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THE NEURODEVELOPMENTAL TOXICITY OF HEAVY METALS: A FISH PERSPECTIVE

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Abstract

The causes of neurodegenerative diseases are complex with likely contributions from genetic susceptibility, and environmental exposures over an organism's lifetime. In this review, we examine the role that aquatic models, especially zebrafish, have played in the elucidation of mechanisms of heavy metal toxicity and nervous system function over the last half-decade. Focus is applied to cadmium, lead and mercury as significant contributors to central nervous system morbidity, and to the application of numerous transgenic zebrafish expressing fluorescent reporters within specific neuronal populations or brain regions enabling high-resolution neurodevelopmental and neurotoxicology research.

INTRODUCTION

The vertebrate central nervous system (CNS) is an evolutionarily conserved system consisting of the brain and spinal cord. During embryogenesis, the brain of all vertebrates partitions along the anterior-posterior axis into the forebrain (prosencephalon), consisting of the telencephalon and diencephalon; midbrain (mesencephalon); and hindbrain (rhombencephalon), consisting of the metencephalon and myelencephalon, which then transition to the spinal cord. In mammals, the telencephalon expands substantially and envelops both the diencephalon and mesencephalon and becomes the cerebral cortex or cerebrum, where the seat of consciousness appears to reside[1], and where voluntary movement is controlled, and learning, memory, language, and sensory processing occur. In other vertebrates including fish, the telencephalon is a considerably smaller structure situated anterior to the mesencephalon and from which the more prominent olfactory bulb projects. In addition to this major difference, the adult brain of fish, reptiles, amphibians and

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birds differs anatomically from the mammalian brain in that the three major subdivisions of the brain (fore-, mid- and hindbrain) remain situated along the anterior-posterior axis of the vertebrate body in contrast to the folding of the fore- and mid-brain into a single, complex structure in mammals, thus exhibiting a simplified architecture relative to their mammalian counterparts. Neurodevelopmental disorders (NDDs) can be broadly defined as defects in growth or development of the central nervous system, which can be caused by genetic or environmental factors. The latter can include physical trauma, exposure to xenobiotics, and biological causes such as viral or bacterial infections[2] during critical periods of nervous system development. In humans, manifestations of neurodevelopmental disorders are wide-ranging and complex, and include intellectual disabilities, communication disorders, traumatic brain injuries, and autism spectrum disorders, epilepsies, and motor and coordination disorders. Many of these human disorders appear to have model organism counterparts including rodents and fish, thus enabling experimentation designed to elucidate the mechanistic bases of their origins. Although outside of the scope of this review, the reader is referred to several excellent reviews discussing the application of model organisms towards understanding complex human neurodevelopmental disorders[3–6].

In this review, we focus on describing transgenic zebrafish generated over the last decade, in which specific neuronal populations are labeled with fluorescent tags for *in vivo* visualization of normal and pathological neurodevelopmental processes, and we review the effect of cadmium (Cd), lead (Pb) and mercury (Hg), on neurodevelopment and neurodevelopmental outcomes by specifically focusing on the contributions that aquatic species, mainly fish, have made toward our understanding of the role these metals have on adverse neurological outcomes in affected populations.

TRANSGENIC ZEBRAFISH USED IN THE STUDY OF NEURODEVELOPMENT

Transgenic zebrafish in which specific neuronal populations or CNS regions are labeled with fluorescent reporters have provided important insights into neurodevelopment, and are a promising resource for understanding the effects of neurotoxic compounds on brain function. The transgenic lines discussed below are summarized in Table 1.

