20229 - EPHE 346 Motor Development and Physical Maturation
Jan - Apr 2013

Name: Evan Fryer

Title of Paper: The effects of prenatal exposure to mercury on childhood development: A teratogen in disguise

Contract: A+

Date of Submission: March 25, 2013

Throughout the history of modern academia, the complexity of pregnancy has consistently posited itself as a significant area of research. Although the abundance of empirical data could be correlated to the shear number of childbirths each year, this trend could very well be associated with the high variability of outcomes in human creation. After searching the literature, it is apparent that there exists a high correlation between prenatal environment and childhood development; that is, toxic levels in the mother's womb can significantly contribute to a wide variety of birth defects. Such an agent that disturbs the development of an embryo or fetus is referred to as a teratogen (Friedman & Polifka, 2000). Although most mothers are knowledgeable with regards to their pregnancy, many teratogenic agents in the environment are disguised in the regularities of everyday life. Thus, education regarding consumption of food and beverage is fundamentally necessary to avoid exposing the delicate embryo or fetus to developmentally detrimental toxins. Among the many drugs, chemicals, and physical agents that are teratogenic in nature, one that has caused significant birth defects in many demographics is mercury. The effects of high doses of mercury exposure prenatally can be extremely deleterious on childhood development. This will be the topic of discussion throughout the paper.

Mercury is a heavy metal occurring in several forms, all of which can produce toxic effects to humans depending on the degree of dose. Not only is mercury exposure detrimental on the developing embryo or fetus, but higher levels can also cause mercury poisoning in adults, specifically resulting in damage to the brain, kidney, and lungs (Clifton, 2007). From the environment, methylmercury is the major source of organic mercury in humans; it is formed by the action of anaerobic organisms in aquatic systems, especially the open ocean (Kerper, Ballatori, & Clarkson, 1992). Since it is not eliminated easily from organisms, it is "biomagnified in aquatic food chains from bacteria…to fish" (1992). Thus, the concentration of methylmercury in larger fish (fish that the general public would consume) is significantly higher than those fish or plankton at the bottom of the food chain. These amounts of toxins in fish have the potential for an epidemic, especially in

those communities that thrive on the fishing industry as their major source of economy. For example, in 1956, there was an excessive release of methylmercury in the industrial wastewater in Minamata Bay, Japan that eventually led to the mercury poisoning and death of 1,784 Japanese people from eating shellfish and fish from the waters (Kershaw, Dhahir, & Clarkson, 1980). To educate the public, many governmental agencies and health organizations have issued guidance for fish consumers, especially those who are pregnant. Recommended intake of fish related to dose of methylmercury will be delineated later in the paper.

A common myth related to methylmercury consumption is that most of the mercury is detected and excreted from the body; however, this is entirely not the case. About 95% of ingested methylmercury is absorbed by the gastrointestinal tract and more detrimentally, easily transported across the blood-brain barrier and across the placenta, where it is absorbed by the developing embryo or fetus (Kerper, Ballatori, & Clarkson, 1992). The primary function of the placenta is to selectively transport nutrients and waste products between the mother and developing embryo or fetus. However, methylmercury completely bypasses the layer of epithelial cells between the maternal and fetal connective tissues and proceeds to enter the fetal bloodstream (1992). Since the fetal liver is unable to deal with waste products effectively, relative to the maternal liver, the placenta is the only means of metabolism. Without this protective organ helping to reject methylmercury concentrations in the blood, methylmercury is easily transported between the maternal and fetal vascular systems (1992). Thus, it is imperative to realize the difference in maternal and fetal organ maturity; that is, their ability to function properly as a single entity. Although the mother may not be affected by high methylmercury content in her body, prenatal exposure to methylmercury concentrations could have an adverse effect on childhood development. Although there will be slight variation between each mother and developing embryo or fetus, methylmercury has a high lipid solubility and is easily transported across the blood-placenta barrier (Al-Saleh et al., 2011). If a mother is concerned about the amount of methylmercury she may have consumed, Al-Saleh et al. found that maternal and

cord blood is a reliable estimate of prenatal mercury exposure (2011). However, even though an estimate can be made, it is difficult for a medical practitioner to determine the exact effects that in utero exposure to mercury will have on childhood development.

