

Methylmercury and Human Embryonic Development

Methylmercury (MeHg) is an organic form of mercury that can damage the developing brains of human fetuses. Women who consume methylmercury during pregnancy can bear children who have neurological issues because methylmercury has toxic effects on the nervous system during embryonic development. During the third week of gestation, the human nervous system begins to form in the embryo. During this gestational period, the embryo's nervous system is particularly susceptible to the influence of neurotoxins like methylmercury that can result in abnormalities. Furthermore, the fetal brain can incur damage despite the lack of signs of poisoning in the pregnant woman. In children, defects due to methylmercury can result in deficits in attention, behavior, cognition, and motor skills.

Methylmercury has both natural and synthetic sources. Natural sources of mercury include volcanic emissions, geologic deposits, and oceanic evaporation. Humans have introduced mercury into the environment with alkali and metal processing, coal-burning, medical waste, and gold and mercury mining. When mercury is released into the air, it circulates in the atmosphere until it is brought down through rain or snowfall, and then it can flow into bodies of water like lakes and streams.

Once in water, bacteria transform the mercury into its more toxic form, methylmercury. In this form, it is absorbed by aquatic plants and animals. Fish can absorb methylmercury from water through their gills and by eating other fish that possess concentrations of methylmercury. Consequently, the concentrations of methylmercury in exposed fish's tissues increases over time, with fish high on the food chain possessing higher concentrations of methylmercury than fish low on the food chain.

Humans expose themselves to methylmercury when they eat contaminated fish. When pregnant women eat contaminated fish, their embryos or fetuses also are exposed to the methylmercury, and they can develop congenital Minamata disease. In 1959, researchers attributed Minamata symptoms to poisoning by methylmercury found in the water of Minamata Bay in Kyushu, Japan. Congenital Minamata disease enabled researchers to identify the poisonous effects of methylmercury, which those near Kyushu consumed when they ate local seafood. Symptoms associated with Minamata disease include: lack of eye coordination, convulsions, neck instability, mental retardation, reflex, growth, and cerebellar deficits, hyperkinesia, hypersalivation, hyperkinesia, dysarthria, strabismus, microcephaly, and paroxysmal symptoms. The congenital disease gets its name from the Minamata Bay, where many cases of intrauterine methylmercury poisoning occurred due to the contamination of water by a nearby acetaldehyde factory of the Chisso Corporation.

The contamination of the water began in 1932 when the factory discharged wastewater that contained methylmercury into Minamata Bay, a practice they continued until 1968. It took approximately ten years from the time of the initial investigations into the causes of the disease for the Japanese government to officially endorse the causal relationship between the wastewater containing mercury dumped into the bay Chisso factory and Minamata disease, thereby compelling Chisso to cease dumping methylmercury into the water.

Many neurophysiological and mental conditions are associated with prenatal exposure to methylmercury. Hideyo Matsumoto, Goyo Koya, and Tadao Takeuchi at Kumamoto University in Kumamoto, Japan, described two case reports of infants from the Minamata Bay area with cerebral palsy that had been identified in 1960 as being afflicted with Minamata disease. In their clinical and pathological findings, conducted while the infants lived and after they died, the researchers described the infants as underdeveloped, unable to move purposefully, having poor mental development, and experiencing convulsions. At the time that the infants were observed, one child was one year and four months old and the other child was three years and seven months old.

The children died at two years and six months old, and six years and three months old, respectively. Matsumoto, Koya, and Takeuchi observed how methylmercury impacted the central nervous system and degenerated and decreased the number of neurons in the brains of those afflicted. In particular, the researchers noted a disappearance of granule and pyramidal cells, elimination of Purkinje cells, a narrowing of the molecular layer, reduced central white matter, diffuse atrophy of the folia in the cerebellum's hemispheres, and lack of myelination in the pons and medulla oblongata both areas of the hindbrain. Purkinje cells are necessary for the functioning of the cerebellum, which coordinates movements and maintains posture. Methylmercury prenatal poisoning yields babies with symptoms similar to those in individuals with cerebral palsy.

