

**American Academy of Clinical Toxicology**  
**Special Interest Group: Herbs & Dietary Supplements**  
**Abstracting Service**  
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1. Makaryus JN, Makaryus AN. Cardiac arrest in the setting of diet pill consumption. *Am J Emerg Med.* 2008;26(6):732 e1-3. PMID: 18606338  
The obesity epidemic currently plaguing the United States has spurred the development of a vast number of drugs to assist in the battle against obesity and its associated complications. The need to loose weight often causes patients to loose sight of or even ignore the serious side effects of some of the most widely used weight-loss medications. Here we present the case of ventricular tachycardia/fibrillation arrest in an otherwise healthy 48-year-old woman who was taking no medications other than phentermine, a common appetite suppressant that functions as a central nervous system stimulant through activation of the noradrenergic pathway of the sympathetic nervous system.
  
2. Genovese RF, Newman DB. Understanding artemisinin-induced brainstem neurotoxicity. *Arch Toxicol.* 2008;82(6):379-85. PMID: 17972063  
Artemisinins are fast-acting and highly efficacious antimalarials. There has been a rapid increase in their use in response to increasing drug resistance and further increases in their use are anticipated as they continue to replace existing therapies. In laboratory studies, artemisinins can produce relatively specific brainstem neurotoxicity. Select nuclei in the medulla, pons and mesencephalon are usually found to be most vulnerable. Species-specific differences in the vulnerability of nuclei may also exist. While not yet completely understood, occurrence of the lesion seems to be dependent upon a sustained, rather than peak, level of circulating drug or metabolite. With daily administrations, the onset of signs of brainstem neurotoxicity frequently develops abruptly and sometimes is observable only at the end of, or after, a regimen of administration. Behavioral correlates of brainstem neurotoxicity in laboratory animals include ataxic symptoms such as tremor, gait impairment and balance disturbance. Symptoms may also include auditory impairment. Screening and diagnostic procedures to guard against artemisinin-induced brainstem neurotoxicity in humans need to be based on the available, albeit limited, data from laboratory studies. Substantial and fundamental gaps in our understanding of artemisinin brainstem neurotoxicity exist including the mode of action of neurotoxicity and the specific conditions under which it occurs. Further, the possibility of increased vulnerability from age-related factors, drug interactions and cumulative administration regimens has not yet been investigated. Substantial progress addressing these issues is needed to maintain appropriate pharmacovigilance as the use of these powerful and life-saving antimalarials increases.
  
3. Gill SK, Rieder MJ. Toxicity of a traditional Chinese medicine, *Ganoderma lucidum*, in children with cancer. *Can J Clin Pharmacol.* 2008;15(2):e275-85. PMID: 18603664  
BACKGROUND: Cancer is one of the most common severe diseases in Canadian children, and chemotherapy treatment leads to numerous, potentially fatal, adverse side effects including febrile neutropenia and leukopenia. In an attempt to prevent opportunistic infections, *Ganoderma lucidum*, a mushroom that has been used in Traditional Chinese Medicine for thousands of years, is being used by some people as an adjunctive to chemotherapy to help boost the immune system. Although extensive research is being conducted to determine its immunostimulatory properties, there is essentially no data on toxicity. OBJECTIVES AND METHODS: The purpose of this study was to determine toxicity of low and high concentrations of 3 different extracts of *G. lucidum* (GL, Reishi and PSGL) on the viability of 1) Jurkat E6.1 cells, 2) LG2 cells, and 3) PBMCs isolated from a) healthy adults, b) healthy children, and c) paediatric patients undergoing chemotherapy. RESULTS: When Jurkat E6.1 and LG2 cells were treated with increasing

concentrations of the 3 extracts, both time- and concentration- dependent decreases in cell viability were observed. However, when human PBMCs were treated with the same extracts, variable results were obtained. Although there was no consistent pattern, toxicity was observed in PBMCs. CONCLUSION: This is the first study that examines the toxicity of 3 different extracts of *G. lucidum* in both adults and children's PBMCs. Contrary to previous belief, our results suggest that extracts of *G. lucidum* should be used with caution as there appears to be potential for toxicity.

