

1.

## **A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning.**

### **Abstract**

#### **"CONTEXT:**

The case fatality from acute poisoning with glyphosate-containing herbicides is approximately 7.7% from the available studies but these have major limitations. Large prospective studies of patients with self-poisoning from known formulations who present to primary or secondary hospitals are needed to better describe the outcome from acute poisoning with glyphosate-containing herbicides. Furthermore, the clinical utility of the glyphosate plasma concentration for predicting clinical outcomes and guiding treatment has not been determined.

#### **OBJECTIVE:**

To describe the clinical outcomes, dose-response, and glyphosate kinetics following self-poisoning with glyphosate-containing herbicides.

#### **METHODS:**

This prospective observational case series was conducted in two hospitals in Sri Lanka between 2002 and 2007. We included patients with a history of acute poisoning. Clinical observations were recorded until discharge or death. During a specified time period, we collected admission (n = 216, including five deaths) and serial (n = 26) blood samples in patients. Severity of poisoning was graded using simple clinical criteria.

#### **RESULTS:**

Six hundred one patients were identified; the majority ingested a concentrated formulation (36%, w/v glyphosate). Twenty-seven percent were asymptomatic, 63.7% had minor poisoning, and 5.5% of patients had moderate to severe poisoning. There were 19 deaths (case fatality 3.2%) with a median time to death of 20 h. Gastrointestinal symptoms, respiratory distress, hypotension, altered level of consciousness, and oliguria were observed in fatal cases. Death was strongly associated with greater age, larger ingestions, and high plasma glyphosate concentrations on admission (>734 microg/mL). The apparent elimination half-life of glyphosate was 3.1 h (95% CI = 2.7-3.6 h).

#### **CONCLUSIONS:**

Despite treatment in rural hospitals with limited resources, the mortality was 3.2%, which is lower than that reported in previous case series. More research is required to define the mechanism of toxicity, better predict the small group at risk of death, and find effective treatments."

#### **Citation:**

Roberts, Darren M., Nick A. Buckley, Fahim Mohamed, Michael Eddleston, Daniel A. Goldstein, Akbar Mehrsheikh, Marian S. Bleeke, and Andrew H. Dawson. "A **Prospective Observational Study of the Clinical Toxicology of Glyphosate-containing Herbicides in Adults with Acute Self-poisoning.**" *Clinical Toxicology* 48.2 (2010): 129-36.

**Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/20136481>

2.

**Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders.**

**Abstract**

**"IMPORTANCE:**

Acetaminophen (paracetamol) is the most commonly used medication for pain and fever during pregnancy in many countries. Research data suggest that acetaminophen is a hormone disruptor, and abnormal hormonal exposures in pregnancy may influence fetal brain development.

**OBJECTIVE:**

To evaluate whether prenatal exposure to acetaminophen increases the risk for developing attention-deficit/hyperactivity disorder (ADHD)-like behavioral problems or hyperkinetic disorders (HKDs) in children.

**DESIGN, SETTING, AND PARTICIPANTS:**

We studied 64,322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002.

**EXPOSURES:**

Acetaminophen use during pregnancy was assessed prospectively via 3 computer-assisted telephone interviews during pregnancy and 6 months after child birth.

**MAIN OUTCOMES AND MEASURES:**

To ascertain outcome information we used (1) parental reports of behavioral problems in children 7 years of age using the Strengths and Difficulties Questionnaire; (2) retrieved HKD diagnoses from the Danish National Hospital Registry or the Danish Psychiatric Central Registry prior to 2011; and (3) identified ADHD prescriptions (mainly Ritalin) for children from the Danish Prescription Registry. We estimated hazard ratios for receiving an HKD diagnosis or

using ADHD medications and risk ratios for behavioral problems in children after prenatal exposure to acetaminophen.

### RESULTS:

More than half of all mothers reported acetaminophen use while pregnant. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95% CI, 1.01-1.27). Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes (ie, HKD diagnosis, ADHD medication use, and ADHD-like behaviors; P trend < .001). Results did not appear to be confounded by maternal inflammation, infection during pregnancy, the mother's mental health problems, or other potential confounders we evaluated.

### CONCLUSIONS AND RELEVANCE:

Maternal acetaminophen use during pregnancy is associated with a higher risk for HKDs and ADHD-like behaviors in children. Because the exposure and outcome are frequent, these results are of public health relevance but further investigations are needed."

### Citation:

Liew, Zeyan, Beate Ritz, Cristina Rebordosa, Pei-Chen Lee, and Jørn Olsen. "Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders." JAMA Pediatrics JAMA Pediatr 168.4 (2014): 313.

