increase the NAD(P)H:quinone oxidoreductase (NQO 1) mRNA, protein and catalytic acitivity in a time and concentration-dependent manner.	Amara and El-Kadi (2011)
Human SH-SY5Y neuroblastoma cells	Cells cultures were treated with MeHg or $HgCl_2$ for 5 h	LC50: MeHg 19.8 μM; $HgCl_2$ 268 μM.		Induce cell death with dose dependent effects; MeHg enhances CNTF evoked STAT3 phosphorylation (1 μM); significantly increase superoxide production at 100 μM $HgCl_2$, 10 μM MeHg and inhibite CNTF-evoked STAT3 phosphorylation.	Jebbett et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Cells	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
Mouse cortical neuronal progenitor cells		LC50: MeHg 6.5 μM; $HgCl_2$ 53.4 μM.		Induce cell death with dose dependent effects; MeHg enhance CNTF evoked STAT3 phosphorylation (100 nM) and GFAP and SOCS3 expression; significantly increase superoxide production at 100 μM $HgCl_2$, 3–10 μM MeHg and inhibite CNTF-evoked STAT3 phosphorylation.	
Human SH-SY5Y cells	Cells were treated with MeHg, $HgCl_2$ and ethylmerncury (EtHg) for 24, 48 and 72 h	$HgCl_2$, MeHg and EtHg 1, 5, 10, 25, 50 μM; LC50 of EtHg, MeHg and $HgCl_2$ after 24 h exposure is 4.6, 4.9 and 40.8 μM respectively.		Decrease in expression and activity of TrxR1, 2, total GSH levels; increase oxidation of Trx1; increase in levels of phosphorylation of ASK-1 and activity of Caspase-3.	Branco et al. (2017)

4.3. Vertebrates

The adverse effects of MeHg on individuals of various vertebrate species have been well documented (see reviews (Wren, 1986b; Wolfe et al., 1998; Wiener et al., 2003; Scheuhammer et al., 2007). Although there are large differences in susceptibility among species, evidence has demonstrated that exposure of vertebrates to MeHg and $HgCl_2$ correlates with neurotoxicity (Wolfe et al., 1998), embryotoxicity (Scheuhammer et al., 2007), physiological disturbances of the liver and kidney (Hoffman et al., 2009), endocrine disruption (Tan et al., 2009) and altered reproductive behavior (Frederick and Jayasena, 2011).

4.3.1. Fish

During mercury poisoning in Japan, severely diminished locomotor activity, impaired escape behavior, emaciated body condition, and lesions in the brain were observed in adult fishes (Takeuchi, 1968). Fish containing 6–16 mg Hg/kg ww in axial muscle tissue was found with low hepatic fat stores, low serum cortisol levels, and low levels of total protein, glucose and alkaline phosphatase in blood serum which may relate to starvation (Lockhart et al., 1972). Increasing evidence supports that changes in biochemical processes, damage to cells and tissues, and reduced reproduction in fish are associated with environmentally relevant concentrations (0.5–1.0 mg/kg ww in axial muscle and a lowest observable adverse effects level (LOAEL) of about 0.3 mg/kg ww in the whole body of fish) (Crump and Trudeau, 2009; Tan et al., 2009; Dillon et al., 2010; Sandheinrich and Wiener, 2011) (Davis et al., 2008). Moreover, Sandheinrich et al. (Hammerschmidt et al., 2002; Drevnick and Sandheinrich, 2003; Sandheinrich and Miller, 2006) and Friedmann et al. (2002, 1996) are more focused on fish reproduction and reported effects of MeHg on reproduction including suppression of gonadal development, egg production, spawning, levels of plasma estradiol (E2) in females and testosterone in males, and disruption of reproductive behavior in fathead minnows (*Pimephales promelas*), largemouth bass and male walleye, as well as in white sturgeon (Webb et al., 2006). Oliveira Ribeiro et al.(Oliveira Ribeiro et al., 2006; Mela et al., 2007) reported that exposure to MeHg increases number of red and white blood cells, hemoglobin concentration, mean corpuscular volume, and damage liver and kidney cells in fish (*Hoplias malabaricus*). Larose et al. (2008) found that exposure to mercury at environmentally relevant concentrations causes lower hepatosomatic indices and reduces enzymes activities in fish. Similarly, dietary MeHg can disrupt feeding behaviors of adult golden shiners (Webber and Haines, 2003), and newly hatched fry of graylings (Fjeld et al., 1998). Overall, low level inorganic and organic mercury exposure leads to changes in swim behavior and decreases in foraging efficiency, while delayed hatching, increased mortality, and the induction of hyperactive behavior associated with decrease in release of neurotransmitters are observed in fish exposed to mid-range concentrations. Modulation of neurotransmitters including dopamine and serotonin in brain may result in changes of behavior related to mercury exposure (Bridges et al., 2017). It should be noted that the teleost fish display 12 to 16 proliferation zones with respect to reactivating adult neurogenesis along the central nervous system, whereas adult neurogenesis in mammalian species appears only in two subdivision (Ganz and Brand, 2016). The prominent and widespread adult neurogenesis in teleost fish may display adaptive phenomenon in a recovery of a significant reduction in the number of cells in hypothalamus and cerebellum occurred after post-exposure to inorganic mercury.

4.3.2. Amphibians and reptiles

Although mercury concentrations in amphibians varied, and were generally associated with food habits and habitat selection, observations support that mercury exposure impacts frog survival and embryo developmental process, declines the reproduction of reptiles, affects salamanders by reducing their ability to successfully execute tasks critical to survival, and induces the genotoxic effects. Exposure of the frog (*Rana cyanophlyctis*) to sublethal concentrations of $HgCl_2$ (0.96 mg/L) inhibits spermatogenesis (Kanamadi and Saidapur, 1992), and to MeHg causes exogastrulation in frog (*Rana pipiens*) embryos, poor tail development and tadpole death (Dial, 1976). A higher toxicity of MeHg over $HgCl_2$ may be related to the higher accumulation of mercury from MeHg than that from $HgCl_2$ by embryos (*Xenopus laevis*) (Prati et al., 2002). The occurrences of delayed limb regeneration and death of the newt (*Triturus viridescens*) were observed in MeHg polluted water (Chang et al., 1976). Moreover, the genotoxic effects, including chromosome breaks and c-mitosis were found in larvae of the newt (*Pleurodeles waltl*) exposed to MeHg and $HgCl_2$ (Zoll et al., 1988).

Elevated levels of blood mercury and THg were observed in turtles (Bergeron et al., 2007; Schneider et al., 2010) and in two-lined salamander (*Eurycea bislineata*) larvae (Bank et al., 2005). A positive correlation between blood mercury concentrations and hematocrit and creatine phosphokinase activity was observed in loggerhead sea turtles (*Caretta caretta*). While lymphocyte cell counts and aspartate aminotransferase are negatively correlated with blood mercury concentrations (Day et al., 2007). The offspring of northern watersnakes (*Nerodia sipedon*) from a historically mercury contaminated river showed less motivation to feed and reduced strike efficiency (Chin et al., 2013). Exposure to sublethal mercury may negatively affect the salamander's prey capture behavior and terrestrial performance (Burke et al., 2010). Collectively, it is clear that exposure of amphibians to mercury causes adverse effects likely related to disruption of hormone production, impairing enzymes activities, damaging cell structures, and altering gene expression, but further studies are required to reveal the

Table 2
Overt effects on wildlife associated with Hg exposure.

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
Daphnia magna	24-h-old neonates and 3 to 4 -day-old juveniles were exposed to $HgCl_2$ for 24 h to 4 days	$HgCl_2$ 5−150 μg/L. LC50 (24 h, μg/L): 12−55.	24 h median lethal body burden (LBB50, mg/kg wet wt): 10−26.	High mercury tolerance accompanied by reduced Hg uptake under low temperature and high pre-exposure to Hg; daphina survival in the following order of sequence: aqueous Hg > whole body Hg > Hg in the metal-sensitive fraction (MSF).	Tsui and Wang (2006)
Caenorhabditis elegans	L1 and L4 stage worms were exposed to MeHg for 48 and 72 h	MeHg 0−125 μM. LC50 (48 h): 95 μM.		Loss of viability with an LC50 of approximately 90 μM; decrease the number of viable progeny; delay in morphogenesis and gonadogenesis; increase in cellular ROS.	Vanduyn et al. (2010)
	Age-synchronized L1 and L4 larvae, and adult nematodes were exposed to MeHg and $HgCl_2$ for 4−48 h	$HgCl_2$ 0.3−200 μM. EC50: for inhibiting growth 11.8 μM; feeding 34.8 μM; reproduction 11.3 μM. MeHg 0.03−50 μM. EC50: for inhibiting growth 11.3 μM; feeding 11.3 μM; reproduction 0.81 μM.		Arrest growth and induce nematode death at concentrations greater than 25 μM; inhibit feeding; decrease in distance, speed, and amplitude. Increase in mRNA levels of GST-1, GST-38, Hsp-16.2 and Hsp-70 with exposure dependent manner.	McElwee and Freedman (2011)
Grass Shrimp from mercury contaminated Piles Creek (PC) and relatively clean area, Big Sheepshead Creek (BSC).	Newly hatched larvae and adults were exposed to mercury for 21 and 14 days, respectively	$HgCl_2$ 0.01 mg/L, MeHg 0.0125 mg/L for larvae; MeHg 0.025, 0.05 mg/L; $HgCl_2$ 0.025, 0.05 mg/L for adults.		Only 28% of the PC and 11% of the BSC larvae in 0.01 mg/L $HgCl_2$ survive at least 21 days, while, 23.7% of PC and 3% of the BSC larvae survive at least 21 days in 0.0125 mg/L MeHg. No BSC larvae metamorphose in the MeHg. Mercury treated larvae from BSC exhibit a significant delay in metamorphosis. Adults from PC were significantly more resistant to mercury than were BSC animals.	Kraus et al. (1988)
Common mussel	Mussels were exposed to $HgCl_2$ for 15 days	$HgCl_2$ 30 μg/L.	The concentrations of mercury in digestive glands at 5th, 10th, and 15th day reached 20.0, 68.5, and 77 μg/g dw.	Increase in micronucleus frequency, lipid peroxidation, and influence SOD acitivity; cause impairments at each stage of protein synthesis.	Pytharopoulou et al. (2013)
Japanese horseshoe crabs *Tachypleus gigas*, *Carcinoscorpius rotundicauda* and Amercian horseshoe crab	Different stages of embryos were exposed to mercury for 24 h or/and continuously Embryos and trilobite larvae were exposed to $Hg(C_2H_3O_2)_2$ for 24, 48 and 72 h or entire experiment	$HgCl_2$ 1, 10, 100 mg/L; $Hg(C_2H_3O_2)_2$ 10, 100 mg/L.		100% lethal to all stages in 10 and 100 mg/L $HgCl_2$, and 100 mg/L $Hg(C_2H_3O_2)_2$; Mercury induces a special type of segment-defective embryo characterized by lost or fused body segments and appendages after treatment at stages 9, 10, and 11. Limb regeneration was normal at less than 0.1 mg Hg/L, very little regeneration at 1.0 mg/L, and in 10 mg/L. The first instars did not molt and larvae died in 100.0 mg/L.	(Itow et al., 1998b) (Itow et al., 1998a) Botton (2000)
Horseshoe crab (*Limulus Polyphemus*)		Nominal concentrations of 0.01 −500 mg/L. LC50: Embryo 24: 12.8 mg/L, 48: 5.1 mg/L, 72: 3.1 mg/L, continuous: 3.2 mg/L. Trilobite 24: 56 mg/L, 48: 19.6 mg/L, 72: 7.6 mg/L, continuous: 0.7 mg/L.		Increase mortality generally with increasing exposure period.	
Atlantic croaker (*Micropogonias undulatus*)	Adult fish were fed MeHg contaminated food for 1 month	0.05, 0.1 mg/kg/day MeHg contaminated food.	Spawned eggs: Control: 0.0010 −0.0014 ng/g; Low: 0.294−0.639 ng/g; High: 0.567−4.574 ng/g.	Maternal transferred MeHg induce concentration dependent effects on survival skills compared to control.	Alvarez Mdel et al. (2006)
Atlantic salmon (*Salmo salar*)	Atlantic salmon parr were exposed to MeHg and $HgCl_2$ via contaminated food for 4 months	$HgCl_2$ 10, 100 mg/kg dw; MeHg 5, 10 mg/kg dw.	MeHg 5 mg/kg: liver 4.06 mg/kg ww, kidney 2.00 mg/kg, brain 1.16 mg/kg; MeHg 10 mg/kg: liver 6.69 mg/kg ww, kidney 3.05 mg/kg, brain 0.68 mg/kg. $HgCl_2$ 10 mg/kg: liver 0.15 mg/	Significantly increase SOD in the brain at 5 mg/kg MeHg; significantly increase lipid peroxidative products (TBARS) and decrease in SOD, GPx in the brain, increase in SOD, GPx in	Berntssen et al. (2003)

(*continued on next page*)

Table 2 (*continued*)