From 1971 to 1972, a population in rural Iraq experienced methylmercury poisoning after they consumed bread tainted with the chemical. Case studies conducted in the area detailed the neurological impact of methylmercury on infant children who had been exposed to methylmercury as embryos. In 1972, Ben Choi, Lowell Lapham, Laman Amin-Zaki, and T. Salam described the pathological changes in the brain of two infants born during the outbreak of methylmercury poisoning. The researchers were doctors from the University of Baghdad in Baghdad, Iraq, and from the University of Rochester Medical Center in Rochester, New York. They reported that one infant died after thirty-three days, and the other soon after birth. Both infants had high methylmercury content in their blood. The team's post mortem examinations of the infants' brains revealed widespread abnormal neuronal migration in the cerebral and cerebellar white matter. They also found disorganization and misalignment of cerebral cortex neurons.

In 1973, Laman Amin-Zaki, Sami Elhassam, Mohamed A. Majeed, Thomas W. Clarkson, Richard A. Doherty, and Michael Greenwood examined the clinical manifestations of methylmercury poisoning in six of fifteen mother-infant pairs. Those researchers also were from the University of Baghdad and the University of Rochester. The infants they studied had been exposed to methylmercury in utero as embryos after their mothers had eaten bread contaminated with methylmercury during the early stages of pregnancy. The researchers collected blood tests of both the mothers and the infants to measure the extent to which they had been exposed to methylmercury. They found that the infants had higher concentrations of methylmercury in their blood than did their mothers, indicating that methylmercury easily transferred from pregnant women to their fetuses or embryos. They noted that the infants with prenatal exposure to methylmercury displayed fretfulness, irritability and excessive crying, impaired vision or blindness, impaired hearing, weak muscles, and impairment of mental development. They also noted that the mothers displayed symptoms of poisoning.

From 1986 to 1987, a research team studied methylmercury concentrations in the blood of umbilical cords. The team included Philippe Grandjean, Pal Weihe, Roberta White, Frodi Debes, Shunichi Araki, Kazuhito Yokoyama, Katsuyuki Murata, Nicolina Sorensen, Rasmus Dahl, and Poul Jorgensen. The researchers were from Boston University in Boston Massachusetts, Tokyo University in Tokyo, Japan, Odense University in Odense, Denmark, and some were government researchers from Denmark and from the Faroe Islands. The team assembled a cohort of 1022 consecutive singleton births in the Faroe Islands. They had 917 of the seven year-olds undergo neurobehavioral examinations. The researchers used umbilical cord blood to discern mercury concentration. They found that mercury in the cord blood was significantly related to lower scores on attention, language, and memory tests, and to a lesser degree visuo-spatial and motor functions involving coordination, speed, and tactile processing.

In the early 2000s, a team of US researchers studied the impact of methylmercury on intelligence. The team included Daniel Axelrad with the US Environmental Protection Agency (EPA) headquartered in Washington D.C., David Bellinger, Louise Ryan from Harvard University in Cambridge, Massachusetts, and Tracey Woodruff from the EPA in San Francisco, California. The team tested neurologic functions to assess childhood intelligence quotients (IQs) of six, seven, and nine year-olds from the Faroe Islands, from New Zealand, and from Seychelles study cohorts. They observed a decrease in IQ of 0.18 IQ points for every part per million mercury in maternal hair.

In addition to the case studies, to further investigate the mechanisms by which methylmercury disrupts embryonic neural development, researchers experimented with methylmercury and animal embryos. In 2000, Kyoko Miura, Seiichiro Himeno, Nori Koide, and Nobumasa Imura from

Wako University and Kitasato University, both in Tokyo, Japan, found that chick embryos exposed to methylmercury had less than normal microtubule mass in nerve fibers. Methylmercury also altered surface membrane structure, and it inhibited nerve fiber growth in the dorsal root ganglion, a cluster of neural bodies that carry signals to the spinal cord in chick embryos. In 2002, a team led by Elaine Faustman from the University of Washington in Seattle, Washington, used primary rat embryo central nervous system (CNS) cells and exposed them to methylmercury. Those cells could not transition to different stages of the cell cycle, and they died.

Two years later, researchers from various universities in Italy observed that chick embryos exposed to methylmercury had degenerative damage on Purkinje cells, granule cells, and astrocytes, the latter of which function in the CNS's function and development, along with impairment of the blood-brain-barrier. In a study published in 2006, a group of researchers throughout the US examined the influence of methylmercury on neuronal cells in rats. They noted that methylmercury altered the cell cycle, preventing cerebellar and cortical neurons from dividing and proliferating.