### Link:

<http://www.ncbi.nlm.nih.gov/pubmed/24566677>

3.

### **Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study.**

#### **Abstract**

"Severe acetaminophen hepatotoxicity frequently leads to acute liver failure (ALF). We determined the incidence, risk factors, and outcomes of acetaminophen-induced ALF at 22 tertiary care centers in the United States. Detailed prospective data were gathered on 662

consecutive patients over a 6-year period fulfilling standard criteria for ALF (coagulopathy and encephalopathy), from which 275 (42%) were determined to result from acetaminophen liver injury. The annual percentage of acetaminophen-related ALF rose during the study from 28% in 1998 to 51% in 2003. Median dose ingested was 24 g (equivalent to 48 extra-strength tablets). Unintentional overdoses accounted for 131 (48%) cases, intentional (suicide attempts) 122 (44%), and 22 (8%) were of unknown intent. In the unintentional group, 38% took two or more acetaminophen preparations simultaneously, and 63% used narcotic-containing compounds. Eighty-one percent of unintentional patients reported taking acetaminophen and/or other analgesics for acute or chronic pain syndromes. Overall, 178 subjects (65%) survived, 74 (27%) died without transplantation, and 23 subjects (8%) underwent liver transplantation; 71% were alive at 3 weeks. Transplant-free survival rate and rate of liver transplantation were similar between intentional and unintentional groups. In conclusion, acetaminophen hepatotoxicity far exceeds other causes of acute liver failure in the United States. Susceptible patients have concomitant depression, chronic pain, alcohol or narcotic use, and/or take several preparations simultaneously. Education of patients, physicians, and pharmacies to limit high-risk use settings is recommended."

**Citation:**

Holubek, William J., Susanne Kalman, and Robert S. Hoffman. "Acetaminophen-induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study." *Hepatology* 43.4 (2006): 880.

**Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/16317692>

4.

**Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study.**

**Abstract**

**"BACKGROUND:**

Aluminum, a contaminant of commercial intravenous-feeding solutions, is potentially neurotoxic. We investigated the effect of perinatal exposure to intravenous aluminum on the neurologic development of infants born prematurely.

## **METHODS:**

We randomly assigned 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding before they could begin enteral feeding to receive either standard or specially constituted, aluminum-depleted intravenous-feeding solutions. The neurologic development of the 182 surviving infants who could be tested was assessed by using the Bayley Scales of Infant Development at 18 months of age.

## **RESULTS:**

The 90 infants who received the standard feeding solutions had a mean (+/-SD) Bayley Mental Development Index of 95+/-22, as compared with 98+/-20 for the 92 infants who received the aluminum-depleted solutions (P=0.39). In a planned subgroup analysis of infants in whom the duration of intravenous feeding exceeded the median and who did not have neuromotor impairment, the mean values for the Bayley Mental Development Index for the 39 infants who received the standard solutions and the 41 infants who received the aluminum-depleted solutions were 92+/-20 and 102+/-17, respectively (P=0.02). The former were significantly more likely (39 percent, vs. 17 percent of the latter group; P=0.03) to have a Mental Development Index of less than 85, increasing their risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with a reduction in the Mental Development Index (P=0.03), with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions.

## **CONCLUSIONS:**

In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development."

## **Citation:**

Bishop, Nicholas J., Ruth Morley, J. Philip Day, and Alan Lucas. "**Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions.**" *New England Journal of Medicine* N Engl J Med 336.22 (1997): 1557-562.

## **Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/9164811>

5.

**Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Delay of Effective Date.**

## **Abstract**

### **"BACKGROUND:**

Aluminum, a contaminant of commercial intravenous-feeding solutions, is potentially neurotoxic. We investigated the effect of perinatal exposure to intravenous aluminum on the neurologic development of infants born prematurely.

### **METHODS:**

We randomly assigned 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding before they could begin enteral feeding to receive either standard or specially constituted, aluminum-depleted intravenous-feeding solutions. The neurologic development of the 182 surviving infants who could be tested was assessed by using the Bayley Scales of Infant Development at 18 months of age.

### **RESULTS:**

The 90 infants who received the standard feeding solutions had a mean (+/-SD) Bayley Mental Development Index of 95+/-22, as compared with 98+/-20 for the 92 infants who received the aluminum-depleted solutions (P=0.39). In a planned subgroup analysis of infants in whom the duration of intravenous feeding exceeded the median and who did not have neuromotor impairment, the mean values for the Bayley Mental Development Index for the 39 infants who received the standard solutions and the 41 infants who received the aluminum-depleted solutions were 92+/-20 and 102+/-17, respectively (P=0.02). The former were significantly more likely (39 percent, vs. 17 percent of the latter group; P=0.03) to have a Mental Development Index of less than 85, increasing their risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with a reduction in the Mental Development Index (P=0.03), with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions.