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
			kg ww, kidney 0.23 mg/kg, brain 0.03 mg/kg; $HgCl_2$ 100 mg/kg: liver 0.96 mg/kg ww, kidney 6.82 mg/kg, brain 0.13 mg/kg.	the liver and had pathological damage, reduce monoamine oxidase (MAO) activity and overall post-feeding activity behavior at 10 mg/kg MeHg; significantly reduce MAO activity and pathological changes (astrocyte proliferation) in the brain at 100 mg/Kg $HgCl_2$.	
Mature Neotropical fish (*Hoplias malabaricus*)	Adult fish were exposed to MeHg via contaminated food for 70 days	Daily normal doses of MeHg 0.015 μg/g fish.		Significant differences in red blood cells and mononuclear cells counts, hemoglobin concentration, hematocrit, leukocytes, neutrophils, and mean corpuscular volume beween MeHg exposed fish and its controls.	Oliveira Ribeiro et al. (2006)
	Age-synchronized L1 and L4 larvae, and adult nematodes were exposed to MeHg and $HgCl_2$ for 4–48 h	$HgCl_2$ 0.3–200 μM. EC50: for inhibiting growth 11.8 μM; feeding 34.8 μM; reproduction 11.3 μM. MeHg 0.03–50 μM. EC50: for inhibiting growth 11.3 μM; feeding 11.3 μM; reproduction 0.81 μM.	Control: liver 0.601 μg/g, muscle 0.67 μg/g. Exposed group: liver 1.069 μg/g, muscle 1.45 μg/g.	Observe morphological lesions in liver (pre-necrotic lesions, necrosis areas and cytoskeleton disarray) and kidney (increase in the number of leukocytes and their phagocytic activity, and necrosis areas).	Mela et al. (2007)
Grass Shrimp from mercury contaminated Piles Creek (PC) and relatively clean area, Big Sheepshead Creek (BSC).	Newly hatched larvae and adults were exposed to mercury for 21 and 14 days, respectively	Daily normal doses of MeHg 0.015 and 0.15 μg/g fish.	Accumulated deposits of Hg in the photoreceptor layer, the inner and outer plexiform layers.	Reveal a cellular deterioration in the photoreceptor layer, morphological changes in the inner and outer segments of rods, structural changes in the plasma membrane of rods and double cones, changes in the process of removal of membranous discs and a structural discontinuity.	Mela et al. (2012)
Catfish (*Ictalurus melas*)	Catfish (mean total length 23.9 ± 2.7 cm; mean weight 171.10 ± 51.19 g) were exposed to Hg^{2+} for 10 days	Nominal concentrations: 35, 70, 140 μg/L.	Mercury concentrations (mg/kg wet weight) in tissue: Control (0.0 μg/L): gills 0.15, liver 0.15, kidneys 0.14, muslce 0.09; 35 μg/L: gills 10.73, liver 6.42, kidneys 11.78, muscle 0.74; 70 μg/L: gills 10.22, liver 4.82, kidneys 9.82, muscle 0.61; 140 μg/L: gills 15.28, liver 8.06, kidneys 17.82, muslce 0.80.	The general metal content in kidney being nearly equal to gill > liver > muscle. Increased activity of GST was observed at all the mercury concentrations. The activity of glyoxalase I increase at 140 μg/L, while glyosalase II and GPx increase at 35 μg/L.	Elia et al. (2003)
Yellow catfish (*Pelteobagrus fulvidraco*)	Juveniles were exposed to Hg^{2+} for 6 weeks	Nominal concentrations of 2 and 10 μg/L.	Exposure to 2 and 10 μg/L Hg^{2+}, increase in splenic Hg concentrations to 232- and 507-fold, and in head kidney 283- and 657-fold total Hg contents compared with control groups.	Decrease in lymphoid cells and increase in melano-macrophage centres in spleen and head kidney; increase CAT, AHR and SOD activity and GSH content in spleen and the head kidney; increase the expression of genes encoding Sod1, Cat, Gpx1, Nrf2, Mt and Hsp70; increase mRNA levels of IL-1β, IL-8, TNF-α, IL-10, TGF-β, Lys and C3 in the spleen.	Yaling Sun et al., 2018 https://doi.org/10.1002/jat.3592.
Common carp (*Cyprinus carpio*)	Carp were exposed to $HgCl_2$ for 12–96 h	$HgCl_2$ 0.01 mg/L	0.0037 mg/kg in exposed specimens.	Decrease SOD, GPx activity in blood, increase CAT activity in liver, reduce GPx activity in liver and gill, and increase lipid peroxidation in blood and protein carbonyl content in brain; increase in DNA damage in gill and liver from 12 h and mean micronucleus frequency in erythrocytes.	Garcia-Medina et al. (2017)
Fathead minnows (*Pimephales promelas*)	Juvenile fish were exposed to MeHg via contaminated dietary until sexual maturity and reproduction	Control diet 0.06 μg/g dw, low 0.88 μg/g, medium 4.11 μg/g and high 8.46 μg/g dw	Male: 0.36 (control diet)-25.5 μg Hg/fish. Female:0.21–14.2 μg Hg/fish.	Dietary MeHg delay spawning. Days to spawning are positively correlated with concentration of total mercury in the carcasses of test fish; both the gonadosomatic index and reproductive effort of female	Hammerschmidt et al. (2002)

Table 2 (*continued*)

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
				fish are inversely correlated with mercury in carcasses.	
Atlantic salmon (*Salmo salar*)	Juvenile fish (90 days after hatching) were exposed to MeHg via contaminated diet until sexual maturity	Control diet 0.06 μg/g dw, low 0.87 μg/g, medium 3.93 μg/g dw	Male: 0.071 (control diet)-3.557 μg/g ww. Female: 0.079–3.842 μg/g ww.	Suppress levels of testosterone (T) in males and 17β-estradio (E2) in females; inhibit gonadal development of females; reduce the reproductive success.	Drevnick and Sandheinrich (2003)
Mature Neotropical fish (*Hoplias malabaricus*)	Adult fish were exposed to MeHg via contaminated food for 70 days	Daily normal doses of MeHg 0.015 μg/g fish.	Male: 0.068 (control diet)-4.225 μg/g ww.	Alter reproductive behavior of males; reduce the reproductive success of pairs of fish.	Sandheinrich and Miller (2006)
	Juvenile fish were exposed to $HgCl_2$ for 10 days	$HgCl_2$ 1.69, 6.79 and 13.57 μg/L	Muscle tissue Hg concentrations:	Consistent performance deficits in foraging efficiency and capture speed.	Grippo and Heath (2003)
	Adults were exposed to MeHg via contaminated diet for 30 days. Larval fish from maternal transfer	Control diet 0.02 ppm; spiked diet 0.72 ppm dw	Pretrial: 0.10 (control)-8.02 μg/g; post-trial: 0.10 (control)-7.27 μg/g. Muscle: 0.084 (control)-0.804 ppm; gonad: 0.024 (control) −0.276 ppm; brain: 0.07 (control)-0.46 ppm; Eggs: 0.01 (control)-0.074 ppm; Larvae: 0.01 (control)-0.064 ppm ww.	Decrease dopamine concentrations in adult forebrain and reduce MAO activity in adult brain tissue; hyperactive behaviors in embryos and changes in embryonic dopamine concentrations and MAO activity.	Bridges et al. (2017)
Zebrafish (*Danio rerio*)	Embryos were exposed to MeHg from <1 to 24 hpf	MeHg 1, 3, 10, 30, 100 nM	Mean tissue dose of THg in F0 (144 hpf). Control: ≤ 5.0 ppb; F0 from 20 to 3000 ppb; F2 ≤ 9.0 ppb.	Hyperactivity and visual deficit in the unexposed descendants (F2 generation); increase sperm epimutations in F2 generation relative to the F0 generation; effects on differential DNA methylation regions (DMRs) associated genes in the neuroactive ligand-receptor interaction and actin-cytoskeleton pathway.	Carvan et al. (2017)
Yellow catfish (*Pelteobagrus fulvidraco*)	Eight-month-old fish (G0) and new generation of fish (G1) were exposed to MeHg via contaminated food for 9 weeks (G0) and whole life span (G1)	Nominal concentrations 0.5, 5 and 50 ppm for G0 fish; 1, 3 and 10 ppm for G1 fish	Hg burden in G1 embryos: control 0.005 ppm. Association of 0.024, 0.212 and 1.067 ppm ww with 0.5, 5 and 50 ppm exposure respectively; Hg burden in G2 embryos: control 0.006 ppm. Assocaition of 0.073, 0.187 and 0.623 ppm ww with 1, 3 and 10 ppm exposure respectively.	Decrease locomotor output in the 6 dpf offspring of fish exposed to 3 and 10 ppm MeHg; increase in locomotor activity in all MeHg exposures in a second test 7 dpf fish and until 16 dpf.	Mora-Zamorano et al. (2016)
Common carp (*Cyprinus carpio*)	Adults were exposed to MeHg via contaminated food for 25 and 50 days	Control 0.08 μg/g dw. MeHg contaminated food 13.5 μg/g dw	Control brain: 0.19 μg/g dw after 25 days and 0.96 μg/g dw after 50 days. Exposure group brain: 30.2 μg/g dw and 46.2 μg/g dw in brain after 25 and 50 days exposure respectively.	Increase in the expression of Sdh, Gfap and Gst along with repression of the Gpx1 after 50 days exposure; an up-regulation of Atp2b3a, Atp2b3b and Slc8a2b after 25 days exposure.	Cambier et al. (2012)
Fathead minnows (*Pimephales promelas*) Eastern mosquitofish (*Gambusia holbrooki*) *Xenopus laevis* American toad (*Bufo americanus*)	Adults were exposed to MeHg via contaminated food for 7, 21 and 63 days	Control 0.08 μg/g dw. MeHg contaminated food 5 and 13.5 μg/g dw	THg in organs from control fish <0.7 μg/g dw; Brain (after 63 days): 21.2 μg/g dw for 5 μg/g dw exposure and 63.5 for 13.5 μg/g dw exposure; skeletal muscle (after 63 days): 15.0 μg/g dw for 5 μg/g dw exposure and 32.7 for 13.5 μg/g dw exposure; liver (after 7 days): 10.0 μg/g dw for 5 μg/g dw exposure and 28.2 for 13.5 μg/g dw exposure.	No changes of 13 genes in expression levels in brain; induce Coxl, Sod and repress Gadd and Rad51 in liver; up-regulate expression of Coxl, Sod, Mt2 and Rad51 gene in liver.	Gonzalez et al. (2005)
	Exposure of adults to MeHg and $HgCl_2$ via contaminated food for 62 days Lifelong exposure of multiple generations to mercury	Low MeHg food: 60 ng Hg/g; MeHg enriched food: 11,580 ng Hg/g; enriched iHg food: 11,920 ng Hg/g Dissolved Hg ($HgCl_2$) in water: Reference < 0.1 μg/L. Medium 18 μg/L. High 42 μg/L	Hg bioaccumulation. Low MeHg: max 536 ng MeHg/g dw in muscle (62 days); MeHg enriched: 31,869 ng/g dw in muscle, 60,591 ng/g dw in liver, 110,653 ng/g dw in brain; iHg enriched: 76 fold lower than MeHg in muscle, 17 fold lower than MeHg in liver, 2612 ng/g dw in brain.	A significant modification of 11 genes' expression level depending on Hg speciation, tissue and exposure time. Disorganised myofibrils, damaged hepatic tissue and severely affected mitochondria related to MeHg exposure; induce metallothionein production in brain.	Gentes et al. (2015)

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Table 2 (*continued*)

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
			Reference: 0.08 μg/g wet mass, range: 0.01–0.51. Medium: 4.13 μg/g, range 1.78–9.07. High: 3.89 μg/g, range: 2.13–6.68.	No significant differences in standard metabolic rate (SMR) among individuals from Hg-exposed or reference populations.	Hopkins et al. (2003)
	Exposure of animals from 8 h after fertilization to 120 h after fertilization	MeHg 0.031, 0.062, 0.125, 0.250, 0.400, 0.500 μM. $HgCl_2$ 0.062, 0.125, 0.250, 0.500, 0.750, 1 μM	Content of Hg in embryos exposed to 0.125 μM mercury for 120 h: Control <10 μg/kg, ww; $HgCl_2$ 810 μg/kg ww; MeHg 6632 μg/kg ww.	Estimated LC50 and TC50 for MeHg was 0.313 μM and 0.236 μM respectively. For $HgCl_2$ was 0.601 μM and 0.513 μM respectively. $HgCl_2$ causes a slight reduction in embryo length.	Prati et al. (2002)
	Contaminated South River, adult toad, and larvae received diets with or without Hg for 26–28 days	The reference and maternally Hg exposed groups with blood THg <250 and >1000 ng/g. Low mercury 2.5 μg/g dw and high mercury 10 μg/g dw	Blood THg of female toad, control 160 ng/g ww. Exposed group 2250 ng/g ww. Egg THg, control 20.6 ng/g dw, exposed group 149 ng/g dw.	Both dietary and maternal Hg exposure significantly affect growth and development of larvae. Maternal Hg exposure affect average swimming speed and responsiveness of larvae.	Bergeron et al. (2011)
Wood frog (*Rana sylvatica*) Northern two-lined salamander (*Eurycea bislineata*) Northern Watersnake (*Nerodia sipedon*)	Tadpoles at Gosner stage 21–23 were exposed to MeHg and $HgCl_2$ via THg contaminated diets until Gosner stage 42–46	Low Hg diet, 2.5 μg/g dw with 2.75% MeHg. High Hg diet, 10 μg/g dw with 1.05% MeHg dw	THg in tadpoles at Gosner 42: control, 0.03 μg/g dw, low Hg diet, 1.06 μg/g dw, high Hg diet, 3.54 μg/g dw. THg in tadpoles at Gosner 46: control, 0.05 μg/g dw, low Hg diet, 0.85 μg/g dw, high Hg diet, 2.57 μg/g dw.	No effects of Hg on the duration of tadpole development, size at metamorphosis, tail resorption time, or hopping performance. No differences in whole-body thyroid hormone concentrations among dietary treatments.	Wada et al. (2011)
Loggerhead sea turtle (*Caretta caretta*)	Adult salamanders from Hg contaminated River and reference sites	Adults were exposed to Hg via contaminated river	THg, Reference site: 256 ng/g dw; contaminated site: 4519 ng/g dw.	Significant effect on speed and responsiveness in the first locomotion trial and eat less prey.	Burke et al. (2010)
	Gravid females captured at reference and Hg contaminated sites.	Females were exposed to Hg via contaminated river	Control: 0.20 mg/kg dw, range 0.06–1.09 mg/kg dw. Contaminated sections: 3.42 mg/kg, dw, range 1.08–10.10 mg/kg, dw.	Mercury concentrations in offspring negatively correlate with motivation to feed and strike efficiency.	Chin et al. (2013)
	Free-ranging turtle	*In vitro* experiment: 0.01, 0.03, 0.05, 0.1, 0.35, and 0.7 μg/g	Blood Hg: 2001: 0.005–0.188 μg/g ww, mean: 0.029 ± 0.008 (SD). 2003: 0.006–0.077 μg/g ww, mean: 0.029 ± 0.002.	Blood Hg levels are positively correlated with hematocrit and creatine phosphokinase activity, and negatively correlated with lymphocyte cell counts and aspartate aminotransferase. *In vitro* exposure of peripheral blood leukocytes to MeHg results in suppression of proliferative responses for B cells and T cells.	Day et al. (2007)
Snapping turtle (*Chelydra serpentina*)	Gravid female snapping turtles from Hg contaminated and uncontaminated river	Females exposed to Hg via contaminated river	Total Hg concentrations: blood 0.01–4.99 ppm (wwt); muscle 0.05–32.29 ppm (dwt); nail 0.15–161.11 ppm (fwt); egg 0.01–6.61 ppm (dwt).	Egg THg negatively correlate with hatch success, and positively correlate with frequency of embryonic mortality during development and frequency of unfertilized eggs.	Hopkins et al. (2013)
Mallard ducks (*Anas platyrhynchos*)	Adult mallards were fed diet containing MeHg for 26 days	Diets containing MeHg 1, 2, 4, or 8 μg/g	Hg in eggs. Control 0, range 0.0–0.01 μg/g ww; 1 μg/g diet 1.6, range 1.4–1.9 μg/g ww; 2 μg/g diet 3.7, range 2.5–5.6 μg/g ww; 4 μg/g diet 5.9, range 4.7–6.9 μg/g ww; 8 μg/g diet 14, range 11–20 μg/g ww.	Reduce survival of duckling and the number of duckling produced per female at the 4 and 8 μg/g dietary mercury exposure.	Heinz et al. (2010)
White ibises (*Eudocimus albus*)	90-day-old nestling white ibises were exposed to MeHg for 3 years via contaminated food.	Low dose 0.05 ppm ww; medium dose 0.1 ppm ww and high dose 0.3 ppm ww	THg concentrations in feathers: control 0.47–0.74 mg/kg fresh-weight (fw); low 4.31–8.20 mg/kg fw; medium 14.13–17.96 mg/kg fw; high 23.86–51.32 mg/kg fw. THg concentrations in blood: control 0.07 mg/kg fw; low 0.73 mg/kg fw; medium 1.60 mg/kg fw; high 3.95 mg/kg fw.	Dose-related increases in male-male pairing behavior (to 55% of males) and decrease in egg productivity (to 30%). Decrease rates of key courtship behaviors.	Frederick and Jayasena (2011)
American toad (*Bufo americanus*)	Contaminated South River, adult toad, and larvae received diets with or without Hg for 26–28 days	The reference and maternally Hg exposed groups with blood THg <250 and >1000 ng/g. Low	Blood THg of female toad, control 160 ng/g ww. Exposed group 2250 ng/g ww. Egg THg,	Alter expression of estradiol and testosterone in both sexes during breeding, albeit not in a consistent pattern; association	Jayasena et al. (2011)

Table 2 (*continued*)