Transgenics that Label Specific Neurons

The ability to generate stable transgenic zebrafish that label specific neuronal populations or particular regions of the brain has been an extremely useful tool to study neurodevelopment in the presence of toxins and toxicants by tracking neuronal outgrowth and circuit formation, and by quantifying changes in fluorescence during exposure as evidence of abnormal neuronal function[7,8]. Examples include double-labeling mitochondria to measure mitochondrial transport, fusion and fission in dopaminergic neuronal axons[9]; visualizing cadherin bases cell-cell interactions in the hindbrain with the *ctnna* promoter[10]; tagging specific neurons with stable GFP expression, including dopaminergic neurons with the *th2* promoter[11], monoaminergic neurons with the *slc18a2* promoter[12], and habenular nuclei with the *kctd12.2* promoter to assess monoamine regulation and study asymmetric brain development[13,14]; and, neural stem cell proliferation and response to neural injury with the *fezf2* promoter[15]. Another increasingly important area of research relates to sensory neurons

and their role in behavior, learning, and emotional disorders[16–18]. Multiple transgenic zebrafish have been developed to study a variety of sensory systems by fluorescently labeling optic nerves using the *gap43* promoter[19]; olfactory neurons using the inducible *hsp70* promoter[20]; and single-cell resolution studies of adult telencephalic neural stem cells using the *gfap* promoter[21,22]. Recently, a transgenic line in which GFP is expressed under the control of enhancers of the *arxa* gene was used to demonstrate that diminished dosage of the *arxa* gene transcript affects neuronal outgrowth and path finding capabilities resulting in neurodevelopmental disturbances similar to those observed in patients with copy number variations of the human ortholog, *ARX*[23]; therefore, opening up possibilities for using this transgenic to characterize xenobiotics that could impact gene dosage and lead to new therapies. Finally, the impact of support cells, including glial cells, oligodendrocytes, and corticotropic cells should not be underestimated as these cells outnumber neurons 10:1[24]. Transgenic lines for support cell imaging include *mpz,* and *olig2*, which label oligodendrocytes[25–28]; *pomca,* which labels corticotropic cells in the anterior pituitary[29–31]; and *gfap,* which allows visualization of radial-glial cells[32].

Transgenics that Alter Neuronal Function

While the transgenic lines listed above can be used to visualize cell types, and investigate chemical influence, it is also possible to assess how gain or loss of function mutations impact toxicant susceptibility. An evaluation of viral insertional mutants and their related phenotypes uncovered novel genomic lesions resulting in defects in gliogenesis, glial patterning, neurogenesis, and axon guidance that may be useful in future studies of neuronal function under different environmental conditions[33]. Other gain or loss of function transgenics include the loss of function mutant *hdac1*^{hi1618}, which regulates neural progenitor differentiation into neurons, and glial-dependent myelination through integration of the Hedgehog, Notch, and Wnt signaling pathways[34–35]; a genetically-encoded calcium indicator, GCaMP5G, that coupled with optoacoustic imaging enables visualization of calcium-based neuronal activity[36]; and a gain of function mutant of *fhf1b*, which causes early-onset epileptic encephalopathy, and may be a useful mutant for studying chemical influence on voltage-gated sodium channels[37].

Transgenics to Study Neural Degeneration

Advances in public health have led to greater longevity giving rise to an increased number of people suffering from neurodegenerative diseases, including Parkinson’s and Alzheimer’s disease[38]. Although robust causal factors for these increases have eluded epidemiological analyses, the accumulation of exposures over prolonged lifespans is one possible mechanism suspected for the observed increase in neurodegenerative diseases[39]. Zebrafish have emerged as an important tool to study neurodegenerative diseases[40], resulting in the development of new transgenic lines that may be used to study these diseases. For example, mutations in *MAPT*, which encodes the tau protein, have been causally associated with frontotemporal dementia[41]. A commonly occurring human tau mutation, A152T-tau, consisting of a single G > A nucleotide change, diminishes tau binding to microtubules and increases neurofibrillary tangle formation. Recently, this mutation has been introduced into zebrafish and observed to cause neurodegeneration and proteasomal deficiencies, which could be partially rescued by pharmacologically upregulating autophagy[41]. A second tau transgenic

has been used to study factors influencing oligomer formation and disease progression[42]. A second devastating neurological disorder, amyotrophic lateral sclerosis (ALS), is often associated with an expansion of a GGGGCC repeat in a non-coding region of the chromosome 9 open reading frame 72 (*C9orf72*) locus[43]. Recently, a zebrafish *C9orf72*-GFP transgenic was developed as a means to characterize therapeutic interventions for ALS[43], and could potentially be used to better understand the influence of toxic insults on disease onset and progression. Many neurodegenerative diseases are marked by programmed cell death, and having an effective and efficient way to replicate the disease progression could be instrumental in developing treatments[44]. This line of research could benefit from established transgenic zebrafish such as a recently developed line that allows for cell type-specific caspase-mediated (*ca8*) apoptosis based on a tamoxifen-inducible system[44].