### **CONCLUSIONS:**

In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development."

### **Citation:**

Food and Drug Administration. "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Delay of Effective Date." Federal Register. N.p., 26 Jan. 2001.

### **Link:**

<https://www.federalregister.gov/articles/2001/01/26/01-2125/aluminum-in-large-and-small-volume-parenterals-used-in-total-parenteral-nutrition-delay-of-effective>

## **Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration**

### **Abstract**

"Gulf War Syndrome is a multi-system disorder afflicting many veterans of Western armies in the 1990-1991 Gulf War. A number of those afflicted may show neurological deficits including various cognitive dysfunctions and motor neuron disease, the latter expression virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS) except for the age of onset. This ALS "cluster" represents the second such ALS cluster described in the literature to date. Possible causes of GWS include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide. In an initial series of experiments, we examined the potential toxicity of aluminum hydroxide in male, outbred CD-1 mice injected subcutaneously in two equivalent-to-human doses. After sacrifice, spinal cord and motor cortex samples were examined by immunohistochemistry. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer's disease and frontotemporal dementia. A second series of experiments was conducted on mice injected with six doses of aluminum hydroxide. Behavioural analyses in these mice revealed significant impairments in a number of motor functions as well as diminished spatial memory capacity. The demonstrated neurotoxicity of aluminum hydroxide and its relative ubiquity as an adjuvant suggest that greater scrutiny by the scientific community is warranted."

### **Citation:**

Shaw, Christopher A., and Michael S. Petrik. "**Aluminum Hydroxide Injections Lead to Motor Deficits and Motor Neuron Degeneration.**" *Journal of Inorganic Biochemistry* 103.11 (2009): 1555-562.

### **Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/19740540>

7.

## **Aspirin and Reye syndrome: a review of the evidence.**

### **Abstract**

"Reye syndrome is an extremely rare but severe and often fatal disease. Death occurs in about 30-40% of cases from brainstem dysfunction. The disease typically is preceded by a viral infection with an intermediate disease-free interval of 3-5 days. The biochemical explanation for Reye-like symptoms is a generalized disturbance in mitochondrial metabolism, eventually resulting in metabolic failure in the liver and other tissues. The etiology of 'classical' Reye syndrome is unknown. Hypothetically, the syndrome may result from an unusual response to the preceding viral infection, which is determined by host genetic factors but can be modified by a variety of exogenous agents. Thus, several infections and diseases might present clinically with Reye-like symptoms. Exogenous agents involve a number of toxins, drugs (including aspirin [acetylsalicylic acid]), and other chemicals. The 'rise and fall' in the incidence of Reye syndrome is still poorly understood and unexplained. With a few exceptions, there were probably no new Reye-like diseases reported during the last 10 years that could not be explained by an inherited disorder of metabolism or a misdiagnosis. This may reflect scientific progress in the better understanding of cellular and molecular dysfunctions as disease-determining factors. Alternatively, the immune response to and the virulence of a virus might have changed by alteration of its genetic code. The suggestion of a defined cause-effect relationship between aspirin intake and Reye syndrome in children is not supported by sufficient facts. Clearly, no drug treatment is without side effects. Thus, a balanced view of whether treatment with a certain drug is justified in terms of the benefit/risk ratio is always necessary. Aspirin is no exception.."

**Citation:**

Schrör, Karsten. "Aspirin and Reye Syndrome." *Pediatric Drugs* 9.3 (2007): 195-204.

**Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/17523700>

8.

**Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks.**

**Abstract**

**"OBJECTIVE:**

To study the efficacy and tolerability of 1 g of intravenous magnesium sulfate as acute treatment of moderate or severe migraine attacks.



## BACKGROUND:

Migraine is a common disorder in which not only the pain but also the accompanying symptoms such as nausea and vomiting reduce activity and productivity of sufferers. Many drugs used for the treatment of acute migraine attacks have many side effects, are not well tolerated, are ineffective in some patients, or cannot be used during pregnancy or in patients with ischemic heart disease. Magnesium deficiency has been proposed to play a role in the pathophysiology of migraine, and recently treatment of migraine with magnesium has gained considerable interest.