4. Fergusson DM, Boden JM. Cannabis use and adult ADHD symptoms. *Drug Alcohol Depend.* 2008;95(1-2):90-6. PMID: 18242878  
BACKGROUND: The present study examined the associations between cannabis use in adolescence and young adulthood and self-reported adult attention deficit/hyperactivity disorder (ADHD) symptoms in adulthood. METHODS: A 25-year prospective longitudinal study of the health, development, and adjustment of a birth cohort of 1265 New Zealand children. Measures included assessments of adolescent and young adult cannabis use and ADHD symptoms at age 25, measures of childhood socioeconomic disadvantage, family adversity, childhood and early adolescent behavioural adjustment and cognitive ability, and adolescent and young adult other drug use. RESULTS: Cannabis use by age 25 was significantly ( $p < .0001$ ) associated with increasing self-reported adult ADHD symptoms at age 25. Adjustment of the association for potentially confounding factors from childhood and early adolescence reduced the magnitude of the association, but it remained statistically significant ( $p < .0001$ ). However, control for the mediating effects of other drug use in adolescence and early adulthood reduced the association between cannabis use and adult ADHD symptoms to statistical non-significance ( $p > .20$ ). CONCLUSIONS: The current study suggested that the association between cannabis use and adult ADHD symptoms was mediated by other substance use that was associated with cannabis use. The results suggest that cannabis use leads to other drug use, which in turn leads to increased ADHD symptoms. However, it should be noted that the potential influence of such factors as genetic predispositions may still be unaccounted for.
5. Anderson HA. Eighth International Conference on Mercury as a Global Pollutant (ICMGP): human health and exposure to methylmercury. *Environ Res.* 2008;107(1):1-3. PMID: 18374911
6. Barboni MT, da Costa MF, Moura AL, Feitosa-Santana C, Gualtieri M, Lago M, Medrado-Faria Mde A, Silveira LC, Ventura DF. Visual field losses in workers exposed to mercury vapor. *Environ Res.* 2008;107(1):124-31. PMID: 17719027  
Visual field losses associated with mercury (Hg) exposure have only been assessed in patients exposed to methylmercury. Here we evaluate the automated visual field in 35 ex-workers (30 males; 44.20 $\pm$ 5.92 years) occupationally exposed to mercury vapor and 34 controls (21 males; 43.29 $\pm$ 8.33 years). Visual fields were analyzed with the Humphrey Field Analyzer II (model 750i) using two tests: the standard automated perimetry (SAP, white-on-white) and the short wavelength automated perimetry (SWAP, blue-on-yellow) at 76 locations within a 27 degrees central visual field. Results were analyzed as the mean of the sensitivities measured at the fovea, and at five successive concentric rings, of increasing eccentricity, within the central field. Compared to controls, visual field sensitivities of the experimental group measured using SAP were lower for the fovea as well as for all five eccentricity rings ( $p < 0.05$ ). Sensitivities were significantly lower in the SWAP test ( $p < 0.05$ ) for four of the five extra-foveal eccentricity rings; they were not significant for the fovea ( $p = 0.584$ ) or for the 15 degrees eccentricity ring ( $p = 0.965$ ). These results suggest a widespread reduction of sensitivity in both visual field tests. Previous reports in the literature describe moderate to severe concentric constriction of the visual field in subjects with methylmercury intoxication measured manually with the Goldman perimeter. The present results amplify concerns regarding potential medical risks of exposure to

environmental mercury sources by demonstrating significant and widespread reductions of visual sensitivity using the more reliable automated perimetry.