In many cases, the effect of teratogens often depends on what period in the pregnancy the child is exposed to the toxin. However, with respect to mercury exposure, there is a lack of empirical data suggesting that there are safe periods in prenatal developmental. Despite the minimal evidence, Jin et al. believe that mercury exposure has the potential to be harmful at any time during the pregnancy (2013). Although there are no safe periods, different developmental outcomes are associated with mercury exposure during particular stages of prenatal development. These stages are broken up as follows: the pre-implantation stage, the embryonic period, and the fetal phase. The first stage is pre-implantation and is defined as the time from conception to fertilization. In this stage, teratogenic exposure to the embryo likely results in death through miscarriage or resorption (Diav-Citrin & Koren, 2000). Secondly, the embryonic period begins at fertilization and continues until around the 10th week of gestation. This is the period of maximum sensitivity to mercury poisoning since embryonic tissue and organs are rapidly being created (2000). As a result, birth defects are typically visible as structural anomalies depending on the organ system being differentiated at the time of mercury exposure (Jin et al., 2013). Finally, the third stage in prenatal development is the fetal phase, which begins at the end of the embryonic stage and lasts until term. During this phase, the developing fetus' organs are beginning to mature functionally and the occurrence of system integration is prevalent. Fetal overexposure to mercury will most likely affect the size and/or function of a specific organ, as opposed to visual deformities (Diav-Citrin & Koren, 2000). Ultimately, regardless of the timing of mercury exposure to the developing fetus, high doses will undoubtedly cause some sort of detrimental effect. Thus, it is important to refrain from a high amount of fish consumption throughout pregnancy.

Despite the overwhelming warning against fish consumption for risk of prenatal methylmercury poisoning, very small doses of mercury crossing the blood-placenta barrier have been found to show no effect on the developing fetus (Clarkson & Magos, 2006). This result is evidence of a phenomenon called the threshold effect (Diav-Citrin & Koren, 2000). That is, mercury exposure is relatively harmless in small doses, but becomes harmful when prenatal exposure reaches a certain level or threshold (2000). In their review of associated literature, Clarkson & Magos also reported that toxic damage to the fetus appears to be determined by the peak value of mercury, and not the length of exposure (2006). Although there is evidence to suggest that the concentration of mercury attained is correlated to birth defects, there is still some controversy as to the amount levels of methylmercury in the diet that can result in adverse effects. Experts are unable to determine an exact amount due to human variability, however, Oliveira et al. found that 50 μg Hg^{2+}/mL of blood was enough to cross blood-placenta barrier and cause change in fetuses' PBG-synthase activity (2012). Since the amount of methylmercury in fish is determined by many factors, it is fundamentally important to check local advisories about the safety of fish caught in local lakes, rivers, and coastal areas. As a general guideline, the US Food & Drug Administration and the Environmental Protection Agency believe that pregnant mothers should not eat more than 6 ounces of fish per week (US Department of Health & Human Services, 2004). They also state that pregnant mothers should avoid swordfish, shark, king mackerel, and tilefish completely due to their high concentration of methylmercury. Although dose of methylmercury plays a critical role in determining if adverse effects will occur on the developing fetus, duration of exposure plays less of a role (Kershaw et al., 1980). This is due to the fact that methylmercury has a high attraction to proteins in the blood and thus, is not readily eliminated from the body. In fact, methylmercury has a half-life of about 50 days and will sometimes take months for the agent to completely disappear from a human's vascular system (1980). Therefore, it is important to recognize that methylmercury in the mother's bloodstream will continue to cross the placenta for an extended period of time and contribute to a summated teratogenic response on the developing fetus.

Another factor that determines whether or not mercury will have adverse effects on the developing fetus is the genetic makeup of the individual. That is, possessing (or not possessing) certain genes has the potential to make the fetus more susceptible to the effects of prenatal mercury exposure. Although the exact genes have remained unidentified throughout research, Park et al. recently found that the absence of either the gene hgcA and/or hgcB, decreases the likelihood for methylmercury poisoning (2013). This is evidence that heredity is a major factor in determining whether prenatal methylmercury will have any effect. Furthermore, as mentioned earlier, human variability also plays a critical role. For example, concentration of red blood cells in the vascular system and permeability of the placenta are factors determining whether or not methylmercury will penetrate the fetus in large doses (Kershaw et al., 1980). However, extremely high levels of methylmercury in the blood will still cross the blood-placenta barrier, regardless of the variability of human genetic composition and physiological differences.

Evidently, there are many factors associated with prenatal mercury exposure that can cause various detrimental effects on childhood development. In general, there are three main effects that mercury exposure could cause: effects on cognitive function, effects on motor function, and effects on social behaviour.