## METHODS:

This was a randomized, single-blind, placebo-controlled trial including 30 patients with moderate or severe migraine attacks. Fifteen patients received 1 g intravenous magnesium sulfate given over 15 minutes. The next 15 patients received 10 mL of 0.9% saline intravenously. Those in the placebo group with persisting complaints of pain or nausea and vomiting after 30 minutes also received 1 g magnesium sulfate intravenously over 15 minutes. The patients were assessed immediately after treatment, and then 30 minutes and 2 hours later. Intensity of pain, accompanying symptoms, and side effects were noted.

## RESULTS:

All patients in the treatment group responded to treatment with magnesium sulfate. The pain disappeared in 13 patients (86.6%); it was diminished in 2 patients (13.4%); and in all 15 patients (100%), accompanying symptoms disappeared. In the placebo group, a decrease in pain severity but persisting nausea, irritability, and photophobia were noted in 1 patient (6.6%).

Accompanying symptoms disappeared in 3 patients (20%) 30 minutes after placebo administration. All patients initially receiving placebo were subsequently given magnesium sulfate. All of these patients responded to magnesium sulfate. In 14 patients (93.3%), the attack ended; in 1 patient (6.6%), pain intensity decreased; and in all 15 patients (100%), accompanying symptoms disappeared. Both the response rate (100% for magnesium sulfate and 7% for placebo) and the pain-free rate (87% for magnesium sulfate and 0% for placebo) showed that magnesium sulfate was superior to placebo. Twenty-six patients (86.6%) had mild side effects which did not necessitate discontinuing treatment during magnesium sulfate administration.

## CONCLUSION:

Our results show that 1 g intravenous magnesium sulfate is an efficient, safe, and well-tolerated drug in the treatment of migraine attacks. It is possible that magnesium sulfate could be used in a broader spectrum of patients than other drugs commonly used for attack treatment. In view of these results, the effect of magnesium sulfate in acute migraine should be examined in large-scale studies"

## Citation:

Demirkaya, Seref, Okay Vural, Babur Dora, and Mehmet Akif Topcuoglu. "Efficacy of Intravenous Magnesium Sulfate in the Treatment of Acute Migraine Attacks." Headache Headache: The Journal of Head and Face Pain 41.2 (2001): 171-77.

**Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/11251702>

9.

**Dietary methanol and autism**

**Abstract**

"The authors sought to establish whether maternal dietary methanol during pregnancy was a factor in the etiology of autism spectrum disorders. A seven item questionnaire was given to women who had given birth to at least one child after 1984. The subjects were solicited from a large primary care practice and several internet sites and separated into two groups – mothers who had given birth to a child with autism and those who had not. Average weekly methanol consumption was calculated based on questionnaire responses. 550 questionnaires were completed by women who gave birth to a non-autistic child. On average these women consumed 66.71 mg. of methanol weekly. 161 questionnaires were completed by women who had given birth to an autistic child. The average estimated weekly methanol consumption for this group was 142.31 mg. Based on the results of the Wilcoxon rank sum-test, we see a significant difference between the reported methanol consumption rates of the two groups. This study suggests that women who have given birth to an autistic child are likely to have had higher intake of dietary sources of methanol than women who"

**Citation:**

Walton, Ralph G., and Woodrow C. Monte. "Dietary Methanol and Autism." Medical Hypotheses 85.4 (2015): 441-46.

**Link:**

<http://www.sciencedirect.com/science/article/pii/S0306987715002443>

10.

**Intestinal permeability and inflammation in patients on NSAIDs**

**Abstract**

## "Background

The frequency with which non-steroidal anti-inflammatory drugs (NSAIDs) increase small intestinal permeability and cause inflammation is uncertain.

## Aims

To examine small intestinal permeability and inflammation in a large number of patients on long term NSAIDs.

## Methods

Sixty eight patients receiving six different NSAIDs for over six months underwent combined absorption-permeability tests at three different test dose osmolarities (iso-, hypo-, and hyperosmolar). Two hundred and eighty six patients on 12 different NSAIDs underwent indium-111 white cell faecal excretion studies to assess the prevalence and severity of intestinal inflammation.

## Results

The iso- and hyperosmolar tests showed significant malabsorption of 3-0-methyl-D-glucose, D-xylose, and L-rhamnose. Intestinal permeability changes were significantly more pronounced and frequent with the hypo- and hyperosmolar as opposed to the iso-osmolar test. Sequential studies showed that four and nine patients (of 13) developed inflammation after three and six months treatment with NSAIDs, respectively. There was no significant difference ( $p>0.1$ ) in the prevalence (54-72%) or severity of intestinal inflammation in the 286 patients taking the various NSAIDs apart from those on aspirin and nabumetone, these having no evidence of intestinal inflammation. There was no significant correlation between the inflammatory changes and age, sex, dose of NSAID, length of disease, or NSAID ingestion.

