Articles You Might Have Missed

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Energy drinks • Metal-on-metal hip replacements

Argos M, Kalra T, Rathouz PJ et al. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. Lancet 2010; 376:252–8

Background: Arsenic exposure from contaminated ground-water is a worldwide public health concern. An estimated 35–77 million people in Bangladesh have been chronically exposed to inorganic arsenic after installation of millions of deep tube wells intended to provide a pathogen-free water supply. Prospective investigation of an association between arsenic exposure and mortality with individual level data has not been performed.

Research question: Is chronic arsenic exposure, as measured by repeated individual total urinary arsenic levels, associated with increased all-cause and chronic-disease mortality?

Methods: A prospective cohort study was performed on adult (age 18–75 years) residents of Araihaaz, Bangladesh. Study participants were recruited over a 2-year period and follow-up was performed biennially. Trained physicians

blinded to arsenic concentrations in local well water utilized a verbal autopsy questionnaire and collected clinical samples. Well water was analyzed for arsenic concentration. A Cox proportional hazards model was used to analyze hazard ratios for mortality.

Results: Eleven thousand seven hundred forty-six participants were recruited over the study period. Mean follow-up time was 6.5 years. Four hundred seven deaths were detected from the beginning of recruitment to the end of the follow-up period. Multivariate-adjusted hazard ratios showed an increased risk of mortality at all concentrations of arsenic in well water. A one-quartile increase in arsenic concentration in well water was associated with 15% increase in all-cause mortality (95% CI 1.05–1.26). Recent change in exposure did not have a significant effect on mortality. Investigators estimated that over 20% of deaths could be attributed to elevated arsenic concentrations in drinking water.

Conclusion: Chronic exposure to arsenic in well water was associated with increased all-cause and chronic-disease mortality.

Critique: The method employed for measuring the concentration of urinary arsenic levels did not allow for speciation; therefore, estimation of nontoxic organic arsenic compounds such as arsenobetaine was unavailable. Arsenic dose was calculated in part by employing self-reported estimates of water intake. Furthermore, assigning the cause of death relied on accurate description of chronic diseases and symptoms in the deceased by relatives or neighbors. A longer follow-up period might better show the effects of remediation efforts, as subjects with decreasing urinary arsenic levels did not show a similar decline in mortality risk.

Implication for toxicologists: This study highlights the consequences of an ongoing public health crisis. Strategies

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for the remediation of elevated arsenic in drinking water while providing a safe water supply are needed. Continued follow-up of this cohort may further clarify the effects of remediation efforts as arsenic exposure decreases.

Mozaffarian et al. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. *N Engl J Med.* 2011; 364:1116–25

Background: Moderate consumption of fish may be cardioprotective. However, exposure to methylmercury from fish has been potentially linked to an increased risk in cardiovascular disease.

Research question: Does exposure to dietary mercury increase the risk of cardiovascular disease?

Methods: Three thousand four hundred twenty-seven participants with cardiovascular incidents were identified from two US cohorts: the Health Professionals Follow-up Study and the Nurses' Health Study. Mercury concentrations from the stored toenail clippings of study participants and of a matched risk set sample control group were measured with the use of neutron activation analysis. Validated questionnaires were used to assess other demographic characteristics, cardiovascular risk factors, fish consumption, and lifestyle habits. Associations between mercury exposure and incident cardiovascular disease were evaluated with the use of conditional logistic regression.

Results: Median toenail mercury concentrations were 0.23 µg/g in the case participants and 0.25 µg/g in controls. Mercury exposure was not correlated with a higher risk of cardiovascular disease. Relative risks were: coronary heart disease, 0.85 (95% CI, 0.69 to 1.04; $P=0.10$ for trend); stroke, 0.84 (95% CI, 0.62 to 1.14; $P=0.27$ for trend); and total cardiovascular disease, 0.85 (95% CI, 0.72 to 1.01; $P=0.06$ for trend).

Conclusion: There was no evidence of any clinically relevant adverse effects of mercury exposure on coronary heart disease, stroke, or other cardiovascular disease among US adults at the exposure levels seen in this study.

Critique: The study methodology was generally sound. However, the analysis did not differentiate organic from inorganic mercury. Thus, the authors essentially presume that the source of mercury exposure was dietary. There are some factors that limit the generalization of the study findings. First, mercury concentrations were modest in both cohorts and controls. Second, the cohorts were composed of very distinct population of subjects that do not represent the general population.

Implication for toxicologists: This study provides some evidence that subjects with moderate fish consumption that have modest concentrations of mercury are not at increased risk of cardiovascular disease. Further investigation is warranted.

Seifert SM, Schaechter JL, Hershorin ER, et al. Health Effects of Energy Drinks on Children, Adolescents, and Young Adults. *Pediatrics* 2011; 127:511–28

Background: Energy drinks are the fastest growing beverages in the USA with sales expected to surpass US \$9 billion in 2011. These drinks contain caffeine, taurine, guarana, vitamins, herbal supplements, and sugar/sweeteners and are marketed, especially to the youth, to improve energy, weight loss, stamina, athletic performance, and concentration.