OVERVIEW OF HEAVY METALS AND NEUROTOXICITY

Heavy metals are naturally occurring metals exhibiting high atomic weights and high densities. Many heavy metals, including copper, iron, manganese, nickel, selenium, and zinc have important biological roles as cofactors for numerous proteins and enzymes. However, a significant number of heavy metals have no known biological roles, including cadmium, lead, and mercury but instead exhibit highly toxic properties when consumed by animals, including humans, and are classified as toxic heavy metals. Although naturally occurring, human activities, particularly through industrial processes, have led to widespread distribution of toxic metals throughout the biosphere. The widened distribution range increases the likelihood that humans will be exposed to toxic heavy metals through air, water, contaminated soil, and food. The World Health Organization lists cadmium, lead, and mercury in its list of top 10 chemicals of major public health concern[45], and exposure to these metals has been linked to numerous neurodevelopmental and neurodegenerative disorders in humans[46,47]. In the following section, we summarize the latest research on the neurotoxicity of these three elements, with emphasis on the contributions made by aquatic models, primarily zebrafish, to our understanding of their toxic mechanisms.

PATHOLOGICAL EFFECTS OF HEAVY METALS ON FISH NEURODEVELOPMENT

Cadmium (Cd)

A variety of fish species have been used to study the effects of Cd exposure, including fathead minnow, rainbow trout, and sea bass[48–51]. These studies, summarized in Table 2, were performed in larvae, juveniles and adults, and showed that Cd is capable of increasing auditory thresholds, increasing growth rates, impairing social and escape behavior, accumulating in the olfactory bulbs, and damaging the sensory macula and neuromast[48–51]. Even at very low levels (1.9 ppb), Cd accumulates in the brain, causing an increase in expression of apoptotic genes (e.g., *c-jun*), and detoxifying genes (e.g., *mt1* and *mt2*)[52]. This trend continues as the dose is increased to 200 ppb, as long as the exposure time remains less than 24 hours with one study showing an induction of the antioxidant gene, *nrf-2*, in the olfactory bulb and telencephalon[53] and another showing induction of *mt2* and *smtb* in the brain[54]. As the exposure time (2 – 30 days) and concentration increase (180 – 1000 ppb),

these protective mechanisms appear to be overwhelmed and signs of stress and tissue damage appear[55–58]. This damage includes changes in retinal neuronal morphology, increased sensitivity to light, decreases in glial fibrillary acidic protein (an astroglial cell cytoskeleton protein), and increases in reactive oxygen species (ROS), nitric oxide, and malondialdehyde[55–58]. The LC50 levels for Cd are approximately 27 ppm, which is coupled to AChE inhibition[59], whereas brain homogenates exposed to LC50 levels for 10 minutes show evidence of nucleotide hydrolysis[60], indicative of DNA damage. In larval zebrafish the trend seems similar, including increases in *mt2* and *smtb* expression[61] followed by oxidative stress, abnormal histology, immunotoxicity, cell death, and a reduction in olfactory-dependent predator responses seen at mid-range levels (112 – 970 ppb)[20,62,63]. These data suggest that in adult and larval fish, Cd exposure induces oxidative stress that at high doses or chronic exposures overwhelms natural defense systems leading to systemic damage, possibly through apoptotic mechanisms.