## Conclusions

Intestinal permeability test dose composition is an important factor when assessing the effects of NSAIDs on intestinal integrity. All the conventional NSAIDs studied were equally associated with small intestinal inflammation apart from aspirin and nabumetone which seem to spare the small bowel. "

## **Citation:**

Sigthorsson, G., J. Tibble, J. Hayllar, I. Menzies, A. Macpherson, R. Moots, D. Scott, M. J. Gumpel, and I. Bjarnason. "Intestinal Permeability and Inflammation in Patients on NSAIDs." Gut 43.4 (1998): 506-11.

## **Link:**

11.

Longitudinal analysis of the association between removal of dental amalgam, urine mercury and 14 self-reported health symptoms

**Abstract**

"Background

Mercury vapor poses a known health risk with no clearly established safe level of exposure. Consequently there is debate over whether the level of prolonged exposure to mercury vapor from dental amalgam fillings, combining approximately 50% mercury with other metals, is sufficiently high to represent a risk to health. The objective of our study is to determine if mercury exposure from amalgam fillings is associated with risk of adverse health effects.

Methods

In a large longitudinal non-blind sample of participants from a preventative health program in Calgary, Canada we compared number of amalgam fillings, urine mercury measures and changes in 14 self-reported health symptoms, proposed to be mercury dependent sub-clinical measures of mental and physical health. The likelihood of change over one year in a sample of persons who had their fillings removed was compared to a sample of persons who had not had their fillings removed. We use non-parametric statistical tests to determine if differences in urine mercury were statistically significant between sample groups. Logistic regression models were used to estimate the likelihood of observing symptom improvement or worsening in the sample groups.

Results

At baseline, individuals with dental amalgam fillings have double the measured urine mercury compared to a control group of persons who have never had amalgam fillings. Removal of amalgam fillings decreases measured urine mercury to levels in persons without amalgam fillings. Although urine mercury levels in our sample are considered by Health Canada to be too low to pose health risks, removal of amalgam fillings reduced the likelihood of self-reported symptom deterioration and increased the likelihood of symptom improvement in comparison to people who retained their amalgam fillings.

Conclusions

Our findings suggest that mercury exposure from amalgam fillings adversely impact health and therefore are a health risk. The use of safer alternative materials for dental fillings should be encouraged to avoid the increased risk of health deterioration associated with unnecessary exposure to mercury."

**Citation:**

Zwicker, Jennifer D., Daniel J. Dutton, and John Charles Herbert Emery. "**Longitudinal Analysis of the Association between Removal of Dental Amalgam, Urine Mercury and 14 Self-reported Health Symptoms.**" Environmental Health Environ Health 13.1 (2014)

**Link:**

<https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-13-95>

12.

**Mercury Exposure and Antinuclear Antibodies among Females of Reproductive Age in the United States: NHANES**

**Abstract**

"Background: Immune dysregulation associated with mercury has been suggested, although data in the general population are lacking. Chronic exposure to low levels of methylmercury (organic) and inorganic mercury is common, such as through fish consumption and dental amalgams.

Objective: We examined associations between mercury biomarkers and antinuclear antibody (ANA) positivity and titer strength. Methods: Among females 16–49 years of age (n = 1,352) from the National Health and Nutrition Examination Survey (NHANES) 1999–2004, we examined cross-sectional associations between mercury and ANAs (indirect immunofluorescence; cutoff  $\geq$  1:80). Three biomarkers of mercury exposure were used: hair (available 1999–2000) and total blood (1999–2004) predominantly represented methylmercury, and urine (1999–2002) represented inorganic mercury. Survey statistics were used. Multivariable modeling adjusted for several covariates, including age and omega-3 fatty acids.

Results: Sixteen percent of females were ANA positive; 96% of ANA positives had a nuclear speckled staining pattern. Geometric mean (geometric SD) mercury concentrations were 0.22 (0.03) ppm in hair, 0.92 (0.05)  $\mu\text{g/L}$  blood, and 0.62 (0.04)  $\mu\text{g/L}$  urine. Hair and blood, but not urinary, mercury were associated with ANA positivity (sample sizes 452, 1,352, and 804, respectively), after adjusting for confounders: for hair, odds ratio (OR) = 4.10 (95% CI: 1.66, 10.13); for blood, OR = 2.32 (95% CI: 1.07, 5.03) comparing highest versus lowest quantiles. Magnitudes of association were strongest for high-titer ( $\geq$  1:1,280) ANA: hair, OR = 11.41 (95% CI: 1.60, 81.23); blood, OR = 5.93 (95% CI: 1.57, 22.47).