Research question: There are multiple goals in this literature review but especially important questions for the toxicologist include: What are the current data reported to poison centers regarding caffeine and energy drink overdoses? What are the potential problems of energy drinks among children and adolescents?

Methods: This is a review of the current literature and internet sources using PubMed and Google. Search terms included “energy drink”, “sports drink”, “guarana”, “caffeine”, “taurine”, “ADHD”, “diabetes”, “children”, “adolescents”, “insulin”, “eating disorders”, and “poison control center”.

Results: Eighty-one of the 121 (67%) references were from the primary literature. The large majority of the information came from the USA. With respect to poison center data, the US poison control centers (PCCs) have not specifically tracked the prevalence of energy drinks (until recently) rather exposures were coded as “caffeine” or “multi-substance exposure”. During 2006–2008, there were 15,996 calls to PCCs to report caffeine toxicity. Germany has tracked energy drinks since 2002 and has reported outcomes that include liver damage, kidney failure, respiratory disorders, agitation, seizures, psychotic disorders, and rhabdomyolysis. Cardiac disorders such as dysrhythmias, hypertension, heart failure, and death have also been reported.

Because of the risk for cardiac dysrhythmias, high doses of caffeine can exacerbate cardiac conditions that children may have such as ion channelopathies and hypertrophic cardiomyopathy. Similarly, children who are being treated with stimulants for ADHD (approximately 2.5 million in USA) may be at an increased risk of cardiac events when energy drinks are consumed.

Conclusion: The authors felt that toxicity surveillance of energy drinks in the USA should be improved. Even though the long-term consequences of these products have yet to be determined, exposure to high levels of caffeine, guarana, and taurine may put some children at risk for developing serious adverse health effects. Screening and routine counseling by pediatricians were encouraged.

Critique: This extensive literature review provides the reader an opportunity to appreciate the health effects (known and unknown) of energy drinks. While the focus of this review was not on toxicity, it did highlight the challenges faced by PCCs on monitoring and tracking energy drink toxicity, especially in the pediatric population.

Implication for toxicologists: Energy drinks are increasing in popularity with our youth. This review identified the need to be aware of the potential adverse events and consequences of consumption, especially in children with preexisting conditions. Energy drink consumption screening should be considered when evaluating children and young adults with apparent stimulant symptoms.

Langton DJ, Jameson SS, Joyce TJ et al. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: a consequence of excess wear. J Bone Joint Surg [Br]. 2010; 92-B:38–46

Background: There is an increased concern and litigation related to elevated cobalt and chromium levels in patients with metal-on-metal (MoM) hip replacements.

Research question: This study evaluated the failure rate of chromium (Cr) and cobalt (Co) containing hip-resurfacing prostheses and its association with metal debris.

Methods: This was a prospective study that analyzed 660 consecutive MoM resurfacings using Birmingham hip resurfacing (BHR) and articular surface replacement (ASR) devices. It also included ASR total hip replacements. Clinical outcomes (including Harris hip scores and UCLA activity scores), radiographical findings, routine blood testing, and metal ion levels were followed on all patients. Those patients requiring revision had explant pathology studies and lymphocyte transformation testing for metal ion sensitivity.

Results: Of the original 660 enrolled patients, 17 required revision. ASR resurfacing and ASR THR prostheses had an increased failure rate relative to BHR hips (3% and 6% vs. 0%). Data analysis revealed associations between failed joints and smaller ASR components, suboptimal acetabular orientation, and elevated blood Co and Cr levels. Histological

analysis of explants revealed histiocyte infiltration and Cr > Co sequestration in the joint tissue. Twelve patients requiring joint revision underwent lymphocyte stimulation test and only one showed mild reaction to Cr and Co.

Conclusions: Smaller components and suboptimal acetabular orientation with ASR hip prostheses are associated with higher than expected joint failure rates and elevated blood metal levels.

Critique: This paper represents a thorough analysis attempting to identify the pathophysiology of MoM joint failure and elevated blood metal levels. The positive histological analysis generates the chicken vs. the egg question: Is the inflammation a response to breakdown of the hip surface or does it cause the breakdown? There are three outcomes from this study arguing against an immune-initiated breakdown. First, there does not appear to be a difference in Cr and Co levels between ASR (highest failure rate) and BHR (lowest failure rate). Secondly, only one patient showed mild metal reactivity to Cr and Co in the lymphocyte test. Thirdly, all of the failures had normal ESR and CRP testing. These data suggest that mechanical failure is the primary cause of hip failures. There are weaknesses in the study. Unfortunately, only 17 patients were ultimately analyzed. The authors focused on local symptoms only and there was no attempt to identify possible systemic effects of the elevated metal ions. There is a significant overlap of metal levels between groups. Details of the statistical analysis are missing.

Implication for toxicologists: Elevated metal ion levels appear to be associated more with mechanical failure. Immunogenic causes may have a smaller role than previously thought. Unfortunately, the clinical implications of elevated cobalt and chromium levels are still unclear.