In zebrafish, low level (40 ppb) developmental exposure to cadmium results in hyperactivity, decreased otolith size (inner ear gravity sensing biocrystals), and increases in rotational movement[16]. While short term (24 – 120 hours) moderate exposures (112 – 560 ppb), as seen in larvae, show increases in antioxidant and detoxifying (*cyp19a1b* and *mt1*) gene expression, oxidative stress, immunotoxicity, damage to the olfactory pits and neuromast cells, and a reduction in olfactory-dependent predator response[64–67]. An interesting finding from a recently published study revealed that *in vivo* and *in vitro* exposure to 112 ppb Cd resulted in anti-estrogenic activity[64], although the mechanism remains unknown. At higher concentrations (2 ppm), indications of neural crest effects were apparent, including disruptions in neural crest gene expression patterns and hypopigmentation; in addition, neuromast damage, and eye hypoplasia were reported[68,69]. Paradoxically, two studies using very high Cd levels (~7 and 11 ppm) found hyperpigmentation, as well as reductions in retinal ganglion projections, optic neuronal projections, a complete absence of photoreceptors, decreased head size, unclear brain divisions, and reduced proneuronal gene expression[70,71]. Longer (50 days) exposure to 20 ppb Cd resulted in reduction of olfactory-dependent predator response in juvenile fish, in a manner similar to that observed in the larval studies referenced above[20,62,72], which may reflect equivalent accumulations of cadmium in the three studies despite the differences in Cd levels at the onset of the experiments. Overall, embryonic Cd exposure in zebrafish shows similar responses as in adults, including indicators of oxidative stress but the developing sensory system appears to be particularly sensitive to Cd toxicity.

Lead (Pb)

Lead has received attention in recent years due to contamination of multiple public water systems. The effects of lead on zebrafish have been summarized in a recent review by Lee and Freeman (2014), including discussions on neurodegenerative diseases and the role of Pb in their development, and the use of zebrafish as a model organism[73]. As such we discuss results published since 2014, which are summarized in Table 3. Unlike Cd studies, the effects of Pb exposure during development have been examined at much lower concentrations, ranging from 10 to ~200 ppb. At lower levels (< 100 ppb), studies show that Pb alters a number of genes associated with nervous system development[74], including

increased GABA gene and protein expression early in development, which decreases after hatching[75]. These changes are possibly associated with decreased neuronal axon length, and reduced activity (hypoactivity)[76]. At levels above 100 ppb, zebrafish exhibit decreased adult learning, and altered color preferences[77,78], with the former persisting for up to three generations after the initial exposure. These findings confirm previous observations regarding interference with axon development, and learning and memory deficits but the underlying mechanisms and windows of susceptibility require further investigation[73].

Methylmercury (MeHg)

Studies investigating the effects of mercury exposure have used both zebrafish and fathead minnows (see Table 4). In adults, these studies have shown that at levels less than 200 ppb, MeHg inhibits membrane adenosine deaminase, and results in *mt2* gene induction in the brain but otherwise has minimal impact on other brain transcripts[79–81]. Mid-range levels (between 720 to 5500 ppb) show significant Hg accumulation in the brain[82], delayed hatching, and increased mortality[83], and the induction of hyperactive behavior coupled with decreased levels of the neurotransmitters, serotonin and dopamine[84,85]. At high doses (10 – 13 ppm), studies show alterations in proteins associated with gap junctions and oxidative phosphorylation, large increases in *mt2,* and mitochondrial dysfunction[81,82,86].

Studies in zebrafish embryos find that this stage is significantly more sensitive to MeHg with significant molecular, cellular and behavioral effects emerging at much lower levels. For example, embryonic exposure to Hg levels less than 30 ppb results in adult visual deficits,[87] decreased neural tube cell profileration[88], hyperactivity, and mortality[89]. Levels above 50 ppb result is significant toxic outcomes including delayed hatching[88], decreased head size[90], altered cAMP signaling[90], and mortality[88].

CONCLUSION

Research is still needed to expand understanding into the effects of heavy metal exposure on neurodevelopment and neurodegenerative diseases. However, recent advances in the production of transgenic zebrafish lines for neurodevelopment studies, and the use of other aquatic species to study metal toxicity have returned promising results that can be used to understand mechanisms of metal toxicity, and may lead to interventions for exposed populations or new regulatory policies aimed at reducing the levels of heavy metals in the environment. Although still a vexing problem, the current is moving in the right direction and aquatic models are helping navigate the perilous waters of heavy metal toxicity.