Conclusions: Methylmercury, at low levels generally considered safe, was associated with subclinical autoimmunity among reproductive-age females. Autoantibodies may predate clinical disease by years; thus, methylmercury exposure may be relevant to future autoimmune disease risk.."

**Citation:**

Somers, Emily C., Martha A. Ganser, Jeffrey S. Warren, Niladri Basu, Lu Wang, Suzanna M. Zick, and Sung Kyun Park. "**Mercury Exposure and Antinuclear Antibodies among Females of Reproductive Age in the United States: NHANES.**" *Environmental Health Perspectives* (2015)

**Link:**

<http://ehp.niehs.nih.gov/1408751/>

## **Methanol, formaldehyde, and sodium formate exposure in rat and mouse conceptuses: a potential role of the visceral yolk sac in embryotoxicity.**

### **Abstract**

#### **"BACKGROUND:**

Methanol (CH<sub>3</sub>OH) is believed to be teratogenic based on rodent studies. The mouse is more sensitive than the rat, but mechanisms of toxicity and identification of teratogenic metabolites are uncertain.

#### **METHODS:**

Rat and mouse whole embryo cultures are used to distinguish toxicity of CH<sub>3</sub>OH and its metabolites, formaldehyde (HCHO) and formate (HCOONa), which are produced following transit through the visceral yolk sac (VYS), via addition to culture medium, or by direct embryonic exposure through microinjection into the amnion.

#### **RESULTS:**

Embryonic viability, increased dysmorphogenesis, and decreased growth parameters were altered in a dose-dependent fashion for each compound. Mouse embryos were more sensitive than rat, as indicated by significant decreases in viability at comparable, lower concentrations. HCHO produced dysmorphogenesis and caused embryo lethality at nearly 1000-fold lower concentrations (0.004 mg/ml) than seen with either CH<sub>3</sub>OH or HCOONa. All agents produced incomplete axial rotation and delayed neural tube closure in mice, but only CH<sub>3</sub>OH elicited similar effects in the rat. Increased growth retardation, blood pooling in the head and VYS, enlarged pericardium, accumulation of necrotic matter in the amnion, and hypoplastic prosencephalon were observed in both species with all compounds. Microinjection of compounds into the amnion produced higher mortality in mouse and rat, compared to equimolar amounts added to the culture medium. CH<sub>3</sub>OH did not prevent neural tube closure in the rat when microinjected.

#### **CONCLUSIONS:**

HCHO is the most embryotoxic CH<sub>3</sub>OH metabolite and elicits the entire spectrum of lesions produced by CH<sub>3</sub>OH. The VYS serves a general protective role against toxicity and inherent differences in the embryonic metabolism of CH<sub>3</sub>OH may determine species sensitivity."

#### **Citation:**

Hansen, Jason M., Kristi M. Contreras, and Craig Harris. "**Methanol, Formaldehyde, and Sodium Formate Exposure in Rat and Mouse Conceptuses: A Potential Role of the Visceral Yolk Sac in Embryotoxicity.**" Birth Defect Res A Birth Defects Research Part A: Clinical and Molecular Teratology 73.2 (2005)

**Link:**

<http://www.ncbi.nlm.nih.gov/pubmed/15578646>

14.

**Neurobehavioural Effects of Developmental Toxicity**

**Abstract**

"Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants—manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse."

**Citation:**

Bignami, G., G. Laviola, E. Alleva, R. Cagiano, C. Lacomba, and V. Cuomo. "**Developmental Aspects of Neurobehavioural Toxicity.**" *Toxicology Letters* 64-65 (1992): 231-37.

**Link:**

[http://www.thelancet.com/journals/laneur/article/PIIS1474-4422\(13\)70278-3/abstract](http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(13)70278-3/abstract)

15.

**Placental DNA Methylation Related to Both Infant Toenail Mercury and Adverse Neurobehavioral Outcomes**

**Abstract**



**"Background:** Prenatal mercury (Hg) exposure is associated with adverse child neurobehavioral outcomes. Because Hg can interfere with placental functioning and cross the placenta to target the fetal brain, prenatal Hg exposure can inhibit fetal growth and development directly and indirectly.

**Objectives:** We examined potential associations between prenatal Hg exposure assessed through infant toenail Hg, placental DNA methylation changes, and newborn neurobehavioral outcomes.