7. Bose-O'Reilly S, Lettmeier B, Gothe RM, Beinhoff C, Siebert U, Drasch G. Mercury as a serious health hazard for children in gold mining areas. *Environ Res.* 2008;107(1):89-97. PMID: 18321481  
In many developing countries, mercury is used to extract gold from ore in small-scale mining areas. Exposure through mercury in these small-scale mining communities is a serious health hazard, especially to the children living and working there. Many children begin working with immediate contact to mercury from the very early age of seven. In Indonesia and Zimbabwe, 166 children were clinically examined for mercury. The mercury concentration in the blood, urine, and hair was analyzed. Compared to the control groups, the exposed children showed typical symptoms of mercury intoxication, such as ataxia. The children working with mercury had high levels of this substance in the various biomonitors. The exposure derives mainly from the liquid mercury used to bind gold, forming an amalgam. The amalgam is heated and the smelting amalgam releases mercury vapor plus the wanted gold. Mercury vapor in contrast to liquid mercury is highly toxic. This elemental, vaporized mercury is the main form of exposure. Since in over 50 countries children live in small-scale gold mining areas and are exposed in a similar way to mercury, immediate action is needed to reduce this severe chemical health hazard for children. Child labor with hazardous substances such as mercury must be stopped.
8. Liu J, Shi JZ, Yu LM, Goyer RA, Waalkes MP. Mercury in traditional medicines: is cinnabar toxicologically similar to common mercurials? *Exp Biol Med (Maywood).* 2008;233(7):810-7. PMID: 18445765  
Mercury is a major toxic metal ranked top in the Toxic Substances List. Cinnabar, which contains mercury sulfide, has been used in Chinese traditional medicines for thousands of years as an ingredient in various remedies, and 40 cinnabar-containing traditional medicines are still used today. Little is known about toxicology profiles or toxicokinetics of cinnabar and cinnabar-containing traditional medicines, and the high mercury content in these Chinese medicines raises justifiably escalations of public concern. This minireview, by searching the available database of cinnabar and by comparing cinnabar with common mercurials, discusses differences in their bioavailability, disposition, and toxicity. The analysis showed that cinnabar is insoluble and poorly absorbed from the gastrointestinal tract. Absorbed mercury from cinnabar is mainly accumulated in the kidneys, resembling the disposition pattern of inorganic mercury. Heating cinnabar results in release of mercury vapor, which in turn can produce toxicity similar to inhalation of these vapors. The doses of cinnabar required to produce neurotoxicity are 1000 times higher than methyl mercury. Following long-term use of cinnabar, renal dysfunction may occur. Dimercaprol and succimer are effective chelation therapies for general mercury intoxication including cinnabar. Pharmacological studies of cinnabar suggest sedative and hypnotic effects, but the therapeutic basis of cinnabar is still not clear. In summary, cinnabar is chemically inert with a relatively low toxic potential when taken orally. In risk assessment, cinnabar is less toxic than many other forms of mercury, but the rationale for its inclusion in traditional Chinese medicines remains to be fully justified.
9. Litzow MR. Arsenic trioxide. *Expert Opin Pharmacother.* 2008;9(10):1773-85. PMID: 18570609  
BACKGROUND: The ancient drug, arsenic, has remarkable efficacy in the treatment of relapsed acute promyelocytic leukemia (APL) and this success has led to exploration of its use in other malignancies. OBJECTIVE: To provide an overview of the mechanism of action of arsenic and summarize its development in the treatment of APL and other malignant disorders. METHODS: A 20-year search of MEDLINE, EMBASE and Web of Science was conducted. RESULTS/CONCLUSIONS: A series of clinical trials with arsenic trioxide has confirmed its

benefit in the therapy of APL. Its role in the treatment of other malignancies remains to be determined. Careful attention to the clinical management of patients on arsenic trioxide therapy can significantly lessen the risk of major side effects.