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Table 1

List of Transgenic Zebrafish Lines

Gene Symbol	Genotype	Reporter	Type	Neurological Endpoint	Reference
mt	Tg(UAS:mtPAGFP:mtDsRed2)	GFP/dsRed2	Structural	Dopaminergic axons and mitochondrial transport	Dukes *et al.* (2016)
gfap	Tg(gfap:GFP)mi2001	GFP	Structural	Adult neural stem cell behavior and Müller glia	Bernardos and Raymond (2008)
th2	Tg(th2:GFP-dlx5/6:mCherry)	GFP/mCherry	Structural	Dopaminergic neurons from embryonic neural precursors	McPherson *et al.* (2016)
slc18a2	Tg(ETvmat2:GFP)	GFP	Structural	Monoaminergic neurons	Wen *et al.* (2015)
mpz	Tg(mpz:EGFP)	GFP	Structural	CNS oligodendrocytes	Bai *et al.* (2014)
gap43	Tg(GAP43:GFP)	GFP	Structural	Optic nerves	Udvadia *et al.* (2008)
hsp70	Tg(hsp70:GFP)	GFP	Structural	Olfactory neurons	Halloran *et al.* (2000)
olig2	Tg(olig2:EGFP)	GFP	Structural	Oligodendrocytes	Shin *et al.* (2003)
pomca	Tg(-1.0pomca:GFP)	GFP	Structural	Corticotropic cells	De Marco *et al.* (2016)
kctd12.2	Tg(UAS:kctd12.2:mt)vu442	GFP	Structural	Habenular nuclei	Taylor *et al.* (2011)
ascl1a	Tg(ascl1a:GFP)	GFP	Structural	Müller glia and retinal regeneration	Wan *et al.* (2012)
th2	Tg(th2:Gal-VP16-UAS-E1b:NTR-mCherry)	Gal/mCherry	Structural	Hypothalamic neurons	McPherson *et al.* (2016)
arxa	Tg(arxa:mCherry-ARX_enhancer:Kal4)	mCherry	Structural	Forebrain	Ishibashi *et al.* (2015)
tau	A152T-tau	none	Neural Degeneration	Neurodegeneration and proteasome compromise	Lopez *et al.* (2017)
C9orf72	C9orf72 associated repeat	GFP	Neural Degeneration	Dipeptide repeat protein associated toxicity in ALS/ FTLD	Ohki *et al.* (2017)
ca8	Tg(ca8:FMA-TagRFP-2A-casp8ERT2)	RFP	Neural Degeneration	Target ablation of cerebellar Purkinje cells	Weber *et al.* (2016)
tau	Tg(tau-GFP)	GFP	Neural Degeneration	Neurodegeneration by tau proteins	Wu *et al.* (2016)
ctnna	ct3aGt	Citrine (YFP)	Functional	Cadherin-mediated based hindbrain cell-cell interactions	Žigman *et al.* (2011)
GCaMP5G	GCaMP5G calcium indicator	optoacoustic	Functional	Neural activity	Deán-Ben *et al.* (2017)
fhf1b	mutant FHF1B	gain of function	Functional	Early-onset epileptic encephalopathies	Siekierska *et al.* (2016)
fezf2	Tg(fezf2-GFP)	GFP	Functional	Neural stem cells proliferation	Berberoglu *et al.* (2009)

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Table 2

Summary of Studies Measuring Neurological Effects of Cadmium (Cd) Exposure in Fish