Also in 2006, Christin Bland and Matthew Rand at the University of Vermont in Burlington, Vermont, showed that methylmercury alters Notch signaling between developing nerve cells in used fruit fly embryos. The Notch signaling pathway is a mechanism within and between cells in developing organisms that affects cell fate, proliferation, migration, and neurite growth. Also in 2006, Christoffer Tamm's research team at Uppsala University in Uppsala, Sweden, used a neural stem cell line from mice and primary embryonic cortical neural stem cells from rats to investigate the effect of methylmercury on those cells. The team found that when exposed to methylmercury, the cells die, which then reduces the number of progenitor cells in a cell population.

In 2008, researchers from several universities across Brazil and the US observed that in mice exposed to methylmercury as embryos had impaired Glutathione (GSH) antioxidant systems as newborns. This effect can damage a newborn's aerobic metabolism. Researchers from Egypt and the US observed in 2011 that zebrafish embryos exposed to methylmercury at low concentrations had delayed neuronal development, whereas higher concentrations killed the embryos, which failed to develop complete neural tubes. Then in 2014, Gregory Engel and Rand at the University of Vermont, using fruit fly embryos, discerned that methylmercury disrupts the production of a key protein in developing muscles, which then disrupts the signals between motor neurons and those muscles.

In 2004, the US Federal Drug Administration, headquartered in Silver Spring, Maryland, and the US Environmental Protection Agency, headquartered in Washington D.C., issued a joint statement. The statement advised people that to prevent adverse exposure to methylmercury, people should eat no more than twelve ounces of commercially-caught fish per week and no more than six ounces of locally-caught fish per week.

Prenatal exposure to methylmercury can produce various harmful neurological effects during embryonic development, and consumption of fish contaminated with mercury is the primary cause of human ingestion of methylmercury. By the early decades of the twenty-first century, researchers had yet to determine, a dose-effect but they noted that people should reduce their exposure to methylmercury. The neurotoxin can transfer to an embryo through the placenta and because the embryo is highly susceptible to neurotoxicity, the damage to the developing nervous system in utero can be severe.

Sources

1. Amin-Zaki, Laman, Mohammed A. Majeed, Sami B. Elhasani, Thomas W. Clarkson, Michael R. Greenwood, Richard A. Doherty. "Prenatal Methylmercury Poisoning. Clinical Observations Over Five Years." *JAMA Pediatrics* 133 (1979): 172-177.
2. Amin-Zaki, Laman, Sami Elhassam, Mohamed A. Majeed, Thomas W. Clarkson, Richard A. Doherty, Michael Greenwood. "Intra-uterine Methylmercury Poisoning in Iraq." *Pediatrics* 5 (1974): 587 -595.
3. Artavanis-Tsakonas, Spyros, Matthew D. Rand, and Robert J. Lake. "Notch Signaling: Cell Fate Control and Signal Integration in Development." *Science* 284 (1999): 770-776.