10. Phillips TD, Afriyie-Gyawu E, Williams J, Huebner H, Ankrah NA, Ofori-Adjei D, Jolly P, Johnson N, Taylor J, et al. Reducing human exposure to aflatoxin through the use of clay: a review. *Food Addit Contam.* 2008;25(2):134-45. PMID: 18286403  
Innovative sorption strategies for the detoxification of aflatoxins have been developed. NovaSil clay (NS) has been shown to prevent aflatoxicosis in a variety of animals when included in their diet. Results have shown that NS clay binds aflatoxins with high affinity and high capacity in the gastrointestinal tract, resulting in a notable reduction in the bioavailability of these toxins without interfering with the utilization of vitamins and other micronutrients. This strategy is being evaluated as a potential remedy for acute aflatoxicosis, and as a sustainable human intervention for aflatoxins via the diet. Phase I and II clinical trials confirmed the apparent safety of NS for further study in humans. A recent study in Ghanaians at high risk for aflatoxicosis has indicated that NS (at a dose level of 0.25%) is effective in decreasing biomarkers of aflatoxin exposure and does not interfere with the levels of serum vitamins A and E, and iron and zinc. In summary, enterosorption strategies/therapies based on NS clay are promising for the management of aflatoxins and as a sustainable public health intervention. The NS clay remedy is novel, inexpensive and easily disseminated. Based on the present research, aflatoxin sequestering clays should be rigorously evaluated in vitro and in vivo, and should meet the following criteria: (1) favourable thermodynamic characteristics of mycotoxin sorption, (2) tolerable levels of priority metals, dioxins/furans and other hazardous contaminants, (3) safety and efficacy in multiple animal species, (4) safety and efficacy in long-term studies, and (5) negligible interactions with vitamins, iron and zinc and other micronutrients.
11. Dalla Corte CL, Fachinetto R, Colle D, Pereira RP, Avila DS, Villarinho JG, Wagner C, Pereira ME, Nogueira CW, et al. Potentially adverse interactions between haloperidol and valerian. *Food Chem Toxicol.* 2008;46(7):2369-75. PMID: 18474410  
This study was designed to determine whether the treatment with haloperidol (HP), valerian or both in association impairs the liver or kidney functions. Valerian alone did not affect oxidative stress parameters in the liver or kidney of rats. HP alone only increased glutathione (GSH) depletion in liver, but not in kidney. However, when HP was associated with valerian, an increase in lipid peroxidation levels and dichlorofluorescein (DCFH) reactive species production was observed in the hepatic tissue. Superoxide dismutase (SOD) and Catalase (CAT) activities were not affected by the HP plus valerian treatment in the liver and kidney of rats. HP and valerian when administered independently did not affect the activity of hepatic and renal delta-aminolevulinatase (delta-ALA-D), however, these drugs administered concomitantly provoked an inhibition of hepatic delta-ALA-D activity. The delta-ALA-D reactivation index was higher in rats treated with HP plus valerian than other treated groups. These results strengthen the view that delta-ALA-D can be considered a marker for oxidative stress. Serum aspartate aminotransferase (AST) activity was not altered by any treatment. However, serum alanine aminotransferase (ALT) activity was higher in the HP group and HP plus valerian group. Our findings suggest suggest adverse interactions between haloperidol and valerian.
12. Barski L, Rabaev E, Sztarkier I, Delgado J, Porath A, Jotkowitz AB. Autoimmune hepatitis and hypergammaglobulinemic purpura associated with herbal medicine use. *Isr Med Assoc J.* 2008;10(5):390-1. PMID: 18605369
13. Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J Gen Intern Med.*

2008;23(6):854-9. PMID: 18415652

**INTRODUCTION:** Herbal products have gained increasing popularity in the last decade, and are now used by approximately 20% of the population. Herbal products are complex mixtures of organic chemicals that may come from any raw or processed part of a plant, including leaves, stems, flowers, roots, and seeds. Under the current law, herbs are defined as dietary supplements, and manufacturers can therefore produce, sell, and market herbs without first demonstrating safety and efficacy, as is required for pharmaceutical drugs. Although herbs are often perceived as "natural" and therefore safe, many different side effects have been reported owing to active ingredients, contaminants, or interactions with drugs. **RESULTS:** Unfortunately, there is limited scientific evidence to establish the safety and efficacy of most herbal products. Of the top 10 herbs, 5 (ginkgo, garlic, St. John's wort, soy, and kava) have scientific evidence suggesting efficacy, but concerns over safety and a consideration of other medical therapies may temper the decision to use these products. **CONCLUSIONS:** Herbal products are not likely to become an important alternative to standard medical therapies unless there are changes to the regulation, standardization, and funding for research of these products.