Firstly, with regards to cognitive function, Montgomery et al. found in their study on lab mice that even small doses of prenatal mercury exposure have been proven to decrease mnemonic function and overall brain activity (2008). This was assessed using a variety of tests including footprint assessment, open field activity chamber, and the Morris water maze (2008). This decrease in cognitive function was often discovered well into the adolescent years of maturation. For example, Debes et al. found, only after 14 years, that deficits in cued naming were apparent in the cohort of 1022 births in the Faroe Islands (2006). However, other studies found delayed mental performance in infants (1 year olds) exposed to mercury prenatally (Jedrychowski et al., 2006). Mental performance in the latter case was tested using the BSID-II Test (2006). Also, Cohen, Bellinger, & Shaywitz found a correlation between dosage of prenatal mercury exposure and Intelligence Quotient (IQ),

through their meta-analysis of several studies (2005). They found that the impact might range from 0 to 1.5 IQ points per microgram increase in the concentration of mercury per gram of maternal hair (2005). Evidently, the supporting research proves that there are long-lasting consequences on cognitive function.

Prenatal exposure to mercury can also result in decreased motor function in early childhood and infancy. Montgomery et al. explains that coordination abilities are among the most common effects (2008). Longitudinally, Debes et al. found that after 14 years, deficits in finger tapping and reaction time were apparent, with the changes being multi-focal and permanent in nature (2006). In infancy, research shows delayed psychomotor performance in infants (1 year olds) exposed to mercury prenatally; furthermore, the Relative Risk (RR) for performance increases more than threefold, RR = 3.58 (Jedrychowski et al., 2006). Neurologically, Murata et al. found that there was reduced parasympathetic activity and/or a sympathovagal shift in offspring who had that in utero exposure to mercury (2006). Recently, Jin et al. found that mercury is associated with an elevated risk of neural tube defects (2013). They attained this conclusion by taking a collection of maternal placenta at birth, and examining the concentration of mercury in those mothers whose offspring had spina bifida (2013). Measured using an inductively coupled plasma mass spectrometer, they found the median concentration of mercury in neural tube defect cases was 1.09 ng/g higher that control cases (2013). Ultimately, motor function damage accounts for the large majority of maturational deterioration due to the timing of exposure during their critical growth periods in the mother's womb.

Finally, although only minimal research has been attempted, prenatal exposure to mercury has also been linked to learning in the classroom and to social behaviour as a whole. In one case, Boucher et al. reported association between prenatal mercury exposure and Attention Deficit Hyperactivity Disorder (ADHD) (2012). However, more information is still needed to draw prenatal exposure to other social disorders. This is especially true because Franzblau et al. found that there is little to know effect between prenatal mercury exposure and sensory nerve function (Franzblau et al., 2012). Finally, it is important to note that there is no

association between mercury exposure fetal prematurity in birth or fetal growth indicators (King et al., 2013) and also no effect on the pregnant mother (Oliveira et al., 2012) unless dose of exposure exceeds the mother's typical blood concentration.

Pregnancy is a stressful time in one's life, and is made more stressful by the creation of many myths in today's society. Thus, it is fundamentally important to be knowledgeable regarding the effects of too much fish consumption, especially depending on your locale in the world. A little bit of fish consumption will not be detrimental to maternal or fetal health. In fact, a little bit of fish is actually rich in nutrients and omega-three that are important for the developing fetus. Therefore, finding a balance can be extremely challenging, especially when the effects of mercury exposure on childhood development can be so severe as described above. Ultimately, education is key. If we can spread awareness regarding appropriate amounts of fish consumption in different communities around the world and encourage people to check-in with government agencies and health advisories, then the masquerade of the teratogenic effects of mercury will be unveiled forever.

References:

Al-Saleh, I., Shinwari, N., Mashhour, A., Mohamed, G. E. D., & Rabah, A. (2011). Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women. *International Journal of Hygiene and Environmental Health, 214*(2), 79-101. doi:10.1016/j.ijheh.2010.10.001

Boucher, O., Jacobson, S. W., Plusquellec, P., Dewailly, E., Ayotte, P., Forget-Dubois, N., … , Muckle, G. (2012). Prenatal methylmercury, postnatal lead exposure, and evidence of attention deficit/hyperactivity disorder among Inuit children in arctic Québec. *Environmental Health Perspectives, 120*(10), 1456-1461. doi:10.1289/ehp.1204976

Clarkson, T. W., & Magos, L. (2006). The toxicology of mercury and its chemical compounds. *Critical Reviews in Toxicology, 36*(8), 609-662. doi:10.1080/10408440600845619

Clifton, J. C. (2007). Mercury exposure and public health. *Pediatric Clinics of North America, 54*(2), 237-281. doi:10.106/j.pcl.2007.02.005