4. Axelrad, Daniel A., David D. Bellinger, Louise M. Ryan, and Tracey J. Woodruff. "Dose-Response Relationship of Prenatal Mercury Exposure and IQ: An Integrative Analysis of Epidemiologic Data." *Environmental Health Perspectives* 115 (2007): 609-615. <http://www.jstor.org/stable/4150364> (Accessed August 14, 2015).
5. Bakir, Farhan, Salem F. Damluji, Laman Amin-Zaki, Mahdi Murtadha, A. Khalidi, N.Y. Al-Rani, Sa'adoun Tikriti, H.I. Dahir, Thomas W. Clarkson, T.J.C. Smith, and R.A. Roherty. "Methylmercury Poisoning in Iraq." *Science* 181 (1971): 230-241.
6. Bertossi, Mirella, Francesco Girolamo, Mariella Errede, Daniela Virgintino, Giuliano Elia, Luigi Ambrosi, Luisa Roncali. "Effects of Methylmercury on the Microvasculature of the Developing Brain." *NeuroToxicology* 25 (2004): 849-857.
7. Bland, Christin, and Matthew D. Rand. "Methylmercury Induces Activation of Notch Signaling." *NeuroToxicology* 27 (2006): 982-991.
8. Burke, Kelly, Yinghong Chang, Baogang Li, Alex Petrov, Pushkar Joshi, Robert Berman, Kenneth R. Reuhl, and Emanuel DiCicco-Bloom "Methylmercury elicits rapid inhibition of cell proliferation in the developing brain and decreases cell cycle regulator, cyclin E." *NeuroToxicology* 27 (2006): 970-981. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2013736/> (Accessed October 28, 2014).
9. Choi, Ben H., Lowell W. Lapham. Laman Amin-Zaki, T. Salam. "Abnormal Neuronal Migration, Deranged Cerebral Cortical Organization, and Diffuse White Matter Astrocytosis of Human Fetal Brain: A major effect of methylmercury poisoning in utero." *Journal of Neuropathology & Experimental Neurology* 42 (1978): 719-733.
10. Ceccatelli, Sandra, Elizabeth Dare, and Michaela Moors. "Methylmercury-induced neurotoxicity and apoptosis." *Chemico-Biological Interactions* 188 (2010): 301-308.
11. Engel, Gregory L. and Matthew D. Rand. "The Notch Target E(spl)md is a Muscle-Specific Gene Involved in Methylmercury Toxicity in Motor Neuron Development." *Neurotoxicology and Teratology* 43 (2014): 11-18.
12. Engleson, Gunnar, and Torsten Herner. "Alkyl Mercury Poisoning." *Acta Paediatrica* 41 (1952): 289-294.
13. Eto, Komyo, Masumi Marumoto, and Mothiro Takeya. "The Pathology of Methylmercury Poisoning." *Neuropathology* 30 (2010): 471-479. <http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1789.2010.01119.x/abstract> (Accessed August 14, 2015).
14. Faustman, Elaine M., Rafael A. Ponce, Ying C. Ou, Ma Ailean C. Mendoza, Thomas Lewandowski, and Terrance Kavanagh. "Investigations of Methylmercury-Induced Alterations in Neurogenesis." *Environmental Health Perspectives* 110 (2002): 859-864. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241261/pdf/ehp110s-000859.pdf> (Accessed October 28, 2014).
15. Grandjean, Philippe, Pal Weihe, Roberta F. White, Frodi Debes, Shunichi Araki, Kazuhito Yokoyama, Katsuyuki Murata, Nicolina Sorensen, Rasmus Dahl, Poul J. Jorgensen. "Cognitive Deficit in 7-Year-Old Children with Prenatal Exposure to Methylmercury." *Neurotoxicology and Teratology* 19 (1997): 417-428.
16. Harada, Masazumi. "Minamata Disease: Methylmercury Poisoning in Japan caused by Environmental Pollution." *Critical Reviews in Toxicology* 25 (1995): 1-24.
17. Harada, Masazumi. "Congenital Minamata Disease: Intrauterine Methylmercury Poisoning." *Birth Defects Research* 88 (2010): 906-909.
18. Harada, Masazumi, Hirokatsu Akagi, Toshihide Tsuda, Takako Kizaki, and Hidoki Ohno. "Methylmercury level in umbilical cords from patients with congenital Minamata disease." *Science of the Total Environment* 234 (1999): 59-62.
19. Hassan, S. A., Eid A. Moussa, and Louise C. Abbott. "The Effect of Methylmercury Exposure on Early Central Nervous System Development in the Zebrafish (*Danio rerio*) Embryo." *Journal of Applied Toxicology* 32 (2012): 707-13.
20. Ishitobi, Hiromi, Sander Stern, Sally W. Thurston, Grazyna Zareba, Margaret Langdon, Robert Gelein, and Bernard Weissi. "Organic and Inorganic Mercury in Neonatal Rat Brain After Prenatal Exposure to Methylmercury and Mercury Vapor." *Environmental Health Perspectives* 118 (2010): 241-248. <http://ehp.niehs.nih.gov/wp-content/uploads/118/2/ehp.0900956.pdf> (Accessed August 14, 2015).
21. Goyer, Robert A., Vasken Aposhian, L. Arab, D. Bellinger, T. Burbacher, T. Burke, J. Jacobson,