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
		mercury 2.5 μg/g dw and high mercury 10 μg/g dw	control 20.6 ng/g dw, exposed group 149 ng/g dw.	of endocrine changes with changes in reproductive behavior, reduce reproductive success and alter mate choice in males.	
Tree swallow (*Tachycineta bicolor*)	Adult swallows breeding on contaminated sites along the South River		Blood Hg concentration of less-successful clutches (≤50% hatching), 2.15 μg/g and female with more successful clutches (≥75% hatching) 2.60 μg/g. Feather Hg concentration of deceased nestling, 12.89 μg/g and fledging nestling, 7.41 μg/g.	At nestling stage, association between nestlings living or dying and feather Hg concentrations. The nestling stage as the most vulnerable life stage.	Taylor and Cristol (2015)
Common loon (*Gavia immer*)	Adult loons inhabited in freshwater lakes, and some area with the highest Hg levels	Including nearly 5500 loons Hg measurement over an 18-year period	Adult blood Hg levels range 0.13−11.80 μg/g ww; Egg Hg levels range 0.20−9.03 μg/g ww; Feather Hg levels range 1.4−75.7 μg/g fw.	Significant changes in aberrant incubation behavior, lethargy and wing area asymmetry.	Evers et al. (2008)
Zebra finch (*Taeniopygia guttata*)	Birds were exposed to MeHg via contaminated food for whole lives including the egg	Nominal dose 1.2 μg/g ww	Control blood 0.011 μg/g ww. Exposed birds blood 17.79 μg/g ww.	Decrease cognitive performance in a spatial memory assay; induce a behavioral phenotype of hyperactivity and decrease social dominance.	Swaddle et al. (2017)
Loggerhead sea turtle (*Caretta caretta*)	Offspring of F0 breeding pairs were exposed to MeHg diet and F1 birds were exposed to MeHg diet until 50 days post hatching	Diet dosed with 1.20 μg/g ww MeHg-cysteine	Hg concentrations in blood of Juvenile F1 at 25 days after hatching, control 0.004 μg/g ww, exposed group 7.411 μg/g ww; Hg concentrations in blood of Juvenile F1 at 50 days after hatching, control 0.005 μg/g ww, exposed group 10.498 μg/g ww; Hg concentration in eggs laid by F1 finches, control 0.0013 μg/g ww, exposed 0.039 μg/g ww.	Notably reduce reproductive success in adulthood related to exposure to MeHg solely during embryonic and juvenile development.	Paris et al. (2018)
Guinea-pigs	MeHg was administered on one of days 21, 28, 35, 42 or 49 of gestation of pregnant guinea-pigs.	7.5 mg Hg/animal (weighing 500−800 g)	Maternal Hg (ug/g ww): 3 weeks: liver 2.3; kidney 18.6; whole blood 0.7; blood plasma 0.034.4 weeks: liver 3.4; kidney 25.6; whole blood 1.2; blood plasma 0.043.5 weeks: liver 4.3; kidney 29.0; whole blood 1.7; blood plasma 0.051.6 weeks: liver 6.1; kidney 19.1; whole blood 2.4; blood plasma 0.061.7 weeks: liver 8.1; kidney 73.4; whole blood 3.0; blood plasma 0.108. Control: liver <0.05; kidney <0.05; whole blood <0.05; blood plasma no detectable. Fetal Hg (ug/g ww): 3 weeks: liver 2.3; kidney 1.1; whole blood 1.1; blood plasma 0.035.4 weeks: liver 3.8; kidney 1.9; whole blood 2.0; blood plasma 0.063.5 weeks: liver 4.0; kidney 2.4; whole blood 2.4; blood plasma 0.084.6 weeks: liver 5.2; kidney 3.2; whole blood 3.5; blood plasma 0.113.7 weeks: liver 6.4; kidney 4.6; whole blood 3.9; blood plasma 0.177. Control: liver <0.05; kidney <0.05; whole blood <0.05; blood plasma no detectable.	The fetal brains are disturbed in the development following treatment at 3, 4 and 5 weeks of pregnancy. The thinned cerebral cortex, reduced size of nucleus caudatus putament and the hippocampal formation and dilated the lateral ventricles are observed in fetal brain. The focal degeneration of the neuronal cells in the fetal neocortex, severe spongy degeneration and dysgenetic hydrocephalus are noted following treatment at 6 and 7 weeks of pregnancy.	Inouye and Kajiwara (1988)
Mice	Male, 6 weeks old. MeHg exposure via drinking water for 8 weeks	30 ppm, 1.5 mk/kg/day	Cerebral cortex: around 18 ppm; Hippocampus: around 25 ppm; Cerebellum: around 20 ppm.	Neuronal degeneration in cerebral cortex; upregulate expression of *c*-fos and BDNF.	Fujimura and Usuki (2017b)
Rat Mice	10 weeks old. MeHg exposure via drinking water from gestating day (GD) 1 to postnatal day (PND) 21	0−10 ppm, 0.05, 0.25, and 0.5 mg/kg/day 0.5 mg/kg/day	Female: 5 ppm, PND 36 Cerebral cortex: 0.08 ppm; Hippocampus: 0.11 ppm; Cerebellum: 0.09 ppm; blood:	Pups in the 5 ppm group show significant impairment in motor coordination and decrease SPP-positive neurons, but in the 1	Fujimura et al. (2012)

(*continued on next page*)

Table 2 (*continued*)

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
	Mice were exposed to MeHg from gestational day 7 until postnatal day 7 via drinking water		0.21 ppm; liver: 0.23 ppm; kidney: 2.37 ppm. Brain: PND 8: 2.60 μg/g ww; pup: 0.93 μg/g ww. 4 weeks old: 0.045 μg/g ww; control: < 0.006 μg/g ww.	−5 ppm without general neuropathological changes in the cerebellum. Decrease exploratory activity, disturb learning, depressive-like behavior.	Onishchenko et al. (2007)
Cat	Adult domestic cats were exposed to MeHg via contaminated fish and capsules containing MeHg for 12−14 weeks	0.25 mg Hg/kg	Total Hg: ppm (μg/g). Control: Blood 0.37; anterior cerebral cortex 0.35; posterior cerebral cortex 0.35; cerebellum 0.36; spinal cord 0.28; sciatic nerve 0.88; liver 3.16; kidney 1.65; gastroncnemius 1.04. Dosed with capsules: Blood 14.2; anterior cerebral cortex 18.5; posterior cerebral cortex 18.9; cerebellum 29.3; spinal cord 8.83; sciatic nerve 8.90; liver 74.5; kidney 37.1; gastroncnemius 22.6. Dosed with fish: Blood 17.3; anterior cerebral cortex 17.4; posterior cerebral cortex 17.4; cerebellum 27.1; spinal cord 10.0; sciatic nerve 10.9; liver 72.7; kidney 37.0; gastroncnemius 24.9.	Clinical signs: ataxia, intention tremor, impaired righting reflex and convulsions between 55 and 96 days. Lesions are found in the cerebellar vermis and the cerebral cortex.	Charbonneau et al. (1976)
Human	Mercury vapor, the period of exposure was less than 8 h	44.3 mg/m^3	Two patients received British Anti-Lewisite (BAL) daily beginning on the second day of their illness, and excreted 1060−2256 μg/24 h and 1160−3075 μg/24 h for five days respectively.	Complained of chills, fever, chest pain and weakness. Three men had diffuse pulmonary infiltrates on chest x-ray. Lack of ambition and loss of interest in sexual activity.	McFarland and Reigel (1978)
Zebra finch (*Taeniopygia guttata*)	Exposure to MeHg via contaminated fish dietary	132 hair samples, range 1−67 years old from fishermen and their families	The THg in the hair 14.1−20.8 on the average. The number of subjects with a THg level over 10 ppm was 75%, 66.7% and 86.4% in Barreiras, Rainha or Sao Luiz do Tapajos, respectively.	Among 50 subjects with a hair THg more than 20 ppm, 17 complained of numbness, 12 vertigo and dizziness, 12 headache, 11 lassitude, 9 pain in limb extremities, 7 pain in back, 7 reduction in vision, 6 trembling, 6 irritability, 5 reduction in hearing, 5 loss of memory, 5 motor disturbance and 4 isomnia.	Harada et al. (2001)
	Mothers, mean age 25.8 years		Maternal (n = 263) blood mercury concentrations for THg < LOD-16.8 μg/L; MeHg ND-15.4 μg/L; iHg ND-2.17 μg/L.	Significant association of higher MeHg with higher Systolic BP and pulse pressure, and of higher iHg with lower pulse pressure.	Wells et al. (2017)
Guinea-pigs	Adult. Exposure to MeHg via contaminated whale meat		Hair mercury: Geometric mean 14.9 μg/g (n = 194) ranges: 1.1−101.9 μg/g.	The dietary survey demonstrated a significant positive correlation between daily whale meat consumption and hair mercury levels. After evaluating 35 clinical endpoints, there are no significant correlations between hair mercury levels and neurological outcomes and suggest sufficient Se intake might be one of causes.	Nakamura et al. (2014)
Mice	Prenatal and postnatal exposures age 66 months via fish dietary	THg in fish: 0.004−0.75 ppm	Maternal hair level of THg: 6.8 ppm (n = 711), ranges 0.5−26.7 ppm. Child hair level of THg at 66 months: 6.5 ppm (n = 708), ranges 0.9−25.8 ppm.	The development of these children is proceeding well without any detectable adverse influence of MeHg.	Davidson et al. (1998)
Rat	Prenatal exposure	Cord blood Hg (μg/L): Mother age: <25: 11.8; 25−35: 13.9; ≥35: 18.0	Children (n = 166). Cord blood Hg (μg/L) 14.7, range 1.53−47.1.	An increase in cord blood Hg concentrations in Apolipoprotein E epsilon 4 allele carriers is consistently associated with an increased score for all Child Behavior Checklist (CBCL) syndromes and general externalizing and aggressive syndromes are significantly higher.	Ng et al. (2015)

Table 2 (*continued*)

Organisms	Exposure	Concentrations	Total Hg in carcass	Adverse effects	References
Mice	Prenatal exposure via fish dietary	Maternal blood (n = 2239)	Median maternal blood concentration of Hg 1.03 μg/L, range 0–13.8. Median Hg dietary exposure 0.15 μg/kg bw/week, range 0–1.51.	Increased dietary mercury exposure is significantly associated with improved speech and language assessment scale (SLAS) when mothers had a seafood intake blow 400 g/week. Significant adverse association between those above the 90th percentile dietary mercury exposure and the SLAS scores.	Vejrup et al. (2018)
Cat	Prenatal exposure via fish dietary		Participants at 22 years (n = 571). The average prenatal MeHg exposure was 6.8 ppm in maternal hair. Recent postnatal MeHg exposure was 5 ppm. Participants at 24 years (n = 577). The average prenatal MeHg exposure was 5.91 ppm in maternal hair. Recent postnatal MeHg exposure was 4.08 ppm.	No adverse associations between prenatal MeHg exposure and any of the measured endpoints of neurodevelopmental outcomes. Prenatal and recent postnatal MeHg exposure is not adversely associated with neurobehavioral development.	van Wijngaarden et al. (2017)
Human	Prenatal exposure	Maternal (total number 70) hair mercury (μg/g): 4.9, range 1.4–15.1	Children 279. Cord blood Hg (μg/L) 21.8, range 1.0–99.3. Current children: Blood (n = 278) Hg (μg/L) 4.7, range 0.1–34.1; Hair (n = 277) Hg (μg/g) 6.9, range 0.3–45.0.	Children with cord mercury ≥7.5 μg/L are four times as likely to have an IQ score <80, the clinical cut-off for borderline intellectual disability. The beneficial effects from DHA intake can obscure adverse effects of mercury exposure.	Jacobson et al. (2015)

distribution of mercury among tissues and cells, and decode the adverse outcome pathways.

4.3.3. Birds

Numerous studies have reported that the increasing concentrations of MeHg have been found in some seabirds during the past century (Thompson et al., 1992; Monteiron and Furness, 1997). Loss of motor skill, coordination, and reduction in motivation are recognized as the most common acute neurological effects related to mercury exposure in birds (Wolfe et al., 1998). Exposure of birds to mercury at sublethal concentrations can cause brain lesions, demyelination of neurons, changes in hematology and hormone levels, and vacuolar changes in hepatocytes and increased liver inflammation (Heinz and Locke, 1976; Spalding et al., 2000) (Nicholson, 1984; Snelgrove-Hobson et al., 1988; Spalding et al., 1994) (Hoffman et al., 2009). Furthermore, the association-positive correlation between brain MeHg and density of muscarinic cholinergic receptor and negative correlations between brain MeHg and density of N-methz-D-aspartate (NMDA) receptor were observed in fish-eating birds (Scheuhammer et al., 2008).

Altering reproductive behavior, reducing embryonic survival, and disrupting early development are found to be associated with mercury intoxication (Hoffman and Moore, 1979; Scheuhammer, 1987; Heinz and Hoffman, 1998; Wiener et al., 2003). In addition, reduced hatchability due to increased in early mortality of embryos, eggshell thinning, reduced clutch size, increased numbers of eggs laid outside the nest, and aberrant behavior of juveniles are found to be correlated with mercury intoxication (Fimreite, 1971; Heinz, 1975, 1979; Scott, 1977). It has been estimated that productivity among loons (*Gavia immer*) was reduced to half the maximum when mercury concentrations in fish prey were 0.21 mg/kg (Burgess and Meyer, 2008). The similar observations were reported on common loon chicks (Wiener et al., 2003), common terns (*Sterna hirundo*) (Fimreite, 1974), California clapper rails (*Rallus longirostris obsoletus*) (Schwarzbach et al., 2006), white ibises (*Eudocimus albus*) (Frederick and Jayasena, 2011), swallows (*Tachycineta bicolor*) (Brasso and Cristol, 2008), snowy egrets (*Egretta thula*) (Hill et al., 2008), and black-legged kittiwakes (*Rissa tridactyla*) (Tartu et al., 2013). Based on a systematic analysis of MeHg effects on bird from 23 species, the estimated thresholds for risk assessment are approximately 0.2 to >1.4 mg/kg in diet, 0.05 mg/kg/d to 0.5 mg/kg/d on a dose basis, 0.6–2.7 mg/kg in eggs, and 2.1 to >6.7 mg/kg ww in parental blood for adverse effects on reproduction (Fuchsman et al., 2017). Taken all the evidence together, exposure of birds to mercury at sublethal cocentrations (<5 μg/g MeHg) generally leads to reducing reproductive output, compromising immune function, and causing avoidance of high-energy behaviors (Whitney and Cristol, 2018). To better understand how mercury is affecting birds, the further studies are required to elucidate a consistent relationship between gene expression profiles and adverse effects.