**Methods:** The methylation status of > 485,000 CpG loci was interrogated in 192 placental samples using Illumina's Infinium HumanMethylation450 BeadArray. Hg concentrations were analyzed in toenail clippings from a subset of 41 infants; neurobehavior was assessed using the NICU Network Neurobehavioral Scales (NNNS) in an independent subset of 151 infants.

**Results:** We identified 339 loci with an average methylation difference > 0.125 between any two toenail Hg tertiles. Variation among these loci was subsequently found to be associated with a high-risk neurodevelopmental profile (omnibus p-value = 0.007) characterized by the NNNS. Ten loci had  $p < 0.01$  for the association between methylation and the high-risk NNNS profile. Six of 10 loci reside in the EMID2 gene and were hypomethylated in the 16 high-risk profile infants' placentas. Methylation at these loci was moderately correlated (correlation coefficients range, -0.33 to -0.45) with EMID2 expression.

**Conclusions:** EMID2 hypomethylation may represent a novel mechanism linking in utero Hg exposure and adverse infant neurobehavioral outcomes."

**Citation:**

Maccani, Jennifer Zeynab Joukhadar, Devin C. Koestler, Barry Lester, E. Andres. Houseman, David A. Armstrong, Karl T. Kelsey, and Carmen J. Marsit. "**Placental DNA Methylation Related to Both Infant Toenail Mercury and Adverse Neurobehavioral Outcomes.**" Environ Health Perspect Environmental Health Perspectives (2015)

**Link:**

<http://ehp.niehs.nih.gov/1408561/>

16.

**Prenatal and perinatal analgesic exposure and autism: an ecological link.**

**Abstract**

## "BACKGROUND:

Autism and Autism Spectrum Disorder (ASD) are complex neurodevelopmental disorders. Susceptibility is believed to be the interaction of genetic heritability and environmental factors. The synchronous rises in autism/ASD prevalence and paracetamol (acetaminophen) use, as well as biologic plausibility have led to the hypothesis that paracetamol exposure may increase autism/ASD risk.

## METHODS:

To explore the relationship of antenatal paracetamol exposure to ASD, population weighted average autism prevalence rates and paracetamol usage rates were compared. To explore the relationship of early neonatal paracetamol exposure to autism/ASD, population weighted average male autism prevalence rates for all available countries and U.S. states were compared to male circumcision rates - a procedure for which paracetamol has been widely prescribed since the mid-1990s. Prevalence studies were extracted from the U.S. Centers for Disease Control and Prevention Summary of Autism/ASD Prevalence Studies database. Maternal paracetamol usage and circumcision rates were identified by searches on Pub Med.

## RESULTS:

Using all available country-level data (n = 8) for the period 1984 to 2005, prenatal use of paracetamol was correlated with autism/ASD prevalence (r = 0.80). For studies including boys born after 1995, there was a strong correlation between country-level (n = 9) autism/ASD prevalence in males and a country's circumcision rate (r = 0.98). A very similar pattern was seen among U.S. states and when comparing the 3 main racial/ethnic groups in the U.S. The country-level correlation between autism/ASD prevalence in males and paracetamol was considerably weaker before 1995 when the drug became widely used during circumcision.

## CONCLUSIONS:

This ecological analysis identified country-level correlations between indicators of prenatal and perinatal paracetamol exposure and autism/ASD. State level correlation was also identified for the indicator of perinatal paracetamol exposure and autism/ASD. Like all ecological analyses, these data cannot provide strong evidence of causality. However, biologic plausibility is provided by a growing body of experimental and clinical evidence linking paracetamol metabolism to pathways shown to be important in autism and related developmental abnormalities. Taken together, these ecological findings and mechanistic evidence suggest the need for formal study of the role of paracetamol in autism."

## Citation:

Bauer, Ann Z., and David Kriebel. "**Prenatal and Perinatal Analgesic Exposure and Autism: An Ecological Link.**" *Environmental Health Environ Health* 12.1 (2013)

## Link:

17.

## **Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ**

### **Abstract**

**Background:** Although prenatal methylmercury exposure has been linked to poorer intellectual function in several studies, data from two major prospective, longitudinal studies yielded contradictory results. Associations with cognitive deficits were reported in a Faroe Islands cohort, but few were found in a study in the Seychelles Islands. It has been suggested that co-exposure to another contaminant, polychlorinated biphenyls (PCBs), may be responsible for the positive findings in the former study and that co-exposure to nutrients in methylmercury-contaminated fish may have obscured and/or protected against adverse effects in the latter.