Exposure Duration	Age at Exposure	Species	Chemical	LOEC[1](ppb[2])	Major Endpoints	Reference
4d	Adult	Fathead minnows	Cd[3]	2.5	Increase in auditory threshold	Low and Higgs (2015)
1d	2–5 dpf	Rainbow trout	Cd[3]	2	Higher growth rate, altered social behavior & olfactory accumulation	Sloman *et al.* (2003)
4h/day for 8d	Juveniles	Sea bass	Cd[3]	0.5	Sensory macula damage and impaired escape behavior	Faucher *et al.* (2008)
4h	Juveniles	Sea bass	Cd[3]	5	Neuromast damage	Faucher *et al.* (2006)
21d	Adults (Males)	Zebrafish	Cd[3]	1.9	Increased apoptotic (*c-jun*) & detoxifying genes (*mt1 & mt2*) at 21d	Gonzalez *et al.* (2006)
1d	Adults	Zebrafish	Cd[3]	110	Induction of *nrf2* antioxidant genes (increased olfactory neuron cell death)	Wang and Gallagher (2013)
30d	Adults	Zebrafish	Cd chloride($CdCl_2$)	183	Changes in retinal morphology & ultrastructure, increased light sensitivity	Avallone *et al.* (2015)
1 – 6h	Adults	Zebrafish	Cd[3]	200	Increased *mt2* and *smtb*	Wu *et al.* (2016)
2d, 7d, 16d	Adults	Zebrafish	$CdCl_2$	613	Decrease in glial fibrillary acidic protein	Monaco *et al.* (2016)
1d, 4d	Adult (Females)	Zebrafish	Cd[3]	1000	Increased ROS, nitric oxide, & malondialdehyde in brain and liver	Zheng *et al.* (2016)
3d	Adult (Females)	Zebrafish	Cd[3]	1000	Induction of *mt2*, *smtb*, and accumulation of Cd in ovaries and F1 larvae at 72hpf	Wu *et al.* (2012)
2d	Adults	Zebrafish	$CdCl_2$	26122	LC50 and AChE inhibition	Zhang *et al.* (2017)
10m	Adult Brain	Zebrafish	Cd acetate $Cd(CH_3COO)_2$	28102	Nucleotide hydrolysis	Senger *et al.* (2006)
2d	3–5 dpf	Zebrafish	CdCl2	9	Increased *mt2* and *smtb*	Wu *et al.* (2008)
4d	3–7 dpf	Zebrafish	Cd[3]	112	Cell death, altered histological and changes in olfactory dependent behavior.	Matz and Krone (2007)
3h	80 – 83 hpf	Zebrafish	Cd[3]	562	Reduced olfactory dependent predator response	Blechinger *et al.* (2007)
12h	Juvenile	Zebrafish	Cd[3]	970	Increased ROS and immunotoxicity	Zheng *et al.* (2017)
50d	0–50 dpf	Zebrafish	Cd[3]	20	Lower survival at 24 hpf and reduced olfactory-dependent predator response (64 dpf)	Kusch *et al.* (2008)
3d	0–72 hpf	Zebrafish	CdCl2	112	*cyp19a1b* gene expression and anti-estrogenic activity	Chouchene *et al.* (2016)
3d	0–72 hpf	Zebrafish	CdCl2	112	Altered adult hyperactivity and antioxidant physiology	Ruiter *et al.* (2016)
4d	0–96 hpf	Zebrafish	Cd[3]	112	Behavioral alteration, oxidative stress, immunotoxicity	Jin *et al.* (2015)
5d	0–120 hpf	Zebrafish	CdCl2	560	Induction of *mt* in olfactory pits and neuromast	Chen *et al.* (2007)

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Exposure Duration	Age at Exposure	Species	Chemical	LOEC[1](ppb[2])	Major Endpoints	Reference
4d	0–96 hpf	Zebrafish	Cd[3]	2000	Reduction in neural crest gene expression and hypopigmentation	Zhang *et al.* (2015)
3d	0–72 hpf	Zebrafish	Cd[3]	2040	Neuromast damage	Sonnack *et al.* (2015)
~1d	4–24 hpf	Zebrafish	CdCl2	6893	Hyperpigmentation, reduced retinal ganglion projections, no photoreceptors, reduced neuronal projections	Hen Chow *et al.* (2009)
~1d	4–24 hpf	Zebrafish	CdCl2	11241	Decreased head size, unclear brain divisions, reduced proneuronal gene expression	Chow *et al.* (2008)

[1] Lowest Observed Effect Concentration;

[2] parts per billion;

[3] Species not specified.