4.3.4. Mammals

In mammals, mercury exposure leads to ataxia, weakness, tremors, convulsions, sensory impairment, and ultimately death (Heinz, 1996; Wiener et al., 2003). Chronic exposure to dietary MeHg causes obviously neurological signs and mortality in adult mink and otter (Wren et al., 1987; Dansereau et al., 1999). The evidence for motor impairment was gathered from experimental studies of cats (Charbonneau et al., 1976), dogs (Mattsson et al., 1981), mice (Inouye et al., 1985), and monkeys (Rice, 1996). The behaviors of mammals related to visual (Burbacher et al., 1990), cognitive (Montgomery et al., 2008), and emotional (Onishchenko et al., 2007) functions are also affected by MeHg. In addition, the association of density of muscarinic cholinergic receptor and NMDA receptor with brain MeHg were observed in the wild mink (Basu et al., 2005b, 2007), and Greenlandic polar bears (Basu et al., 2009). MeHg exposure during early gestation can result in the development of neural tube defects, cleft palate, eye abnormalities, neurobehavioral modifications and classic adverse birth outcomes, such as body weight changes and mortality (Robinson et al., 2010b). Moreover retarded righting reflex, impaired or retarded swimming

ability, decrease in spontaneous activities, impaired maze and avoidance learning, and deficits in operant learning were observed in mice and rats exposed to MeHg at various times during gestation (Bartolome et al., 1984; Inouye et al., 1985; Fredriksson et al., 1996; Onishchenko et al., 2007). Similarly, significant deficits of visual recognition memory, more nonsocial passive behavior, and less social play were reported for infants born to female macaques (*Macaca fascicularis*) exposed to MeHg (Gunderson et al., 1988; Burbacher et al., 1990). Additionally, adverse effects on reproduction, including reduction in litter size, a lengthening of the oestrus cycle, and a decrease in the body weight of female have been reported in laboratory rodents and guinea pigs (USEPA, 1995; Davis et al., 2001).

Studies of dietary MeHg dosing on a variety of mammalian species have shown that brain mercury concentrations of 5–10 mg/kg ww and higher are commonly associated with severe toxicity and lethality (Shore et al., 2011). Whilst for non marine mammals, 25–30 mg/kg ww Hg in liver is considered as the threshold, and above which animals are likely to experience MeHg intoxication and death (Shore et al., 2011). Notably, various neurochemical changes in brains of free living otter and mink were observed in relation to brain-Hg concentrations <5 mg/kg ww (Basu et al., 2005a, 2005b).

Humans are exposed to two major forms of mercury i.e. mercury vapor and organic mercury (MeHg and ethylmercury (EtHg). Edwards (1865) gave the first record of fatal occupational MeHg poisoning in the 19th century. Nowadays, the nervous system, immune system, and kidneys are known to be the primary targets of acute exposure to Hg depending on the exposure route (EU, 2007). The signs of dyspnoea, chest pain, nausea and vomiting are associated with acute intoxication of mercury vapor, while chronic exposure most commonly manifests as a triad of increased excitability and irritability, tremors, and gingivitis (McFarland and Reigel, 1978; Ozuah, 2000; Magos and Clarkson, 2006). The neurologic signs of MeHg intoxication consist of sensory disturbance, ataxia, constriction of the visual field, speech disturbance, hearing impairment, intension tremor, impaired righting reflex, and convulsion (see (Mc and Araki, 1958; Bakir et al., 1973; Aschner and Aschner, 1990; Farina et al., 2011; Grandjean and Herz, 2011)). Nowadays deficits in motor, psychomotor, visual and/or cognitive functions still were found in fish eating populations living in Mediterranean and within the Brazilian Amazon (Lebel et al., 1998; Dolbec et al., 2000; Harada et al., 2001; Carta et al., 2003; Yokoo et al., 2003).

Studies have shown that mercury levels in cord blood tend to be higher than in maternal blood (Vahter et al., 2000) (Cernichiari et al., 1995). In addition, infants born to MeHg exposed mothers presented severe cerebral palsy like symptoms, even though the mothers had mild or no manifestation of the poisoning (Harada, 1978). Sublethal concentrations of mercury in neonates can cause severe neurodevelopmental deficits (Maccani et al., 2015), including reduced newborn cerebellum size (Cace et al., 2011), adverse behavioral outcomes (Gao et al., 2007), central nervous system damage (Choi, 1989), poor psychomotor development (Llop et al., 2012), cognitive developmental delays (Freire et al., 2010) such as lower performance on tests of language, attention and memory in children (Crump et al., 1998; Steuerwald et al., 2000; Grandjean et al., 2003), and later-life effects including increased diabetes susceptibility (He et al., 2013).

Despite the shortage of direct indications, currently growing evidence supports that exposure of human to mercury is sufficient to alter normal function of cardiovascular (Chan and Egeland, 2004; Grandjean et al., 2004; Sorensen et al., 2004; Stern, 2005; Virtanen et al., 2005), including coronary heart disease, acute myocardial infarction, ischemic heart disease, and heart rate variability (HRV) (see review (Houston, 2011; Roman et al., 2011), immune (Gardner and Nyland, 2016; Nyland et al., 2011) and metabolic systems (Tinkov et al., 2015). Moreover, a significant association between blood mercury concentrations and the incidence of hypertension was noted (Sorensen et al., 1999; Pedersen et al., 2005; Fillion et al., 2006; Thurston et al., 2007; Valera et al., 2009).

Exposure to mercury leads to a significant increase in the levels of serum proinflammatory cytokines and antinucleolar antibodies (Gardner et al., 2010a, 2010b; Gump et al., 2012). Furthermore, results indicate that mercury exposure induces autoimmune processes (Schiraldi and Monestier, 2009) and Kawasaki disease (Mutter and Yeter, 2008). Some evidence support the notion of an association between mercury exposure and obesity, diabetes mellitus, insulin resistance and dyslipidemia (Tinkov et al., 2015; Roy et al., 2017). The USEPA (USEPA, 2006) and the Occupation Health and Safety Agency (OSHA) recommended that levels of mercury should not exceed 5.0 μg/L in whole blood or 1.0 mg/kg in hair (ATSDR, 1999). Taken together, available data support the notion that exposure to inorganic and organic mercury causes. Multiple adverse effects including neurotoxicity, nephrotoxicity, and immunotoxicity in human, and in primate and rodent models depending on the length and doses of exposure. However, despite extensive studies on mechanisms of toxic action and genes/proteins regulation, we are still unable to reveal the ultimate mechanism resulted in adverse effects, because mercury may affect biological process at both the cellular and sub-cellular levels.

4.3.5. Plants and others

Macrophytes are considered as a putative entry point of Hg into the food web, and the calculated bioaccumulation factors from natural and artificial sediments to macrophyte roots range from 10 kg/kg to 0.01 kg/kg for THg (Cosio et al., 2014). Microalgae form the base of aquatic food chains and take up Hg (Faucheur et al., 2014). Exposure of microalgae to Hg at concentrations of 4 μM–20 μM causes a decrease in photosynthesis efficiency in *Spirulina platensis* (Lu et al., 2000), and an increase in reactive oxygen species, which in turn lead to cellular lipid peroxidation and decreased growth in *C. reinhardtii* (Elbaz et al., 2010). Of note, a paradoxical increase in photosynthesis efficiency is observed in *C. reinhardtii* exposed to mercury at concentrations of 10^{-11} and 10^{-10} M $Hg(NO_3)_2$ and 3.6×10^{-11} and 3.7×10^{-10} M MeHg, representing the low environmental Hg concentrations. The most likely explanation is the strong increased expression of genes involved in chlorophyll biosynthesis (Beauvais-Fluck et al., 2016, 2017). Similarly, exposure of macrophytes (*Phragmites australis* and *Juncus maritimus*) to 0.001–10 μM mercury leads to inhibition of photosynthesis and a decrease in the growth rate (Cosio et al., 2014). Moreover, inhibition of elongation of seedlings and stopping germination are observed when *Oryza sativa* was exposed to $HgCl_2$ at a concentration of 0.5 mM and 6 mM respectively. However, these endpoints are not significant affected at concentrations of Hg found in water (10^{-6} μM) (Beauvais-Fluck et al., 2016). Exposure to $HgCl_2$ and phenylmercuric acetate (PMA) at concentrations of 3 μM leads to a marked decrease in growth rate of *E coli* K-12 MG1655 by stopping cells from doubling (LaVoie and Summers, 2018). Moreover, both of $HgCl_2$ and organic compounds can cause thiol blockage and disturb the electrolyte balance in *E coli* under short time exposure conditions (LaVoie et al., 2015). Collectively, evidence supports the notion that the chloroplast appears to be the first target, and mercury exposure leads to perturbation of the photosystem, which in turn affect energy metabolism, gene regulation, lipid metabolism, the development, oxidative stress and transport.

Overall, there are growing data supporting that exposure to inorganic and organic mercury leads to the adverse effects

including cytotoxicity, neurotoxicity, teratogenicity, nephrotoxicity, and immunotoxicity from microbes to humans, in particular a number of studies have demonstrated that disorganised patterning of cortical layers were observed in prenatally exposed human brains, in primate, rodent, fish and fly models. There are multiple mechanisms of toxic action proposed for mercury including impaired calcium homeostasis, inducing oxidative stress, altering glutamate homeostasis, causing DNA damage, decreasing glutathione activity and affecting cell division, however exception of the possible mechanisms contributing to cytotoxicity and neurotoxicity, we still do not fully understand how mercury and its organic compounds cause teratogenicity, nephrotoxicity and immunotoxicity. Moreover, the biochemical basis for differences in organic and inorganic displaying neurotoxic and nephrotoxic effects remains unclear.

5. Molecular evidence linking to mercurial toxicity

Despite the limited information on biochemical mechanisms of mercurial toxicity, observations suggest that in general, $HgCl_2$ and

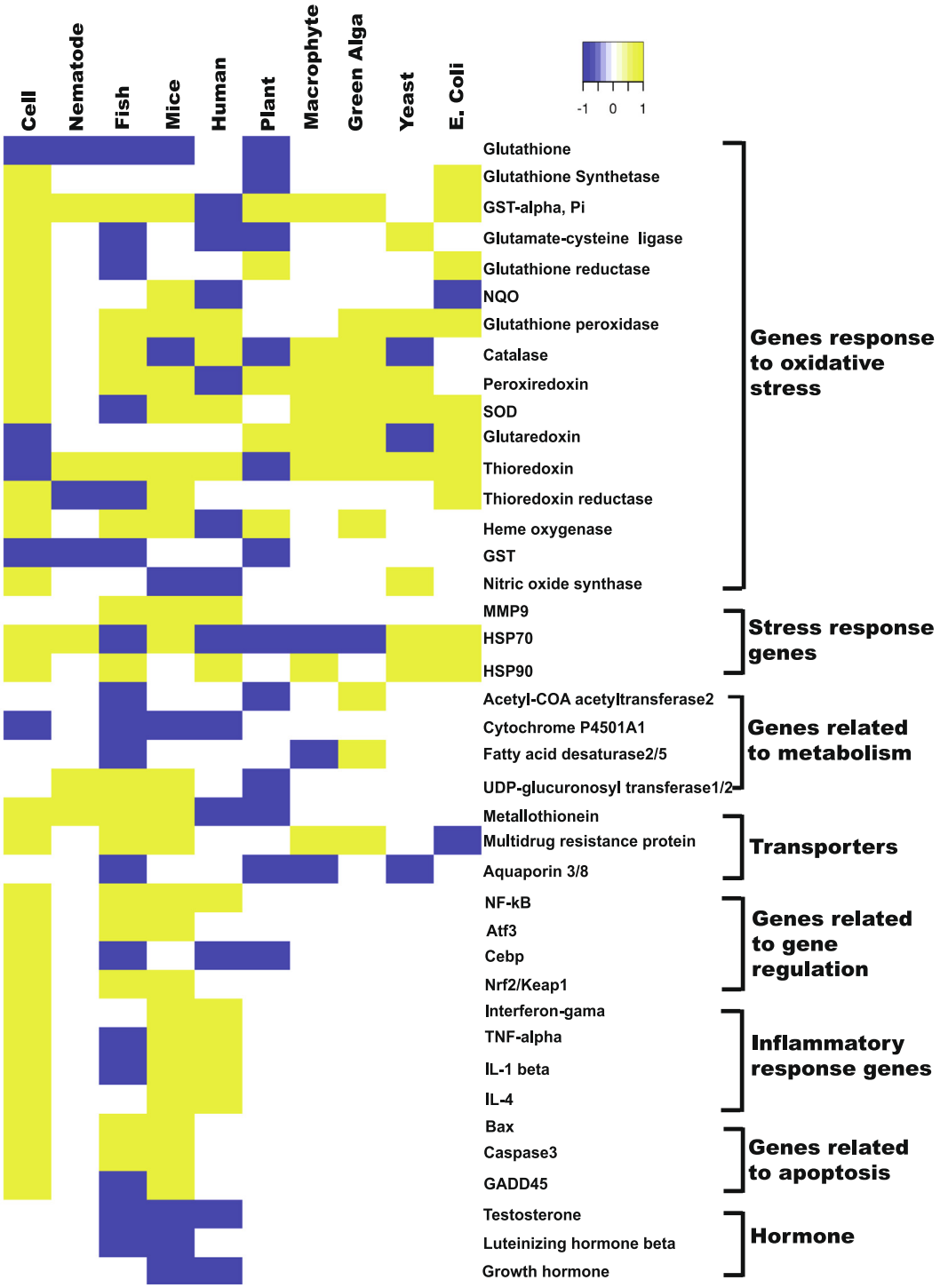


Fig. 1. Summary of genes response to mercurial compounds exposure.

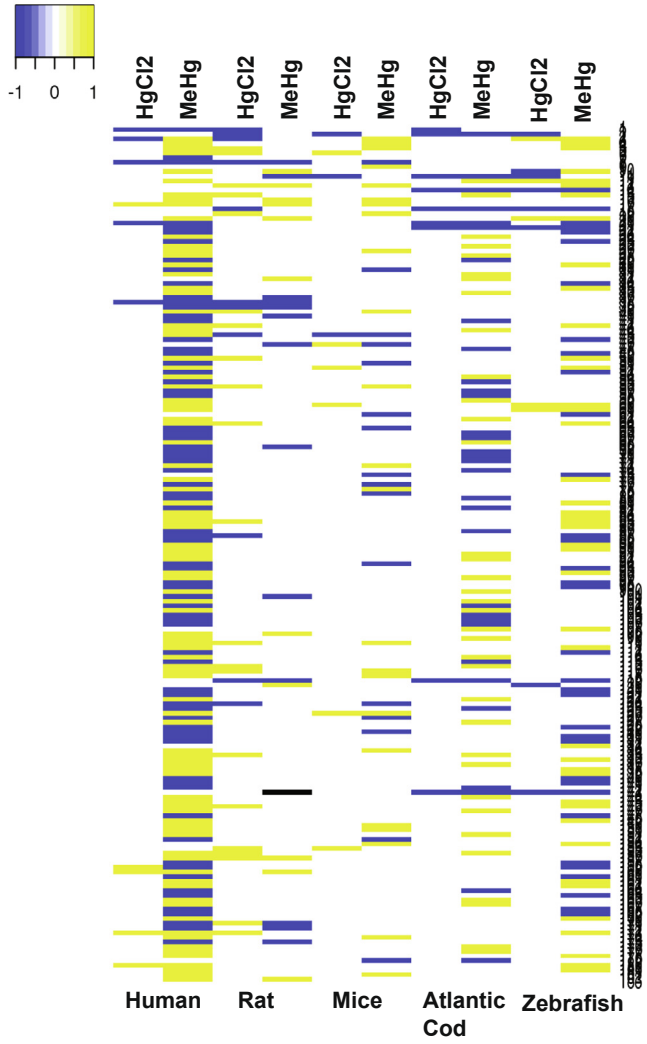


Fig. 2. Summary of genes response to MeHg and $HgCl_2$ exposure.