14. Kile ML, Ronnenberg AG. Can folate intake reduce arsenic toxicity? *Nutr Rev.* 2008;66(6):349-53. PMID: 18522624  
Arsenic-contaminated groundwater is a global environmental health concern. Inorganic arsenic is a known carcinogen, and epidemiologic studies suggest that persons with impaired arsenic metabolism are at increased risk for certain cancers, including skin and bladder carcinoma. Arsenic metabolism involves methylation to monomethylarsonic acid and dimethylarsinic acid (DMA) by a folate-dependent process. Persons possessing polymorphisms in certain genes involved in folate metabolism excrete a lower proportion of urinary arsenic as DMA, which may influence susceptibility to arsenic toxicity. A double-blind placebo-controlled trial in a population with low plasma folate observed that after 12 weeks of folic acid supplementation, the proportion of total urinary arsenic excreted as DMA increased and blood arsenic concentration decreased, suggesting an improvement in arsenic metabolism. Although no studies have directly shown that high folate intake reduces the risk of arsenic toxicity, these findings provide evidence to support an interaction between folate and arsenic metabolism.
15. Posfay-Barbe KM, Schrenzel J, Frey J, Studer R, Korff C, Belli DC, Parvex P, Rimensberger PC, Schappi MG. Food Poisoning as a Cause of Acute Liver Failure. *Pediatr Infect Dis J.* 2008. PMID: 18664929  
We report a 9-year-old girl with cereulide-producing *Bacillus cereus* food poisoning, who developed fulminant hepatitis, renal and pancreatic insufficiency, shock, and prolonged seizures. She was transferred to our institution for hepatic transplantation before her diagnosis was established. As a result of rapid identification of the microorganism and supportive care, liver transplantation was avoided, and she recovered fully.
16. Koepke R, Sobel J, Arnon SS. Global occurrence of infant botulism, 1976-2006. *Pediatrics.* 2008;122(1):e73-82. PMID: 18595978  
**OBJECTIVE:** To summarize the worldwide occurrence of reported infant (intestinal toxemia) botulism cases since first recognition of the disease in 1976. **PATIENTS AND METHODS:** We collected information on infant botulism cases by active and passive surveillance, by provision of therapeutic Human Botulism Immune Globulin to suspected cases, and by searching the medical literature. We defined a case as laboratory-confirmed botulism that occurred in an infant <or=12 months of age that was not caused by the ingestion of botulinum toxin in food. **RESULTS:** Twenty-six countries representing 5 continents reported the occurrence of at least 1 case of infant botulism among their residents. The United States, Argentina, Australia, Canada, Italy, and Japan, in this order, reported the largest number of cases. A history of honey exposure

was significantly more common among case subjects hospitalized outside of the United States than among those who were recently hospitalized in California. CONCLUSIONS: Most countries have not yet reported cases of infant botulism. This limited reporting of the disease to date contrasts with the known global occurrence of *Clostridium botulinum* spores in soils and dust and suggests that infant botulism may be under-recognized, underreported, or both. When bulbar palsies, hypotonia, and weakness are present, physicians should consider the possibility of infant botulism even if the patient has not been fed honey. Publication of additional case reports and surveillance summaries will enhance understanding of the occurrence and extent of this under-recognized disease.

17. Xiang YZ, Shang HC, Gao XM, Zhang BL. A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials. *Phytother Res.* 2008;22(7):851-8. PMID: 18567057  
Panax ginseng C.A. Meyer is a well-known medicinal herb native to China and Korea, and has been used as a herbal remedy in eastern Asia for thousands of years. However, there is different evidence of ginseng efficacy between traditional Chinese medicine (TCM), modern pharmacological experiments and clinical trials. In TCM, ginseng is a highly valued herb and has been applied to a variety of pathological conditions and illnesses such as hypodynamia, anorexia, shortness of breath, palpitation, insomnia, impotence, hemorrhage and diabetes. Modern pharmacological experiments have proved that ginseng possesses multiple constituents (ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, etc.) and actions (central nervous system effects, neuroprotective effect, immunomodulation, anticancer, etc.), ginsenosides as the active ingredients, especially, having antioxidant, antiinflammatory, antiapoptotic and immunostimulant properties. Recently, ginseng has been studied in a number of randomized controlled trials investigating its effect mainly on physical and psychomotor performance, cognitive function, immunomodulation, diabetes mellitus, cardiovascular risk factors, quality of life, as well as adverse effects. Equivocal results have been demonstrated for many of these indications. Because of the poor quality of most clinical trials on ginseng, reliable clinical data in humans are still lacking. Therefore, a broader understanding of medical knowledge and reasoning on ginseng is necessary.
18. Bellinger DC. Neurological and behavioral consequences of childhood lead exposure. *PLoS Med.* 2008;5(5):e115. PMID: 18507501
19. Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, et al. Decreased brain volume in adults with childhood lead exposure. *PLoS Med.* 2008;5(5):e112. PMID: 18507499  
BACKGROUND: Although environmental lead exposure is associated with significant deficits in cognition, executive functions, social behaviors, and motor abilities, the neuroanatomical basis for these impairments remains poorly understood. In this study, we examined the relationship between childhood lead exposure and adult brain volume using magnetic resonance imaging (MRI). We also explored how volume changes correlate with historic neuropsychological assessments. METHODS AND FINDINGS: Volumetric analyses of whole brain MRI data revealed significant decreases in brain volume associated with childhood blood lead concentrations. Using conservative, minimum contiguous cluster size and statistical criteria (700 voxels, unadjusted  $p < 0.001$ ), approximately 1.2% of the total gray matter was significantly and inversely associated with mean childhood blood lead concentration. The most affected regions included frontal gray matter, specifically the anterior cingulate cortex (ACC). Areas of lead-associated gray matter volume loss were much larger and more significant in men than women. We found that fine motor factor scores positively correlated with gray matter volume in the cerebellar hemispheres; adding blood lead concentrations as a variable to the model