Table 3

Summary of Zebrafish Studies Measuring Neurological Effects of Lead (Pb) Exposure

Exposure Duration	Age at Exposure	Chemical	LOEC(ppb)	Major Endpoints	Reference
3d	0–72 hpf	$Pb(CH_3COO)_2$	10	Gene expression changes in 89 genes associated with nervous system development	Lee and Freeman (2014)
3d	0–72 hpf	$Pb(CH_3COO)_2$	10	Altered GABA gene expression	Wirbisky *et al.* (2014)
6d	0–144 hpf	$Pb(CH_3COO)_2$	20	Decreased axon length and decreased locomotion (speed)	Zhu *et al.* (2016)
~3d	2–72 hpf	$Pb(CH_3COO)_2$	100	No change in Alzheimer's disease-associated gene, *sorl1*	Lee *et al.*(2017)
~5d	2–120 hpf	$Pb(CH_3COO)_2$	100	Altered color preference (Adults)	Bault *et al.* (2015)
~2d	2–24 hpf	Lead nitrate ($Pb(NO_3)_2$)	207	Decreased Learning (Adults)	Xu *et al.* (2016)

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Table 4

Summary of Studies Measuring Neurological Effects of Mercury (Hg) Exposure

Exposure Duration	Age of Exposure	Species	Chemical	LOEC(PPB)	Major Endpoints	Reference
1d	Adult	Zebrafish	Mercury chloride ($HgCl_2$)	60	Inhibition of membrane adenosine deaminase	Senger *et al.* (2010)
54d	Adult	Zebrafish	Methylmercury(MeHg)	80	No change in brain gene expression (qpcr)	Gonzalez *et al.* (2005)
7d	Adult	Zebrafish	MeHg	119	*mt2* gene induction in brain	Gentes *et al.* (2015)
30d	Adult	Fathead minnow	MeHg	720	Hyperactivity and decreased dopamine	Bridges *et al.* (2016)
30d	Adult	Fathead minnow	MeHg	870	Hyperactivity & decreased hatching time	Bridges *et al.* (2016)
56d	Adult	Zebrafish	MeHg	5000	Accumulation in Brain	Amlund *et al.* (2015)
1d	Adult	Zebrafish	MeHg	5000	Hyperactivity and decreased serotonin	Maximino *et al.* (2011)
30d	Adult	Fathead minnow	MeHg	5500	Delayed hatching and increased mortality	Bridges *et al.* (2016)
56d	Adult	Zebrafish	MeHg	10000	Altered proteins associated with gap junction signaling, oxidative phosphorylation, and mitochondrial dysfunction	Rasinger *et al.* (2017)
56d	Adult	Zebrafish	MeHg	10000	Accumulation in Brain	Amlund *et al.* (2015)
62d	Adult	Zebrafish	MeHg	11001	*mt2* protein increase in brain	Gentes *et al.* (2015)
49d	Adult	Zebrafish	MeHg	13000	Brain mitochondrial respiration (unaffected)	Bourdineaud *et al.* (2013)
30d	Adult & Embryo	Fathead minnow	MeHg	720	Hyperactivity and decreased dopamine	Cambier *et al.* (2012)
~1d	4–24 hpf	Zebrafish	MeHg	3	Adult visual deficit	Weber *et al.* (2008)
~3d	6 hpf – 72 hpf	Zebrafish	MeHg	10	Decreased neural tube cell proliferation	Hassan *et al.* (2012)
~3d	5 hpf – 72 hpf	Zebrafish	$HgCl_2$	27	Hyperactivity and mortality	Abu Bakar *et al.* (2016)
~3d	6 hpf – 72 hpf	Zebrafish	MeHg	50	Delayed hatching	Hassan *et al.* (2012)
1d	48 hpf – 72 hpf	Zebrafish	MeHg	60	Decrease in head size & alteration of cAMP signaling pathway	Ho *et al.* (2013)
~3d	6 hpf – 72 hpf	Zebrafish	MeHg	100	Mortality	Hassan *et al.* (2012)
2d	2–4 dpf	Zebrafish	MeHg	136	Accumulation in photoreceptors in retina and pineal gland	Korbas *et al.* (2013)
10m	5 dpf	Zebrafish	$HgCl_2$	13576	Accumulation in Brain	Bera *et al.* (2014)

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