MeHg may play a role affecting several biological processes, including increased lipid peroxidation, reactive oxygen species (ROS) generation and glutathione (GSH) depletion *in vivo* and *in vitro* (Berntssen et al., 2003; Shanker et al., 2004; Crespo-Lopez et al., 2009; Franco et al., 2009), reduced cell membrane integrity (Yin et al., 2007; Polunas et al., 2011), altered cell signaling (Worth et al., 2001; Chen et al., 2006), mitochondrial impacts (Yee and Choi, 1996; Dreiem et al., 2005), altered DNA repair (Christie et al., 1985; Gadhia et al., 2012; Pieper et al., 2014; Ryu et al., 2014), immunomodulatory impacts (Fortier et al., 2008; Gallagher et al., 2011; Li et al., 2014b), affected the regulation of Ca^{2+}, in particular, glutamate and calcium dyshomeostasis (Aschner et al., 2007), and changed the DNA methylation (Farina et al., 2011), which in turn cause adverse effects. However, it is still unclear which cellular processes and downstream biochemical pathways are primarily targeted by mercury? How the targeted pathways influence the functions of cells, and link finally with the outcomes of health effects? There are several important reviews to discuss multiple mechanisms of toxic action involving in neurotoxicity and cell damage (Clarkson, 2002; Mergler et al., 2007; Guzzi and La Porta, 2008; Crespo-Lopez et al., 2009; Farina et al., 2011; Antunes Dos Santos et al., 2016) (Risher and Tucker, 2017). The main focus of this review is on synthesizing the key findings of the changes in expression of genes/proteins associated with mercurial toxicity. In particular, we pointed out the similarity and difference in enrichment of genes/proteins related to mercury exposures cross cells to human. This may shed light on revealing mechanisms of toxic action of mercury causing adverse effects (See the details in Figs. 1 and 2).

5.1. Mercurial toxicity – in vitro studies

Studies have reported that the assocations between neuronal death and effects on biological processes in case of MeHg intoxication. It is known that biological processes including inhibition of the microtubule assembly (Miura et al., 1984; Castoldi et al., 2000), variations in the intracellular Ca^{2+} concentration (Limke et al., 2004; Yuan and Atchison, 2007), altering the intracellular redox state (Sarafian, 1993; Shanker et al., 2004), neuritic degeneration (Fujimura et al., 2009), contributing the oxidative damage and stimulating glutamate efflux (Aschner et al., 1993, 2007; Toimela and Tahti, 2001; Allen et al., 2002; Yin et al., 2007) are involving in leading to neuronal death. Although gene expression profiles have not identified any specific genes modifying the kinetics or toxicity of mercury so far, but based on *in vitro* studies, genes/proteins' responses to physiologic stress such as heat-shock proteins (HSP) (Goering et al., 1992, 2000), erythroid related factor 2 (Nrf2) mediated stress response genes (Ni et al., 2010), inflammatory response genes (Das et al., 2008), genes associated with cell proliferative responses (Kawata et al., 2007), DNA strand breaks and repairing (Pieper et al., 2014), as well as genes related to apoptosis and gene regulation (Chen et al., 2010) have been demonstrated to be involved in the mercurial toxic effects in cells (see Tables 1 and 3).

5.1.1. Mercury inhibits activities of proteins involving in combating oxidative stress and alters the intracellular redox state

Mercury exposure produces increased levels of ROS in different cells. Kim and Sharma, (2003, 2004) reported that $HgCl_2$ exposure increases the ROS production in murine T and B lymphoma cells and macrophages, which in turn results in cell death. Similar findings were observed in fish macrophage (Sarmento et al., 2004). Ni et al. (2010) reported that exposure of rat microglial to MeHg causes a rapid concentration- and time-dependent increase in ROS generation. Furthermore, Sutton and Tchounwou (2007) showed that exposure to inorganic mercury induces apoptosis in a dose dependent manner in human renal cells. By using hypothalamic neural cell line, Sarafian et al. (1994) have demonstrated that MeHg induced cell death correlates with more closely with ROS generation than with glutathione levels. Similarly, Park et al. (1996) observed that ROS is involved in the MeHg induced cell death in cerebral neurons. Taken together, evidence supports the notion that Hg-mediated cell death correlates closely with ROS generation.

It is well-known that inorganic and organic mercury can bind strongly to thiol residues, which in turn leads to affect the functions of proteins containing thiol groups. Results indicate that mercury can inhibit the activities of many proteins/enzymes involved in combating oxidative stress in cells, including thioredoxin (Trx) (MeHg and $HgCl_2$), glutaredoxin (Grx) (MeHg) (Carvalho et al., 2008; Robitaille et al., 2016), glutathione peroxidase (Gpx) (MeHg) (Farina et al., 2009), glutathione reductase (GR) (MeHg and $HgCl_2$), thioredoxin reductase (TrxR) (MeHg and $HgCl_2$) (Carvalho et al., 2008, 2011), superoxide dismutase (SOD) (MeHg and $HgCl_2$) (Shinyashiki et al., 1996), neuronal nitric oxide synthase (nNOS) (MeHg) (Shinyashiki et al., 1998), and Keap1 (Toyama et al., 2007). In addition, mercury also can alter the ratio of GSH/glutathione disulfide (GSSH) either by binding directly to GSH, depleting GSH or decreasing the levels of Gpx (Messer et al., 2005; Wataha et al.,

Table 3
Summary of Omics data.

Cell/ Organisms	Cell lines/Species	Concentrations/Exposure time	Regulated genes	Gene ontology enrichment	References
Cells	Murine embryonic stem cells	25 nM MeHg 24–96 h	After 24 h 490 genes. After 48 h 6 genes. After 72 h 29 genes. After 96 h 97 genes.	Downregulate transcription- and development- related genes; upregulate neuro-development and cell motion- related genes.	Theunissen et al. (2011)
	Mouse embryonic fibroblast cells	2.5 μM MeHg 24 h	Upregulated 294 genes. Downregulated 450 genes.	Regulation of protein kinase activity; GSH metabolism; immune and inflammatory response; response to heat and stress; cell death; cell proliferation; extracellular matrix structural constituent; oxidoreductase activity.	Yu et al. (2010)
	Human pluripotent stem cell line H9	1.5 μM MeHg. 0.12 μM $HgCl_2$. 1.3 μM Thimerosal. 0.408 μM $HgBr_2$. 0.253 μM Phenylmercuric acetate (PMA). 5.8 μM 4-Chloromercuribenzoic acid (PCMB). From day of differentiation 0 to 6	MeHg: upregulated 321 genes, downregulated 59 genes. $HgCl_2$: upregulated 2 genes, downregulated 0 gene. Thimerosal: upregulated 0 gene, downregulated 0 gene. $HgBr_2$: upregulated 512 genes, downregulated 383 genes. PMA: upregulated 1355 genes, downregulated 1425 genes. PCMB: upregulated 331 genes, downregulated 437 genes.	Not available	Rempel et al. (2015)
	Human hepatoma HepG2 cells	20 μM $HgCl_2$ for 6 h	On the basis of 481 genes specific to DMNQ: induction 33, repression 20. Phenol: induction 2, repression 1. DMN: induction 9, repression 16.	Cell proliferative responses; oxidative stress.	Kawata et al. (2007)
		1, 2, 3 μg/mL Hg for 24 h	Upregulated 138 genes. Downregulated 45 genes.	Cell cycle; apoptosis; cytokine expression; Na^+/K^+ ATPase; stress responses; G-protein signal transduction; transcription factor; DNA repair; metal-regulatory transcription factor.	Ayensu and Tchounwou (2006)
	Human neuroblastoma SK-N-SH cell line	0.25 μM MeHg and 10 μM $HgCl_2$ for 72 h	MeHg proteins: upregulated 42, downregulated 14; aberrant RNA alternative splicing events: 658. $HgCl_2$ proteins: upregulated 58, downregulated 8; aberrant RNA alternative splicing events: 676.	RNA binding, protein binding, splicesome and transcription cofactor activity protein were enriched in MeHg. Protein binding, splicesome, protein processing in endoplasmic reticulum and RNA binding were enriched in $HgCl_2$.	Li et al. (2018)
Bacterium	*Escherichia coli* (*E.coli* K-12 MG1655)	3 μM $HgCl_2$ and phenylmercuric acetate (PMA) for 10, 30 and 60 min	$HgCl_2$: 10 min, upregulated 894 genes, downregulated 927 genes; 30 min, upregulated 637 genes, downregulated 785 genes; 60 min, upregulated 259 genes, downregulated 304 genes. PMA: 10 min, upregulated 1261 genes, downregulated 920 genes; 30 min, upregulated 1156 genes, downregulated 853 genes; 60 min, upregulated 36 genes, downregulated 29 genes.	Increase in maintaining cellular thiol homeostasis; large fold-changes in iron homeostasis and oxidative stress; increase expression of heat shock chaperonins and protease genes; decrease in expression of ribosomal proteins; downregulate flagellar motility and chemotaxis; large increase in expression of genes involved in biofilm formation and adhesion or dispersal.	LaVoie and Summers (2018)
Yeast	*Saccharomyces cerevisiae*	19, 47 μM $HgCl_2$ for 2 h	19 μM: upregulated 136 genes, downregulated 166 genes. 47 μM: upregulated 147 genes, downregulated 86 genes.	Metal ion transport and homeostasis; detoxification of reactive oxygen species; carbohydrate and fatty acid metabolism; G-protein signaling; protein targeting and transport; sulfur metabolism and response to oxidative stress.	Jin et al. (2008)
Unicellular green alga	Chlamydomonas reinhardtii	In the field exposure for 2 h. Site 1 THg: 6.38×10^{-12} M. Site 2 THg: 11.74×10^{-12} M	Site 1: upregulated 1209 genes, downregulated 401 genes. Site 2: upregulated 2938 genes downregulated 2547 genes.	Gene expression regulation; energy metabolism; nutrition; development (amino acids, hormones, lipids, cell structure); oxidative stress; cell motility.	Dranguet et al. (2017)
		10^{-11}-10^{-8} M MeHg. 10^{-11}-10^{-8} M $Hg(NO_3)_2$ for 2 h	3038 genes were regulated by $Hg(NO_3)_2$. 5423 genes regulated by MeHg.	Cell processes; energy metabolism; photosystems; reduction-oxidation reaction homeostasis; cell motility; nutrition; amino acids metabolism.	Beauvais-Fluck et al. (2017)
Macrophytes	Elodea nuttallii	200 ng/L, 200 μg/L, 2 mg/L $HgCl_2$ for 24 h	Upregulated 84 genes. Downregulated 86 genes.	Cell cycle and DNA processing; interaction with the environment; biogenesis of cellular components; stress response; carbohydrate and protein metabolism; cellular	Regier et al. (2013)

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Table 3 (*continued*)

Cell/ Organisms	Cell lines/Species	Concentrations/Exposure time	Regulated genes	Gene ontology enrichment	References
				signaling; homeostasis of cations and metal ions.	
	Shoots of Elodea nuttallii.	In the field exposure for 2 h. Site 1 THg: 6.38×10^{-12} M. Site 2 THg: 11.74×10^{-12} M	Site 1: upregulated 2699 genes downregulated 3518 genes. Site 2: upregulated 4104 genes downregulated 4596 genes.	Gene regulation; energy metabolism; transport; oxidative stress; cell wall biogenesis; lipid metabolism; amino acid metabolism.	Dranguet et al. (2017)
Nematode	*Caenorhabditis elegans*	MeHg: 0.75 μM, 2.0 μM, 7.5 μM. $HgCl_2$: 2.0 μM, 7.5 μM, 20 μM. Exposure to mercury for 24 h	MeHg: upregulated 35 genes, downregulated 9 at 0.75 μM upregulated 247 genes, downregulated 172 genes at 2.0 μM upregulated 1604 genes, downregulated 1187 genes at 7.5 μM. $HgCl_2$: upregulated 8 genes, downregulated 0 gene at 2.0 μM upregulated 68 genes, downregulated 6 genes at 7.5 μM upregulated 316 genes, downregulated 87 genes at 20 μM.	Regulation of transcription; cell adhesion; response to oxidative stress; response to heat; metabolic process; body morphogenesis; transmembrane transport.	McElwee et al. (2013)
	Caenorhabditis elegans	10 μM MeHg	Modifications of histone H3K4 trimethylation (H3K4me3). 1476 genes with enhanced, and 508 genes with reduced signals.	Larval development; positive regulation of growth rate; Genitalia development; protein transport; translation; organ morphogenesis; RNA metabolic process, etc.	Rudgalvyte et al. (2017)
			Upregulated 541 genes. Downregulated 261 genes.	Larval development; proteolysis; multicellular organism growth; steroid metabolic process, etc.	Rudgalvyte et al. (2013)
Copepods	Tigriopus japonicus	Exposure to 10 μg/L (36.83 nM) $HgCl_2$ for 5 h	Upregulated 53 genes. Downregulated 48 genes.	Mitogen activated protein kinase signaling pathway; antigen processing and presentation; estrogen signaling pathways; protein processing in the endoplasmic reticulum; progesterone mediated oocyte maturation; amino sugar and nucleotide sugar metabolism.	Wang et al. (2017)
	Pseudodiaptomus annandalei		Upregulated 15 genes. Downregulated 3 genes.		
Marine bivalves	Mussels (M. galloprovinicalis) shell length 40 −60 cm. Digestive glands	Exposure to 150 μg/L (750 nM) $HgCl_2$ for 6 days	Total of 24 mussel genes. Upregulated 3 genes. Downregulated 7 genes.	Heavy metal detoxification; stress response; innate defense capability.	Dondero et al. (2006)
Fish	Atlantic salmon kidney	Exposure of fish to 3.8 ± 0.2 mg/kg MeHg via diet for 54 days	Proteomic analysis: Upregulated 3 proteins. Downregulated 7 proteins	Metabolism; inflammation; oxidative stress; protein-folding; cell-structural components.	Nostbakken et al. (2012)
	Atlantic cod brain.	Exposure of fish to 0.5, 2 mg/kg body weight MeHg via intraperitoneal injection for 14 days	Proteomic analysis: Upregulated 33 proteins. Downregulated 7 proteins.	Mitochondrial dysfunction; oxidative stress; altered calcium homeostasis; tubulin/disruption of microtubules; calpain-cleavage; glycolysis; ubiquitin-proteasome system; synthesis of neurotransmitters; axon guidance and regeneration.	Berg et al. (2010)
	Rainbow trout Juvenile (45 days after hatching)	Fish was exposed to 0, 0.5, 5 and 50 ppm MeHg via diets for 6 weeks	162 genes dysregulated.	Iron ion homeostasis and transport; iron binding; glutathione transferase activity.	Liu et al. (2013)
	Zebrafish young adult (30 days after hatching):		1975 genes dysregulated in femal. 320 genes dysregulated in male.	RNA splicing; mRNA processing; regulation of muscle contraction; troponin I binding and calcium dependent protein binding; protein metabolism, folding and axoneme assembly.	
	Adult female zebrafish brain	Exposure of fish to 0.5 μg/g MeHg via intraperitoneal injection for 96 h	Upregulated 79 genes. Downregulated 76 genes.	Protein folding; cell redox homeostasis; steroid biosynthetic process.	Richter et al. (2011)
	Adult male zebrafish skeletal muslces	Fish was exposed to MeHg via diets contaminated with 13.5 μg/g MeHg for 25 days	Upregulated 60 Downregulated 15 genes.	Protein synthesis; oxidative stress and endoplasmic reticulum stress; cell cycle regulation; calcium homestasis; lipid metabolism; muscle contraction.	Cambier et al. (2010)
	Adult zebrafish	Exposure of fish to 200 μg/L $HgCl_2$ for 8, 24, 48, and 96 h	8 h: more than 120 genes were upregulated, and near 200 were downregulated. 24 h: more than 500 genes were upregulated and downregulated. 48 h: more than 500 genes were upregulated and	Protein degradation; stress; acute phase responses; mitochondrial dysfunction; cell damage.	Ung et al. (2010)