attenuated this correlation. **CONCLUSIONS:** Childhood lead exposure is associated with region-specific reductions in adult gray matter volume. Affected regions include the portions of the prefrontal cortex and ACC responsible for executive functions, mood regulation, and decision-making. These neuroanatomical findings were more pronounced for males, suggesting that lead-related atrophic changes have a disparate impact across sexes. This analysis suggests that adverse cognitive and behavioral outcomes may be related to lead's effect on brain development producing persistent alterations in structure. Using a simple model, we found that blood lead concentration mediates brain volume and fine motor function.

20. Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, Lanphear BP, Ho M, Rae MN. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med.* 2008;5(5):e101. PMID: 18507497  
**BACKGROUND:** Childhood lead exposure is a purported risk factor for antisocial behavior, but prior studies either relied on indirect measures of exposure or did not follow participants into adulthood to examine the relationship between lead exposure and criminal activity in young adults. The objective of this study was to determine if prenatal and childhood blood lead concentrations are associated with arrests for criminal offenses. **METHODS AND FINDINGS:** Pregnant women were recruited from four prenatal clinics in Cincinnati, Ohio if they resided in areas of the city with a high concentration of older, lead-contaminated housing. We studied 250 individuals, 19 to 24 y of age, out of 376 children who were recruited at birth between 1979 and 1984. Prenatal maternal blood lead concentrations were measured during the first or early second trimester of pregnancy. Childhood blood lead concentrations were measured on a quarterly and biannual basis through 6.5 y. Study participants were examined at an inner-city pediatric clinic and the Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio. Total arrests and arrests for offenses involving violence were collected from official Hamilton County, Ohio criminal justice records. Main outcomes were the covariate-adjusted rate ratios (RR) for total arrests and arrests for violent crimes associated with each 5 microg/dl (0.24 micromol/l) increase in blood lead concentration. Adjusted total arrest rates were greater for each 5 microg/dl (0.24 micromol/l) increase in blood lead concentration: RR = 1.40 (95% confidence interval [CI] 1.07-1.85) for prenatal blood lead, 1.07 (95% CI 0.88-1.29) for average childhood blood lead, and 1.27 (95% CI 1.03-1.57) for 6-year blood lead. Adjusted arrest rates for violent crimes were also greater for each 5 microg/dl increase in blood lead: RR = 1.34 (95% CI 0.88-2.03) for prenatal blood lead, 1.30 (95% CI 1.03-1.64) for average childhood blood lead, and 1.48 (95% CI 1.15-1.89) for 6-year blood lead. **CONCLUSIONS:** Prenatal and postnatal blood lead concentrations are associated with higher rates of total arrests and/or arrests for offenses involving violence. This is the first prospective study to demonstrate an association between developmental exposure to lead and adult criminal behavior.
21. Castoldi AF, Johansson C, Onishchenko N, Coccini T, Roda E, Vahter M, Ceccatelli S, Manzo L. Human developmental neurotoxicity of methylmercury: impact of variables and risk modifiers. *Regul Toxicol Pharmacol.* 2008;51(2):201-14. PMID: 18367301  
Methylmercury (MeHg) is a widespread environmental and food toxicant which has long been known to affect neurodevelopment in both humans and experimental animals. Risk assessment for MeHg is mainly based on human data coming from the massive episodes of poisoning in Japan and Iraq, as well as from large scale epidemiological studies concerning childhood development and neurotoxicity in relation to in utero exposure in various fish eating communities around the world. Despite the extensive literature and research, the threshold dose for MeHg neurotoxic effects is still unclear, in particular when it comes to subtle effects on neurobehaviour. In this article clinical and epidemiological findings concerning the neurodevelopmental toxicity of MeHg are reviewed. Much attention is focussed on the potential impact of factors, such as diet and nutrition, gender, pattern of exposure and co-exposure to other neurotoxic pollutants, which

may modulate MeHg toxic effects. These factors, together with the notion that some symptoms may ensue or exacerbate with aging, contribute to the difficulties in the definition of safe levels for developmental exposure.