Cohen, J. T., Bellinger, D. C., & Shaywitz, B. A. (2005). A quantitative analysis of prenatal methyl mercury exposure and cognitive development. *American Journal of Preventive Medicine, 29*(4), 353-376. doi:10.1016/j.amepre.2005.06.007

Debes, F., Budtz-Jorgensen, E., Weihe, P., White, R. F., & Grandjean, P. (2006). Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicology & Teratology, 28*(5), 536-547. doi:10.1016/j.ntt.2006.02.005

Diav-Citrin, O. & Koren, G. (2000). Human teratogens: A critical evaluation. *Nausea and vomiting of pregnancy, 1*, 2-4. Retrieved from http://www.nvp-volumes.org/index.htm

Franzblau, A., d'Arcy, H., Ishak, M. B., Werner, R. A., Gillespie, B. W., Albers, J.W., … , Meyer, D. M. (2012). Low-level mercury exposure and peripheral nerve function. *NeuroToxicology, 33*(3), 299-306. Retrieved from http://www.journals.elsevier.com/neurotoxicology/

Friedman, J. M., & Polifka, J. E. (2000). *Teratogenic Effects of Drugs: A Resource for Clinicians* (2nd ed.). Baltimore, MD: The Johns Hopkins University Press.

Jedrychowski, W., Jankowski, J., Flak, E., Skarupa, A., Mroz, E., Sochacka-Tatara, E., … , Perera, F. (2006). Effects of prenatal exposure to mercury on cognitive and psychomotor function in one-year-old infants: Epidemiologic cohort study in Poland. *Annals of Epidemiology, 16*(6), 439-447. doi:10.1016/j.annepidem.2005.06.059

Jin, L., Zhang, L., Li, Z., Liu, J., Ye., R., & Ren, A. (2013). Placental concentrations of mercury, lead, cadmium, and arsenic and the risk of neural tube defects in a Chinese population. *Reproductive Toxicology, 35*, 25-31. doi:10.1016/j.reprotox.2012.10.015

Kerper, L. E., Ballatori, N., & Clarkson, T. W. (1992). Methylmercury transport across the blood-brain barrier by an amino acid carrier. *American Journal of Physiology, 262*(5), 761-765. doi:10.1080/20016491089226

Kershaw, T. G., Dhahir, P. H., & Clarkson, T. W. (1980). The relationship between blood levels and dose of methylmercury in man. *Archives of Environmental Health, 35*(1), 28-36. Retrieved from http://tandfonline.com/

King, E., Shih, G., Ratnapradipa, D., Quillam, D. N., Morton, J., & Magee, S. R. (2013). Mercury, lead, and cadmium in umbilical cord blood. *Journal of Environmental Health, 75*(6), 38-43. Retrieved from http://www.neha.org/JEH/

Montgomery, K. S., Mackey, J., Thuett, K., Ginestra, S., Bizon, J. L., & Abbott, L. C. Chronic, low-dose prenatal exposure to methylmercury impairs motor and

mnemonic function in adult C57/B6 mice. *Behavioural Brain Research, 191*(1), 55-61. doi:10.1016/j.bbr.2008.03.008

Murata, K., Sakamoto, M., Nakai, K., Dakeishi, M., Iwata, T., Liu, X., & Satoh, H. (2006). Subclinical effects of prenatal methylmercury exposure on cardiac autonomic function in Japanese children. *International Archives of Occupational & Environmental Health, 79*(5), 379-386. doi:10.1007/s00420-005-0064-5

Oliveira, C. S., Oliveira, V. A., Ineu, R. P., Moraes-Silva, L., & Pereira, M. (2012). Biochemical parameters of pregnant rats and their offspring exposed to different doses of inorganic mercury in drinking water. *Food & Chemical Toxicology, 50*(7), 2382-2387. doi:10.1016/j.fct.2012.04.046

Parks, J. M., Johs, A., Podar, M., Bridou, R., Hurt, R. A., Smith, S. D., … , Liang, L. (2013). The genetic basis for bacterial mercury methylation. *Science, 339*(6125), 1332-1335. doi:10.1126/science.1230667

US Department of Health & Human Services. (2004). *What you need to know about mercury in fish and shellfish: EPA and FDA advice for women who might become pregnant, women who are pregnant, nursing mothers*. Retrieved March 14, 2013 from http://www.fda.gov/food/foodsafety/product-specificinformation/seafood/foodbornepathogenscontaminants/methylmercury/ucm115662.htm