Table 3 (*continued*)

Cell/ Organisms	Cell lines/Species	Concentrations/Exposure time	Regulated genes	Gene ontology enrichment	References
			downregulated. 96 h: more than 700 genes were upregulated, and more than 800 genes were downregulated.		
	Zebrafish embryos, 24, 48, 120 hpfs	Exposure of embryos to MeHg 50 μg/L for 4–24 hpf; 60 μg/L for 24–48 hpf; 60, 30, 6 μg/L for 96–120 hpfs	24 hpf: 8 genes were upregulated and 6 genes were downregulated. 48 hpf: 77 genes were upregulated and 46 genes were downregulated. 120 hpf (60 μg/L): 81 genes were upregulated and 64 genes were downregulated. 120 hpf (30 μg/L): 11 genes were upregulated and 3 genes were downregulated. 120 hpf (6 μg/L): 5 genes were upregulated.	Protein tyrosine kinase signaling pathways; insulin receptor signaling pathways; amino acid metabolism; acute inflammatory response.	Yang et al. (2007)
	Zebrafish embryos, 72 hpfs	Exposure of embryos to 60 μg/L MeHg for 48–72 hpf	Upregulated 464 genes. Downregulated 379 genes.	Apoptosis; cell redox homeostasis; oxidative stress; transcription factor activity; RNA elongation; DNA double strand break repair.	Ho et al. (2013)
		Exposure of embryos to 5, 25 μg/L MeHg for 72–144 hpf	18 proteins (9 up- and 9 down-regulated) were deregulated at 5 μg/L; 58 proteins (42 up- and 16 down-regulated) were deregulated at 25 μg/L.	Deregulated proteins involving in metabolic process (32%), transport (14%), response to stimulus (14%), developmental processes (4%) and apoptosis (9%).	Cuello et al. (2012)
	Adult Medaka brains	Exposure of fish to 1, 10 μg/L $HgCl_2$ for 60 days	Proteomic analysis: Upregulated 8 proteins. Downregulated 7 proteins.	Cytoskeleton assembly dysfunction; oxidative stress; metabolic disorders.	Wang et al. (2015)
	Adult Medaka livers		Proteomic analysis: 33 proteins remarkably changed.	Cytoskeleton assembly; oxidative stress; energy production.	Wang et al. (2013)
	Atlantic cod (1.5-year-old) livers	Exposure of fish to 0.5, 2 mg/kg body weight MeHg via intraperitoneal injection for 14 days	Upregulated 384 genes. Downregulated 266 genes.	Energy metabolism pathways; amino acid metabolism; glycolysis/ gluconeogenesis; acyl-CoA and fatty acid metabolism; oxidative stress; immune response; cytoskeleton remodeling.	Yadetie et al. (2013)
	Fathead minnows. Adult male and 90-days post-hatch larvae. Livers and gonads	Acute exposure: Exposure of fish to 2 μg/g body mass via intraperitoneal injection for 4 days. Chronic exposure: Fish were exposed to 3.93 μg/g dry mass MeHg via contaminated diets for 600 days	Acute exposure: Liver: upregulated 245 genes, downregulated 405 genes. Gonad: upregulated 75 genes, downregulated 137 genes. Chronic exposure: Liver: upregulated 98 genes, downregulated 169 genes. Gonad: upregulated 27 genes, downregulated 127 genes.	In liver: Biosynthesis; tRNA processing; ribosome biogenesis; protein folding and protein transport. Protein targeting; induction of apoptosis; regulation of transcription; protein processing and immune response to viruses. In gonad: metabolism; antigen presentation; steroid biosynthesis; development; immune system; cell adhesion.	(R. Klaper et al., 2008)
	Juvenile golden grey mullet. Livers	Wild fish were collected in Hg contaminated area. Surface sediments tHg: reference: 25 ± 5 ng/g, exposure: 440 ± 250 ng/g. Livers, more than 2 times of tHg than controls	Increased activities: CAT, GST, GSH. Decreased activities: GPx. Increased concentrations: phosphocholine; glucose; glutathione; glutamate. Decreased concentrations: taurine; tyrosine; phenylalanine; hypoxanthine.	Membrane stabilization/ degradation/repair processes; osmoregulation; energy metabolism; gene expression; antioxidant protection.	Brandao et al. (2015)
	Tusk (Brosme brosme). Female livers	Wild fish were collected in Hg contaminated area. High: 10.3 mg Hg/kg or 2.7 mg MeHg/kg. Low: 2.2 mg Hg/kg or 0.79 mg MeHg/kg	Upregulated 1164 genes. Downregulated 131 genes.	Lipid metablolism and beta-oxidation; oxidative stress.	Olsvik et al. (2013)
Mouse/Rat	Female rats (10-week-old)	Exposure of animals to 4 amalgam fillings (50 mg/ml, 0.05 ml per 100 g) for 6 months	One gene was upregulated and one gene was downregulated in cerebrum. One gene was upregulated in cerebellum. Two genes were upregulated and one gene was downregulated in liver. Two genes were upregulated and 6 genes were downregulated in kidney.	Not availalbe	Takahashi et al. (2012)
	FVBN_NJ mouse pups. Brain	Exposure of animals to EtHg (thimerosal) via subcutaneous injection on postnatal day 1 (P1): 304, 152, 76 μg/kg. P2: 238, 119, 60 μg/kg. P5: 196, 98, 49 μg/kg. P9: 176, 88, 44 μg/kg for 8–12 weeks	The total of 647 genes were upregulated and 1777 genes were downregulated.	Neuronal development; neuronal synaptic function; dysregulation of endocrine system.	Li et al. (2014a)
	Balb/c mice pup brain.	Mices were exposed to MeHg via dietary for 11 weeks (6 weeks prior to and during mating, 3 weeks during gestation, 2 weeks following birth. MeHgCl: Low: 1.5 mg/kg. High: 4.5 mg/kg.	A total of 131 genes were significantly regulated. 50 and 35 probes were regulated only by MeHgCys and MeHgCl exposure respectively.	Zinc/metal ion binding; transcription regulation; cell division; methylation.	Glover et al. (2009)

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Table 3 (*continued*)

Cell/ Organisms	Cell lines/Species	Concentrations/Exposure time	Regulated genes	Gene ontology enrichment	References
		MeHgCys: Low: 1.5 mg/kg. High: 4.5 mg/kg. Pup brains 0.25 ± 0.01 mg/kg ww; pup liver 1.0 ± 0.5 mg/kg ww; Dam liver 21 ± 3 mg/kg			
	Pregnant mice (C57BL/6J and SWV)	Mices were exposed to 4 mg/kg/BW MeHg via intraperitoneal injection on gestational day 8 for 12, 24 h	C57BL/6J: a total of 234 genes was upregulated and 165 genes were downregulated. SWV: The expression of 81 genes was upregulated and 250 genes were downregulated.	Stress responses; cell proliferation; apoptosis; developmental process; metabolism.	Robinson et al. (2010a)
	Pregnant mice (C57BL/6J)	Mices were exposed to MeHg via intraperitoneal injection on gestational day 8 with either 0, 1, 4, 6 mg/kg/BW MeHg for 0, 8, 12 h	The expression of 883 genes was significantly altered.	Development cell adhesion; cell cycle; cell differentiation.	Robinson et al. (2010b)
	Cultured whole rat embryo (one to five somite)	Cultured embryos were exposed to MeHg at 6 mM for 4 h	The expression of 173 genes was significantly altered.	Genes related to development (organ, nervous system, heart, and somitogenesis); cell development; cell adhesion; RNA transport; cell cycle arrest.	Robinson et al. (2010c)
	Long-Evans rats (200 −250 g)	Rats were exposed to 4 mg/m^3 Hg^0 vapor via nose-only for 2 h per day and for 10 consecutive days	Among 588 genes examined, 36 genes were upregulated and 25 genes were downregulated.	Genes related to inflammation, oxidative stress, and antioxidants; transporters.	Liu et al. (2003)
Human	Blood of 2 to 5-year-old boys with Autism (AU); typically development control boys (TD)	Total blood Hg. 0.46 ± 0.73 μg/L for AU; 0.60 ± 0.82 μg/L for TD	A total of 1293 probe sets for TD and 1276 probe sets for AU were significantly correlated with Hg levels.	Genes related to cell death and cell morphology; amino acid metabolism; antigen presentation.	Stamova et al. (2011)
	Adolescents (average age of 14.8 years). Hair	Total Hg: 0.19 (0.07−0.47) μg/g. MeHg: 0.12 (0.05−0.32) μg/g	JAK2, ARID4A and Hist1HA4L in boys; HLAdrb5, PIAS2, MANN1B1, GIT, and ABCA1 for girls.		Croes et al. (2014)
	Blood of 40 healthy male	Hg 1.78 ± 0.1 μg/L	The expression of 1620 genes was altered. The Hg exposed group specifically altered 704 genes ie upregulated 147, and downregulated 558.	Protein synthesis; RNA post-transcriptional modification; gene expression.	Korashy et al. (2017)
Plant	Medicago truncatula. Seedlings	Exposure of seedling to 10 μM $HgCl_2$ for 6, 12, 24 and 48 h	A total of 1176 genes was upregulated and 1406 genes were downregulated.	Stress response; metabolism of secondary products; genes related to metal transporters, sulfate metabolism and cell wall solidification.	Zhou et al. (2013)
	Lycopersicon esculentum. Roots	Exposure of roots to 2.3 mg/kg $HgCl_2$ for 7 days	A total of 322 genes was upregulated and 283 genes were downregulated.	Cellular metabolism process; cellular response to stimulus.	Hou et al. (2015)

2008; Robitaille et al., 2016) (Farina et al., 2011). Mercury exposure results in a dissociation of Nrf2 from the Nrf2/Keap1 complex, which in turn, leads ultimately to an altered the intracellular redox state, contributing to the increased occurrence of ROS generation and oxidative stress (Sarafian and Verity, 1991; Robitaille et al., 2016).

Of note, several lines of evidence support that changes in GSH levels or GSH/GSSG ratio may not directly link to oxidative stress induced by MeHg (Wang et al., 2009) (Farina et al., 2011). Evidence suggests that mercurial compounds may impair the pentose phosphate pathway, which in turn leads to affect the thioredoxin system and the production of NADPH (Rodrigues et al., 2015). Taken together, several lines of evidence support the notion that mercury disturbs the activities of proteins/enzymes or non-enzymatic free radical scavengers involved in antioxidant defense system, which in turn, reduce antioxidant capabilities, leading to an intracellular environment more prone to be oxidative. This notion is further confirmed by the finding that the inhibition of cytokine signaling through oxidative stress, and low basal expression of SOD, Gpx and TrxR (Fujimura and Usuki, 2014) are the important reasons to make neurons more susceptible to death under mercury exposure.

It is of interest to note that the mechanism causing ROS associated with cell death observed at high concentrations of mercury is distinct from the inappropriate enhancement of signaling mediating some of the deleterious effects of exposure to low concentrations of MeHg (Jebbett et al., 2013). Furthermore, results suggest that p38 mitogen activated protein kinase (MAPK) mediated caspase activation and tumor necrosis factor α (TNF-α) regulate mercury induced apoptosis and necrosis in cells (Kim and Sharma, 2004). MeHg-induced apoptosis is caspase-independent (Dare et al., 2001; Fonfria et al., 2002; Vendrell et al., 2007)) or caspase-dependent (Nishioku et al., 2000; Shenker et al., 2000; Belletti et al., 2002; Usuki et al., 2008).

5.1.2. Changing signaling transduction and gene expression

Evidence has demonstrated a complex interaction of mercury with the pathways of apoptosis (Shenker et al., 1999; Eisele et al., 2006; Chen et al., 2010; Morcillo et al., 2016b), oxidative stress response (Kim and Sharma, 2004; Kawata et al., 2007; Chen et al., 2010), detoxification (Ni et al., 2010), activation of proteins including growth factor receptors, G-proteins such as ras (Mattingly et al., 2001), tyrosine kinase such as *c*-src, MAPK (Kim and Sharma, 2004), transcription factors including nuclear factor kappa B (NF-kB) (Woods et al., 2002), NFAT, AP-1 (Korashy and El-

Kadi, 2008), P53 and HIF-1 (Aschner et al., 2007), and JAK/STAT (Jebbett et al., 2013). The associations between alterations in a battery of antioxidant genes/proteins including glutamate-cysteine ligase (GCL), catalase (CAT), NAD(P)H dehydrogenase quinone (NQO), heme oxygenase (HO), phase II detoxification enzymes such as glutathione S-transferases (GSTs) and phase III transporters such as multidrug resistance associated proteins 1 (MRP1) and 2 expression and mercurial toxicity were observed in mouse embryonic fibroblast (Carvalho et al., 2011), hepatocytes (Toyama et al., 2007), rat primary astrocytes and microglia (Wang et al., 2009; Ni et al., 2010, 2011), murine hepatoma cells (Korashy and El-Kadi, 2006), and human pluripotent stem cells (Shinde et al., 2017). These data support the notion that Nrf2/Keap1 pathways may play an important role in response to oxidative stress inudced by mercury. This notion was further confirmed by the finding of that isothiocyanates (ITCs), potent Nrf2 activators, can effectively suppress mercury accumulation after exposure to MeHg both *in vitro* and *in vivo*, leading to decreased cytotoxicity and intoxication (Korashy and El-Kadi, 2006; Toyama et al., 2011).

Observations indicate that trancription factors including Atf2, Atf3, fos, fos-like antigen 1 sl1 (Fosl1), as well as Mafg and Mafk were significantly upregulated by mercury (Yu et al., 2010). Moreover, exposure of cells to mercury can alter the expression of the ubiquitin-proteasome system genes, cell cycle regulation genes, and growth arrest and DNA damage-inducible gene (Ou et al., 1997; Yu et al., 2010). The overexpression of the ubiquitin-protein ligase CDC34 (E3) exhibits significant resistance to MeHg toxicity both in yeast and in human cells (Furuchi et al., 2002; Hwang et al., 2002). Mercury impairs NF-κB activation and transcriptional activity in normal rat kidney epithelial cells (Dieguez-Acuna and Woods, 2000; Dieguez-Acuna et al., 2001; Woods et al., 2002). It has been shown that mercury can completely inhibit neuronal Jak-STAT activation (Monroe and Halvorsen, 2006). Exposure to high dosing of mercury promotes the activation of the ASK-1 pathway leading to caspase activation and apoptosis (Branco et al., 2017).

5.1.3. Disturbance of Ca^{2+} homeostasis

The disturbance of Ca^{2+} homeostasis has been linked to mercurial toxicity (Levesque and Atchison, 1991; Sakamoto et al., 1996; Gasso et al., 2001; Kim and Sharma, 2003). Findings support that mercurial compounds can inhibit several types of voltage gated Ca^{2+} channel (VGCC) (Hajela et al., 2003; Tarabova et al., 2006), and MeHg exposure leads to an increase in Ca^{2+} influx (Choi, 1992). Results support a notion that MeHg induced increases in intracellular Ca^{2+} may contribute to cell mortality (Marty and Atchison, 1998; Limke et al., 2004). This notion was further confirmed by the observation that calcium channel blockers can block MeHg induced toxicity and deficits *in vitro* and *in vivo* in a dose dependent manner (Marty and Atchison, 1998; Limke et al., 2003; Shen et al., 2016a, 2016b). Mercurial compounds were found to potently activate TRPC5, TRPC4 channels via binding to the two extracellular cysteine residues near the channel pore. The observed IQ loss in response to mercury exposure might be caused by the elevated Ca^{2+} through TRPC5 activation and consequently affecting growth cone formation, axonal extension, and the connections between synapses (Xu et al., 2012).