- L. Knobeloch, A. Stern, and L. Ryan. "oxicological Effects of Methylmercury. Washington, DC: National Research Council, 2000. <http://www.nap.edu/openbook.php?isbn=0309071402> (Accessed February 1, 2015).
22. Marsh, David O., Thomas W. Clarkson, Christopher Cox, Gary J. Myers, Laman Amin-Zaki, Ja-adoun Al-Tikrti. "Fetal Methylmercury Poisoning Relationship Between Concentration in Single Strands of Maternal Hair and Child Effects." *Jama Neurology* 44 (2007): 1017 -1022.
 23. Matsumoto, Hideyo, Goyo Koya, and Tadao Takeuchi. "Fetal Minamata Disease. A Neuropathological Study of Two Cases of Intrauterine Intoxication By a Methyl Mercury Compound." *Journal of Neuropathology and Experimental Neurology* 4 (1965): 563-574.
 24. Miura, Kyoko, Seiichiro Himeno, Nori Koide, and Nobumasa Imura. "Effects of Methylmercury and Inorganic Mercury on the Growth of Nerve Fibers in Cultured Chick Dorsal Root Ganglia." *The Tohoku Journal of Experimental Medicine* 192 (2000): 697ndash;78. http://journal.med.tohoku.ac.jp/1923/TJ1923_04.pdf?origin=publication_detail (Accessed October 28, 2014).
 25. Murata, Miwako Dakeishi, Miyuki Shimada, Hiroshi Satoh. "Assessment of intrauterine methylmercury exposure affecting child development: message from the newborn." *The Tohoku Journal of Experimental Medicine* 213 (2007): 187-202. https://www.jstage.jst.go.jp/article/tjem/192/3/192_3_195/_pdf (Accessed August 14, 2015).
 26. Rand, Matthew D., Julie C. Dao, Todd A. Clason. "Methylmercury disruption of embryonic neural development in Drosophila." *NeuroToxicology* 30 (2009): 794-802. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774130/> (Accessed August 14, 2015).
 27. Sellers, Patricia, Carol Kely, John M. Rudd, and Allison MacHutchon. "Photodegradation of methylmercury in lakes." *Nature* 380 (1996): 694-697.
 28. Stringary, James, Adriana K.C. Nunes, Jeferson L. Franco, Denise Bohrer, Solange C. Garcia, Aleir L. Dafre, Dejan Milatovie, Diogo O. Souza, Joao B. T. Rocha, Michael Aschner, and Maralo Farina. "Prenatal Methylmercury Exposure Hampers Glutathione Antioxidant System Ontogenesis and Causes Long-Lasting Oxidative Stress in the Mouse Brain." *Toxicology and Applied Pharmacology* 227 (2008): 147-154. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2955629/> (Accessed October 28, 2014).
 29. Tamm, Christoffer, Joshua Duckworth, Ola Hermanson, and Sandra Ceccetelli. "High Susceptibility of Neural Stem Cells to Methylmercury Toxicity: Effects on Cell Survival and Neuronal Differentiation." *Journal of Neurochemistry* 97 (2006): 69-78. <http://onlinelibrary.wiley.com/doi/10.1111/j.1471-4159.2006.03718.x/full> (Accessed October 28, 2014).
 30. Tollefson, Linda, and Frank Cordl. "Methylmercury in Fish: A Review of Residue Levels, Fish Consumption and Regulatory Action in the United States." *Environmental Health Perspectives* 68 (1986): 203-208. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474253/pdf/envhper00439-0195.pdf> (Accessed October 28, 2014).
 31. Tsuda, Toshide. "Minamata Disease: Catastrophic poisoning due to failed public health response." *Journal of Public Health Policy* 30 (2009): 54-67. <http://www.jstor.org/stable/40207223> (Accessed August 14, 2015).
 32. US Food and Drug Administration. "What You Need to Know About Mercury in Fish and Shellfish." March 2004. <http://www.fda.gov/food/resourcesforyou/consumers/ucm110591.htm> (Accessed on February 1, 2015).
 33. US Geological Survey. "Mercury in the Environment." October 2000. <http://www.usgs.gov/themes/factsheets/00/> (Accessed November 3, 2012).