**Objectives:** We aimed to determine the degree to which co-exposure to PCBs may account for the adverse effects of methylmercury and the degree to which co-exposure to docosahexaenoic acid (DHA) may obscure these effects in a sample of Inuit children in Arctic Québec.

**Methods:** IQ was estimated in 282 school-age children from whom umbilical cord blood samples had been obtained and analyzed for mercury and other environmental exposures.

**Results:** Prenatal mercury exposure was related to poorer estimated IQ after adjustment for potential confounding variables. The entry of DHA into the model significantly strengthened the association with mercury, supporting the hypothesis that beneficial effects from DHA intake can obscure adverse effects of mercury exposure. Children with cord mercury  $\geq 7.5$   $\mu\text{g/L}$  were four times as likely to have an IQ score  $< 80$ , the clinical cut-off for borderline intellectual disability. Co-exposure to PCBs did not alter the association of mercury with IQ.

**Conclusions:** To our knowledge, this is the first study to document an association of prenatal mercury exposure with poorer performance on a school-age assessment of IQ, a measure whose relevance for occupational success in adulthood is well established. This association was seen at levels in the range within which many U.S. children of Asian-American background are exposed."

### **Citation:**

Jacobson, Joseph L., Gina Muckle, Pierre Ayotte, Éric Dewailly, and Sandra W. Jacobson.

"Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ." *Environ Health Perspect Environmental Health Perspectives* (2015)

**Link:**

<http://ehp.niehs.nih.gov/1408554/>

18.

**Therapeutic roles of curcumin: lessons learned from clinical trials.**

**Abstract**

"Extensive research over the past half century has shown that curcumin (diferuloylmethane), a component of the golden spice turmeric (*Curcuma longa*), can modulate multiple cell signaling pathways. Extensive clinical trials over the past quarter century have addressed the pharmacokinetics, safety, and efficacy of this nutraceutical against numerous diseases in humans. Some promising effects have been observed in patients with various pro-inflammatory diseases including cancer, cardiovascular disease, arthritis, uveitis, ulcerative proctitis, Crohn's disease, ulcerative colitis, irritable bowel disease, tropical pancreatitis, peptic ulcer, gastric ulcer, idiopathic orbital inflammatory pseudotumor, oral lichen planus, gastric inflammation, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, diabetic nephropathy, diabetic microangiopathy, lupus nephritis, renal conditions, acquired immunodeficiency syndrome,  $\beta$ -thalassemia, biliary dyskinesia, Dejerine-Sottas disease, cholecystitis, and chronic bacterial prostatitis. Curcumin has also shown protection against hepatic conditions, chronic arsenic exposure, and alcohol intoxication. Dose-escalating studies have indicated the safety of curcumin at doses as high as 12 g/day over 3 months. Curcumin's pleiotropic activities emanate from its ability to modulate numerous signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, NF- $\kappa$ B, cyclooxygenase-2, 5-LOX, STAT3, C-reactive protein, prostaglandin E(2), prostate-specific antigen, adhesion molecules, phosphorylase kinase, transforming growth factor- $\beta$ , triglyceride, ET-1, creatinine, HO-1, AST, and ALT in human participants. In clinical trials, curcumin has been used either alone or in combination with other agents. Various formulations of curcumin, including nanoparticles, liposomal encapsulation, emulsions, capsules, tablets, and powder, have been examined. In this review, we discuss in detail the various human diseases in which the effect of curcumin has been investigated."

**Citation:**

Gupta, Subash C., Sridevi Patchva, and Bharat B. Aggarwal. "Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials." *The AAPS Journal* AAPS J 15.1 (2012): 195-218.

**Link:**

<http://ehp.niehs.nih.gov/1408554/>

19.

### **Water fluoridation to prevent tooth decay**

#### **Abstract**

"Dental caries is a major public health problem in most industrialised countries, affecting 60% to 90% of school children. Community water fluoridation was initiated in the USA in 1945 and is currently practised in about 25 countries around the world; health authorities consider it to be a key strategy for preventing dental caries. Given the continued interest in this topic from health professionals, policy makers and the public, it is important to update and maintain a systematic review that reflects contemporary evidence."

#### **Citation:**

Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny A. "**Water fluoridation for the prevention of dental caries**". Cochrane Database of Systematic Reviews 2015, Issue 6.

#### **Link:**

[http://www.cochrane.org/CD010856/ORAL\\_water-fluoridation-prevent-tooth-decay](http://www.cochrane.org/CD010856/ORAL_water-fluoridation-prevent-tooth-decay)