Taken all the evidence together, polygenic effects might be involved in mercurial toxicity in addition to triggering oxidative stress. Indeed, toxicogenomics studies have demonstrated mercury induced changes in expression of genes across a wide spectrum of gene ontologies not only covering oxidative stress responses. Current findings suggest that changes in gene expression involved in ubiquitin-proteasome system, antioxidant defense system, phase I, II and III enzymes, cell cycle regulation pathways, cell proliferative responses and apoptosis may be the indirect consequence of the cell stress exerted by Hg ions in the cells. However, observations support that misregulation of genes encoding ATP-binding cassette sub-family G, MAPK activating protein, ras homology gene familiy, G-protein signal transduction, and Na^{+}/K^{+} ATPase in mouse embryonic fibroblast cells, human stem cells and human hepatoma HepG2 cell line (Ayensu and Tchounwou, 2006; Kawata et al., 2007; Yu et al., 2010; Rempel et al., 2015) (for detail to see Table 2) could also be the consequence of a direct interference of mercurial compounds with the encoded proteins and processes that they are involved in.

5.2. Mercurial toxicity —in vivo studies

Nowadays, there is no doubt that MeHg is neurotoxic and teratogenic, however there is less agreement on the potential effects of long-term exposure to environmentally relevant concentrations of MeHg (Myers et al., 2003; Stern et al., 2004; Karagas et al., 2012), because of the inconsistent even contradictory observation in human studies.

5.2.1. Genes/proteins response to oxidative stress, transport and xenobiotic metabolism pathway

Toxicogenomic and proteomic studies of tissues derived from whole organisms exposed to organic and inorganic mercurial compounds have demonstrated that the antioxidant enzymes including glutathione synthetase, CAT, HO, Grx, GPx, GR, GCL, GSTs, NQO, SOD, Trx, TrxR, NOS, peroxiredoxin, transporters including metallothioneins (MTs) and MRP, and genes/proteins involved in metabolism including cytochrome P450, etc were significantly impacted and observed in unicellular alga *Chlamydomonas reinhardtii* (Beauvais-Fluck et al., 2017), yeast (Jin et al., 2008), macrophytes (Regier et al., 2013; Dranguet et al., 2017), tomato (*Lycopersicon esculentum*) seedling roots (Hou et al., 2015), *Caenorhabdities elegans* (McElwee and Freedman, 2011; Rudgalvyte et al., 2013), marine bivalves (Dondero et al., 2006), Atlantic salmon (Nostbakken et al., 2012), Atlantic cod (Berg et al., 2010; Yadetie et al., 2013), rainbow trout (Liu et al., 2013), zebrafish (Yang et al., 2007; Ung et al., 2010; Richter et al., 2011; Cambier et al., 2012; Ho et al., 2013), medaka (Wang et al., 2013, 2015), fathead minnows (R. Klaper et al., 2008), golden grey mullet (Brandao et al., 2015), tusk (Olsvik et al., 2013), pregnant mice (Robinson et al., 2010a) (Godefroy et al., 2012), and human (Pinheiro et al., 2008) (Grotto et al., 2010). Taken all the evidence together, mercury exposure can alter the expression of genes/proteins involved in oxidants and antioxidants defences, and xenobiotic metabolism pathway.

MTs have been shown to play an important role in protecting against the cytotoxic effects of mercury (Zalups and Koropatnick, 2000) (Zalups and Koropatnick, 2000). Of note, in beluga liver, no significant correlation was found between MT1 gene expression and THg levels (Scheuhammer et al., 2015). Moreover, evidence supports that divalent metal transporter 1 (DMT1), organic anion transporters (OATs) and MRP transporters are functional on transport and elimination of mercury (Bridges and Zalups, 2017) (Ilback et al., 2008). In comparison to control mice, a strain carrying a null mutation in MRP2 retains higher levels of inorganic mercury from an oral dose and accumulated mercury to higher levels in placenta and fetus (Bridges et al., 2012, 2013). The similar results were observed in MRP mutant and targeted knockdown of MRP Drosophila (Prince et al., 2014). While, human polymorphisms in MRP2 are reported to correlate with differences in urinary excretion of inorganic mercury in an environmentally exposed population (Engstrom et al., 2013). In addition, evidence supports that the peroxisome proliferator-activated receptor gamma coactivator-related gene (Pprc1), a coactivator for Nrf1 and Nrf2, is a

potential key regulator of renal Hg accumulation and elimination (Alkaissi et al., 2016).

5.2.2. Genes/proteins related to neurotoxicity

The association of astrocytes dysfunction with an increased expression of astrocytes-derived GFAP, microglia-derived Iba1, and aquaporin 4 in marmoset exposed to MeHg, supports the notion that MeHg may stimulate astrocytes expressing aquaporin 4, which in turn causes astrocyte dysfunction (Yamamoto et al., 2012). Concentrations of receptors in the brain for neurotransmitters such as acetylcholine (muscarinic receptor) and glutamate (NMDA receptor), can be significantly altered by low level dietary exposure to MeHg in adult birds, polar bears (Basu et al., 2009), wild mink (Basu et al., 2007), loons, and eagles (Scheuhammer et al., 2008). Of note, no significant correlation between mercury concentration and density of either NMDA or mACh neuroreceptors in brain tissue from thick-billed murre and Arctic tern embryos could be measured (Scheuhammer et al., 2015). GABA (gamma-aminobutyric acid) receptor and dopamine D2-receptor levels, monoamine oxidase (MAO) and ChE (cholinesterase) activities were decreased with increasing mercury levels in wild river otters and wild mink (Basu et al., 2005a, 2005b, 2007). In fish, mercury induced biochemical disorders of the nervous system are limited to inhibit key enzymes for neurological function such as Na+/K + -ATPase (Verma et al., 1983), MAO (Ram and Sathyanesan, 1985) and acethylcholine esterase (AChE) (Gill et al., 1990). The activities of cholinesterase (ChE, AChE, and butyrylcholin esterase BCE) decreased in quail (*Coturnix coturnix japonica*) receiving a diet containing MeHg (Dieter and Ludke, 1975). The expression of SKN-1 inhibits the MeHg induced degeneration of dopaminergic neurons (DA) in *C. elegans*, which may involve in regulating GSTs expression (Vanduyn et al., 2010).

Transcriptomic analyses have demonstrated that axonal guidance signaling pathways such as synaptic long term potentiation, CREB singaling, and dopamine-DARPP32 signaling are involved in thimerosal induced neurotoxicity in mouse brain (Li et al., 2014a) (Glover et al., 2009). In addition, expression of genes encoding peroxiredoxin, parvalbumin, interleukin 33, tubulin α8, protein kinase, ataxin 3, sirtuin 5, myosin and LIM domains was altered in the brain of offspring mice exposed to Hg^0 (Yoshida et al., 2014). An increase of genes encoding for plasma membrane Ca^{2+} ATPase (PMCA), Na^+/Ca^+ exchanger (NCX) was observed in zebrafish brain associated with MeHg exposure (Cambier et al., 2012). Moreover, in the responses to acute MeHg exposure, genes involved in protein folding such as Hsp90, Hsp8, Dnaj, redox homeostasis such as selenoprotein, GST, Grx, transcripition factor, neurological functions as well as lipid metabolism were significantly enriched among altered genes in zebrafish brain (Richter et al., 2011; Ho et al., 2013). Proteomic analyses indicate that proteins associated with mitochondrial dysfunction (aconitase), oxidative stress (GST, peroxiredoxin), calcium homeostasis (calmodulin), tubulin/disruption of microtubules (actin, tubulin, keratin), ubiquitin-proteasome system (proteasome activator), synthesis of neurotransmitters (G protien), and axon/dendrite development (protein phosphatase, septin) were altered in brains from Atlantic cod, medaka, beluga exposed to mercury (Keyvanshokooh et al., 2009; Berg et al., 2010; Wang et al., 2015). Taken together, mercury may affect the genes involved in normal neuronal activity, learning, and emergence of neurobehavioral effects, which in turn influences behavior.

5.2.3. Genes/proteins related to development

Extensive studies have demonstrated that *in utero* and childhood exposure to mercury causes later neurologic and psychological impairments (Choi, 1989; NRC, 2000; Gao et al., 2007; Freire et al., 2010; Cace et al., 2011). The finding of MeHg disturbing the expression of zinc finger transcription factors in mice pups could provide an explanation for the teratogenic potential of MeHg (Glover et al., 2009). Observations suggest that prenatal exposure to mercury may alter the activity of Notch signaling, a fundamental cell-cell signaling system that directs cell fate decisions during neurogenesis, which in turn leads to impair neuronal proliferation, migration and pathfinding (Bland and Rand, 2006; Engel et al., 2012). Furthermore, evidence suggests that prenatal exposure to MeHg can suppress the tropomypsin receptor kinase A (TrkA) and decrease eukaryotic elongation factor 1A1 (eEF1A1) expression, leading to reduce neurite outgrowth and synaptic proteins expression in the developing cerebellum (Fujimura et al., 2016). Observation reports that ectopic activation of Mmp9 and Mmp13 in the fin fold plays an important role to impair development of the tail fin primordium in zebrafish embryo exposed to MeHg (Yang et al., 2010), In addition, exposure to MeHg triggers the ectopic expression of Trx in hair cells of the lateral line organ, leading to impact on hair cells development in zebrafish embryo (Yang et al., 2019). It is known that gene response to MeHg toxicity is highly dependent on the developmental stages (Yang et al., 2007). The expression levels of 13, 124 and 155 genes were significantly affected by exposure of embryos to MeHg from 4 to 24 hpf, from 24 to 48 hpf and from 96 to 120 hpf, respectively (Yang et al., unpublished data and (Yang et al., 2007)). Further analysis indicates that genes encoding *slc43a2b*, *slc38a5b*, *rag1*, *sestrin3*, and *zinc finger protein 395a* are regulated only in 4–24 hpf treatment groups. Genes involved in oxidative stress (*trx*, *noxo1a*, *prdx*, *gpx*, *gst*), transcription activity (*aft3*, *homeza*), enzymes (*mmp13*, *serum/glucocorticoid regulated kinase1*), and proteins including *complement component 6* and *3a*, *irf1b*, *angiotensinogen*, *nephronophthisis1*, *cxcl18a*, *sequestosome1*, and *socs3b* were found to respond to MeHg expsoure in both 24 to 48 hpf and 96 to120 hpf groups (Yang et al., 2007). The stage dependent gene response was further confirmed by the finding that correlation between mercury concentration and density of NMDA or/and mACh neuroreceptors in brain differs in adults and embryos of animals (Scheuhammer et al., 2015).

5.2.4. Genes/proteins related to inflammatory

Although the mechanism by which mercurial compounds intoxicate the immune system is not well understood, and clinical sequelae to exposure are often inconsistent (Shenker et al., 2000; Crowe et al., 2017), a body of evidence supports the notion that long term exposure to low concentrations of mercury results in immune dysfunction (Clarkson, 1997; Pollard and Hultman, 1997). Exposure to both organic and inorganic mercury results in immune activation leading to adverse outcomes related to allergy and autoimmune disease (Stejskal et al., 1996; Thuvander et al., 1996; Dantas and Queiroz, 1997), including development of a lupus-like autoimmune syndrome (Abedi-Valugerdi and Moller, 2000; Pollard et al., 2005), accelerating or exacerbating autoimmunity (Pollard et al., 2001; Via et al., 2003; Hultman et al., 2006), inhibiting immune repsonse to infections (Ilback et al., 1996; Silbergeld et al., 2000, 2005), and persistently altering the immune response of offspring in animals (Silva et al., 2005a, 2005b). Moreover, Zhang (Zhang et al., 2011, 2013) has demonstrated that developmental exposure of A. SW mice to $HgCl_2$ induces inflammation in the cerebellum, increases exploratory behaviors in female A. SW mice, and significantly decreases the sociability of SFvF1. Exposure of genetically susceptible strains of mice to mercury induces a lupus-like autoimmune syndrome (Silva et al., 2004; Havarinasab et al., 2005). Higher blood mercury was correlated with increased risk of self-reported atopic dermatitis, and associated with higher incidence of infection and an increase in autoimmune nephritis symptoms in adults (Holmes et al., 2009; Park and Kim, 2011). Exposure to mercury induces cell death, in turn modifies self-

antigens, which are processed and presented to $CD4^+$ T helper cells by monocyte, marcrophages, and dendritic cells, leading to increase in autoantibody production (Silva et al., 2004; Silbergeld et al., 2005; Alves et al., 2006; Gardner et al., 2010b). In mice, mercury induced autoimmunity is genetically restricted and involving both MHC - particularly H-2s and H-2q haplotypes and non-MHC genes. The autoantibody response is targeted to nucleolar autoantigens particularly the U3 ribonucleoprotein component fibrillarin (Hultman et al., 1992, 1993; Abedi-Valugerdi et al., 1997, 2001; Vas and Monestier, 2008). The levels of antibodies in maternal and cord blood, specifically total IgG were significantly associated with fetal mercury and maternal mercury level (Nyland et al., 2011b), yet others show no correlation (Miyake et al., 2011; Karagas et al., 2012).

Although cross-sectional epidemiological studies indicate a differential response to mercury in susceptible individuals, the antinuclear autoantibody (ANA) levels, proinflammatory interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF-α), interferon (IFN)-γ, anti-inflammatory IL-4, and IL-17 cytokine levels are increased upon MeHg exposure (Gardner et al., 2010b; Nyland et al., 2011a). Moreover, mercury-exposed gold miners have higher serum titers of 3760 autoantibodies including GSTA1, tumor necrosis factor ligand superfamily member 13, linker for activation of T cells, signal peptide peptidase like 2B, stimulated by retinoic acid 13, and interferon induced transmembrane protein, suggesting that mercury exposure can induce complex antoimmune dysfunction (Motts et al., 2014). In contrast, a decrease of IL-6, IL-1β, TNF-α, IFN-γ, and IL-4 was found among ANA-positive participants (Nyland et al., 2011a). In addition maternal and fetal blood MeHg was not associated with any cytokines (Nyland et al., 2011b). Moreover, no association between mercury and ANA or seven cytokines including IL-1β, IL-4, IL-10, TNF-α, IL-17, IFN-γ, and IL-1α was observed in the population of avid seafood consumers with median blood mercury 4.58 μg/L (Monastero et al., 2017).

The TNF-α is selectively induced in the brain of mice by MeHg, and evidence support that NF-κB may participate as a transcription factor in that induction (Iwai-Shimada et al., 2016). Furthermore, a decrease of the chemokine CCL2 concentrations in the murine cortex is associated with low levels of MeHg contaminated fish-based diet for 3 months exposure, suggesting that CCL2 may act as a neuroprotective alarm system in brain deficits due to MeHg intoxication (Godefroy et al., 2012).

Results of toxicogenomic studies suggest that genes involved in immune and inflammatory response, and antigen processing and presentation, including Atf3, Cebpg, Irf9, CXC chemokine LIX, TNF-α, TNF-α receptor, macrophage inflammatory protein 1, IL-2, IL-7, and PGE2 receptor were regulated in mercury exposure copepods (Wang et al., 2017), mussels (Dondero et al., 2006), Atlantic salmon (Nostbakken et al., 2012), zebrafish embryo (Yang et al., 2007; Ho et al., 2013), Atlantic cod (Yadetie et al., 2013), fathead minnows (R. Klaper et al., 2008), rat (Liu et al., 2003), and human (Stamova et al., 2011). Experimental evidence suggests that mercury may activate toll-like receptor (TLR)-4, which in turn, activates MAPKs and NF-kB, regulating the proinflammatory response (Assefa et al., 2012).

5.2.5. Genetic differences and DNA methylation

Several lines of evidence support that individual and population genetic differences may influence MeHg toxicity. The magnitude of the assocation between prenatal exposure to MeHg and child neuropsychological development appears to be modified by polymorphisms in CYP3A7 and CYP3A5 genes (Llop et al., 2017). The ATP binding cassette (ABC) transporters, such as MDR1, MRP1 and MRP2 were associated with mercury accumulation in the fetus. Children with the genotype GG of MDR1 rs2032586, CC of MRP1 rs11075290, and GA or AA of MRP2 rs2273697 show a stronger association between maternal fish intake and cord blood mercury concentration (Llop et al., 2014). Furthermore higher hair mercury levels are found in persons lacking expression of both GSTT1 and GSTM1 genes (Gundacker et al., 2009).

Evidence suggests that mercury exposure can lead to functional epigenetic alterations that may persist throughout childhood and are associated with cognitive performance. MeHg exposure has been associated with SEPP1 (encoding a selenoprotein) hypomethylation in adult blood (Goodrich et al., 2011, 2013), suggesting that methylation may be responsive to MeHg exposure. Assessment of prenatal Hg exposure through infant toenail Hg, placental DNA methylation changes and newborn neurobehavioral outcomes has demonstrated that many of the 339 loci with greatest differences by Hg reside in neurodevelopment-, neurogenesis- and behavior-related genes, in particular, 6 of 10 loci reside in the *EMID2* gene and were hypomethylated in the 16 high-risk profile infants' placentas (Maccani et al., 2015). These results suggest that *EMID2* hypomethylation may represent a mechanism linking *in utero* Hg exposure and adverse neurobehavioral outcomes. In addition, GSTM1/5 promoter methylation (Hanna et al., 2012), changes in DNA methylation at TCEANC2 in cord blood (Bakulski et al., 2015), and higher methylation levels of the PON1 in umbilical cord blood from male (Cardenas et al., 2017) are associated with mercury exposure. Similarly, MeHg exposure is associated with DNA hypomethylation in the brain of male polar bears (Pilsner et al., 2010) and a particular gene promoter region (Goodrich et al., 2013). Moreover, mercury exposure can modulate miRNA expression in plants (Zhou et al., 2013). The results of chromatin immunoprecipitation sequencing (ChIP-Seq) studies have demonstrated that among enhanced genes are mostly members of the glutathione-S-transferases family, including GST1, GST5, GST6, GST10 and GST38, as well as lipocalin-related protein and a cuticular collagen, suggesting that widespread epigenetic changes elicited by MeHg could lead to regulate gene expression (Rudgalvyte et al., 2017). Recent finding reports that a large number of F2 generation genes associated with MeHg exposure represents gene ontologies related to metabolic pathways, neuroactive receptor-ligand interactions, actin cytoskeleton, focal adhesion, and MAPK. Developmental MeHg-induced epigenetic transgenerational inheritance of abnormal neurobehaviour is correlated with sperm epimutations in F2 generation adult zebrafish (Carvan et al., 2017).

5.2.6. Genes/proteins related to endocrinotoxicity

Several lines of evidence support that endocrinotoxicity induced by mercury may involve in steroidogenesis, spermatogenesis, sperm function and morphology. Accumulation of mercury in male reproductive organs can cause pathological changes, and alter hypothalamus-pituitary-gland (HPG)-axis feedback. Observations suggest that MeHg may interfere with the dynein ATPase/microtubule assembly to alter sperm motility (Mohamed et al., 1986, 1987). Moreover mercury can block normal estrogen receptor (ER) activation and function by binding to ER (Choe et al., 2003; Martin et al., 2003). Mercury can affect steriod biosynthesis by inhibiting cytochrome p450c21 and aromatase activity, and impairing 21-α-hydroxylase activity which converts 17α-hydroxyprogensterone to 11-deoxycortisol (Veltman and Maines, 1986; Hinfray et al., 2006). Exposure to mercury has been shown to decrease gonadotropin-releasing-hormone (GnRH) in the brain of the beluga (*Huso huso*) and zebrafish (Gharaei et al., 2010; Zhang et al., 2016). Early neonatal exposure to thimerosal causes long lasting dysregulation of sexual endocrine system in adult male mouse, including up-regulation of GnRHR, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and adrenocorticotropic hormone (ACTH) (Li et al., 2014a). In contrast, a

significant down-regulation of GnRH2, GnRH3, FSHβ, LHβ in the brain and FSHR, LHR, AR, Cyp17 and Cyp11b in the testis was observed in adult zebrafish exposed to mercury (Zhang et al., 2016).

5.2.7. Genes/proteins related to genotoxicity

Currently epidemiological studies on genotoxicity of mercury compounds are controversial, however the evidence of cancer incidence supports that MeHg or/and inorganic mercury were probably responsible for increased leukemia (Janicki et al., 1987; Kinjo et al., 1996; Yorifuji et al., 2007), increased mortality by lung and liver cancer (Boffetta et al., 1998; Gomez et al., 2007; Zadnik and Pompe-Kirn, 2007), and mortality from cancers of the digestive tract (Giorgio et al., 1999). The mechamism leading to genotoxicity remains unclear. Hypotheses to explain the mechanims of the mercury genotoxicity centre around the generation of free radicals and oxidative stress (Schurz et al., 2000; Silva de Paula et al., 2016), distruping microtubules (Thier et al., 2003; Bonacker et al., 2004; Stoiber et al., 2004), influencing DNA repair and interacting directly with DNA molecules (Christie et al., 1985; Asmuss et al., 2000; Cebulska-Wasilewska et al., 2005; Li et al., 2006; Crespo-Lopez et al., 2009). Chromosomal genotoxicity, such as chromosomal aberrations and micronuclei was detected in populations of cells chronically exposed to mercury levels below the safety values defined by the WHO (De Flora et al., 1994; Amorim et al., 2000), and DNA damage in lymphocytes is observed in individuals exposed to mercury (Langworth et al., 1993; De Flora et al., 1994; Franchi et al., 1994; Di Pietro et al., 2008). Moreover, Fenstad et al. (2016) reported a significant positive relationship between mercury and DNA double strands break frequency in blood cells of a high-exposed Baltic population of common eiders. It is worthy of note that *in vitro* experimental approaches using cultures of lymphocytes and brain cell lines have demonstrated the genotoxic potentials and DNA strand breakage of mercury (Das et al., 1982; Omata et al., 1986; Betti et al., 1992; Rao et al., 2001; Silva-Pereira et al., 2005; Crespo-Lopez et al., 2007). Gene expression profiling indicated that genes involved in cancer and genetic disorders are altered by MeHg treatment (Richter et al., 2011). Together, evidence supports that mercury exposure may be involved in causing the carcinogenesis, however the causality between mercury exposure and carcinogenesis need further study.

6. Challenges and knowledge gaps

Although intensive studies on the mechanism of mercurial toxicity, and on the linkages between the alterations of expression/function of genes/proteins and mercury have provided more details at the molecular levels, several challenges and knowledge gaps remain for the full understanding of the mercurial toxicity and pathways connected to the adverse outcomes.

6.1. Challenges of connecting existing knowledge on gene/protein responses to mercurial toxicity to the adverse outcomes

Since a living organism responds to mercury exposure in order to mitigate possible hazards, it is necessary to distinguish the perturbed pathways of mercurial toxicity, and molecular initiating events leading to adverse outcomes from those not leading to adversity. Reliance on the Omics technology, large-scale data including totality of genes, mRNA, microRNA, proteins, and metabolites related to mercurial toxicity have been created (in the Comparative Toxicogenomics Database, more than 10,000 genes/proteins were listed which were lined with MeHg exposure, www.ctdbase.org). However, a major challenge relative to use of these data involves to reconstruct core components of molecular, cellular, organ and organism level networks that are responsible for the adverse outcomes. For example, the expression of genes associated with neural tube development, Wnt signaling, cell polarity, cell adhesion, cell cycle, and cell differentiation previously identified to be crucial for successful neurulation is altered by MeHg exposure with a dose- and time-dependent manner (Robinson et al., 2010b). However, how alterations in the expression of these genes resulting in adverse developmental outcomes are still unclear. To tackle the questions, the concepts of adverse outcome pathways (AOP) and pathway of toxicity (PoT) were developed to identify and depict causal linkages between mechanistic data and biological end points (Ankley et al., 2010; Hartung and McBride, 2011). However, there is still a long way to go for applying AOP and PoT to link a molecular initiating event to the adverse outcome. For example, a unidirectional linerarity presented in AOPs is not suitable for dealing with repair processes, multiple hit events, and effect duration (Leist et al., 2017). Furthermore, PoT, the results of (multi-)Omics measurements, which promises to be more detailed (molecular), quantitative, and possibly even representative of the dynamic network pertubation is limited by untargeted identification typically for Omics (Hartung, 2017).

6.2. Challenges of the effects of concentration and exposure duration or/stages on genes expression

In Omics studies, measuring changes in expression of genes/proteins was generally performed at high exposure doses, which could yield erroneous results. Proteomic analysis indicates that low mercury concentrations affect proteins involved in cytoskeleton assembly and oxidative stress, while proteins participating in respiratory metabolism, oxidative stress, phosphorylase activity, and binding activity were altered by high mercury concentrations (Wang et al., 2013). Thus, it is important to explore how the sublethal effects of mercury translate to adverse outcomes. Our previous investigations indicated that MeHg at 6 μg/L can trigger significant changes in genes expression, even the concentration did not cause obviously morphological defects with exception of alteration in transgene expression in tail fin primordium and effects on movement (Yang et al., 2007, 2010). In addition, despite the fact that mercury does not affect clinical chemistry data including alanine aminotransferase activity (ALAT), aspartate aminotransferase activity (ASAT), glucose and cholesterol, organ weights or pathology, the transcriptomics analysis clearly shows that mercury induced genes involve in apoptosis and affects tissue-specific functional genes both in the livers and in the kidney (Hendriksen et al., 2007). Thus, a crucial question is whether the regulated genes that are not obviously correlated with pathological alterations and clinical symptoms are indeed deleterious to the animals.

Differences in exposure duration differ alterations of genes/proteins responses to mercury. Molecular changes in liver and gonad of fathead minnow differ in the duration of MeHg exposure (R. Klaper et al., 2008). A decrease in expression of the CAT gene was observed in fish under chronic exposure to MeHg. In contrary, an increased expression and enzyme activity of CAT was found in the liver of fish with short exposure (Graves et al., 2017). In addition, the considerations of early lifetime exposure, and differences in genes/proteins expression between males and females should be taken into account.

6.3. Challenges of comparing gene/protein response to mercurial exposure in in vivo and in vitro

The similarities of gene expression shown *in vitro* and *in vivo* models in the response to MeHg have been identified, suggesting commonly altered genes across multiple *in vivo* and *in vitro* models despite of the significance of overlapping targets between studies

depending on experimental variables (i.e. dose, time) (Robinson et al., 2011). However, there are clear gaps in the knowledge of mechanism observed in *in vitro* and *in vivo*. *In vivo* study reports that MeHg induces site specific brain lesions such as neurodegeneration in the deep layer of the cerebral cortex without changes in the hippocampus and cerebellum in the adult brain. The site-specific neuronal hyperactivity in response to MeHg is suggested to be involved in *in situ* different antioxidative systems including lowest basal expression levels of GPx1 and SOD mRNA and proteins (Fujimura and Usuki, 2017a, 2017b). Moreover, observations indicate that different tissues/organs of zebrafish can respond to MeHg exposure in a very specific manner (Gonzalez et al., 2005) (Ho et al., 2013). The specificities of tissues/organs response to mercury are difficult even impossible to be observed in *in vitro* experiments. In addition, generally organisms may recover from mercurials insult after cessation of exposure. These may not be observed and assembled the regulated genes/proteins from the *in vitro* experiments as well.

6.4. Challenges of elucidating distinct effects on gene/proteis response to organic and inorganic mercurials

Several lines of evidence support the notion that inorganic and organic mercurial compounds have different mechanism of toxicity, particularly the two mercurials induce many distinct responses of gene expression and have distinct protein structural preferences (McElwee et al., 2013; LaVoie and Summers, 2018). The differences may reflect differential biochemical damage, or could be due to transcriptional polarity. In addition, MeHg is a more potent inhibitor of the thioredoxin system than $HgCl_2$. Upregulation and transposition of Nrf2 occurs significantly slower with MeHg than $HgCl_2$ (Spiller, 2018). Furthermore proteomic results reveal that two third of $HgCl_2$ altered proteins were different in comparison to those induced by MeHg in human neuroblastoma cells: protein modification processes including folding and degradation were mainly affected by $HgCl_2$ (Li et al., 2018). However, a set of consensus genes including Trx, Grx were influenced by five of six mercurial compounds including MeHg, thimerosal, $HgCl_2$, $HgBr_2$, 4-chloromercuribenzoic acid and phenylmercuric acetate in human pluripotent stem cell-based teratogenic Omics prediction test (Shinde et al., 2017). Moreover, approximately 10,000 and 2700 genes/proteins were identified to be enriched in cells or/and wildlife exposed to MeHg and $HgCl_2$, respectively (www.ctdbase.org). Of them, approximately 600 genes/proteins were affected by both $HgCl_2$ and MeHg in at lease one type of cells or/and one species of wildlife.

7. Conclusion and perspectives

We summarized the current data from cell, laboratory animals and plants studies on genes expression in response to mercurial compounds (Figs. 1 and 2). Results indicate that exposure to inorganic and organic mercury leads to the adverse effects including cytotoxicity, neurotoxicity, teratogenicity, nephrotoxicity, and immunotoxicity from microbes to humans, and genes involved in oxidative response, protein folding, metabolic processes, transport, transcription factors, immune response, DNA repair, cell apoptosis, and hormone are enriched in at least one type of cells or/and one species of wildlife. Associations of the possible adverse outcomes including neurotoxicity, immunotoxicity, genotoxicity, developmental toxicity, cardiovascular toxicity, disrupting endocrine systems and metabolic effects with mercury exposure may depend on the doses and length of the exposure, the type of mercury, the age and sex of the animal exposed and the type of exposure. Understanding how mercury acts adverse effects on multiple organs at one time in an organism, and how these indirect and sub-lethal effects affect the health of an organism remains an unmet challenge. Epidemiological studies have explored gene-mercury interactions for human mercury neurotoxicity and identified possible genetic risk modifiers for mercury exposure. However, knowledge of the variance in mercury toxicity susceptibility across population subgroups remains also an unmet challenge. Selenium and the omega-3 fatty acids have been shown to confer protection against MeHg toxicity, however the precise mechanism requires further efforts for unraveling. Finally, the reality of our lives is facing simultaneous exposure to multiple chemicals in addition to mercury, understanding how mercury acts on multiple sequential exposures remain unmet challenges. Currently, much effort has gone into generating Omics data, and tried to tie those changes in genes/proteins/metabolites/methylation patterns to adverse endpoints. The postulated concepts are utility of combination with absorption, disposition, metabolism, excretion data and physiologically based pharmacokinetic modeling, and functional Omic data to connect the changes in gene expression to specific toxic endpoints, and to arrive at toxicological thresholds, which in turn will shed much light on associations of Omics data, adverse outcomes pathways or/and pathways of toxicity with adverse outcomes of mercurial toxicity.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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