Environmental Stressors in Disease and Implications for Human Health

Boston Marriott Long Wharf Hotel
296 State Street, Boston, MA 02109
October 26 – 29, 2014
endocrine.org/pptox

Poster Instructions and Abstracts

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Poster PRESENTER INSTRUCTIONS

Poster presentations will take place on Monday – Tuesday, October 27-28, in the Grand Ballroom, Salon G.

Poster Mounting/Removal

► Abstracts scheduled for presentation in poster sessions are grouped by category, numbered, and will be listed in the Program and Agenda Handout. All poster presenters must be registered to attend PPTOX IV.

► To give maximum viewing time, your poster must be mounted in the morning of your presentation day.
  o  **Mount posters between 7:30 – 8:30 AM**
  o  Only mount your poster on your presentation day
  o  Pushpins will be provided. Please avoid alternative adhesives.
  o  Remove your poster any time after 6:30 PM

► You are responsible for your poster carriers, tubes, or mailers.

► The poster hall (Grand Ballroom, Salon G) will be accessible throughout the conference days (8:30 AM – 6:30 PM), however, the agenda includes specific times for poster sessions. Whenever possible, please attend your poster to address attendee comments and questions during these times. You are not required to be present the entire duration of these sessions
  o  Lunch Poster Session, 12:00 – 1:30 PM
  o  Evening Poster Session, 5:00 – 6:30 PM

Poster Printing Format

The poster board display area is **3’ 9” high by 7’ 9” wide (1.14 m high by 2.36 m wide)**.

You may prepare a poster that is **smaller**, but

**DO NOT EXCEED THESE DIMENSIONS.**

Include the following:

- Poster number
- Title (use your submitted title)
- Co-author information
- Underline presenting author name
- Complete abstract as submitted

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**MON-25**

**The Effects of Lotion on Dry Skin**

John Doe, Mary Smith*, Peter Jones*

*University of Moisturizing, Washington DC

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3’ 9” in or 1.14 m high

7’ 9” or 2.36 m wide

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Poster Tips and Notes

The top of your poster should include the presentation number of your abstract (as noted in your confirmation letter), the presentation title, and authors with the presenting author's name underlined.

- Title lettering for this section should be at least 1” (2.5 cm) high.
- Use large print, at least 1/2” (1.8 cm) high in other cases.
- Illustrations must be made beforehand and be able to be read by interested scientists from distances of 3-5 feet (1-2 meters).
- Charts, drawings, and illustrations should be more heavily drawn than those prepared for slides.
- Do not mount posters on heavy board or posterboard material.
- A short and legible "Introduction" and a "Summary of Conclusions" are helpful for attendees.
- A copy of your abstract (typed in large type) should be included in some format for when you are not in attendance.
- Keep text and figure legends short, but do not omit them.
- Keep illustrative material simple. Simple use of color can add emphasis effectively.
- Pushpins will be supplied for mounting posters to the boards.
- Use matte material for printing when possible (avoid glossy because of glare).
Environmental Stressors in Disease and Implications for Human Health
October 26 – 29, 2014 | Boston Marriott Long Wharf Hotel, Boston, MA
296 State Street, Boston, Massachusetts 02109
Phone: +1.617.227.0800

Boston Long Wharf Marriott Floor Plan

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**Endocrine Society**

**October 23, 2014 | Boston, MA**
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<td>Syed Mushfiqur Rahman</td>
<td>Other: Toxicology and Child Health</td>
<td>Effects of early life manganese exposure through drinking water on child growth and development</td>
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<tr>
<td>Mark Miller, MD, MPH</td>
<td>Other: Translating science</td>
<td>Story of Health multi-media eBook – Using storytelling to translate science for health promotion and disease prevention</td>
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<td>Nicole Acvedo, MS, PhD</td>
<td>Reproductive System</td>
<td>Prenatal exposure to environmentally relevant levels of bisphenol decreases reproductive success by affecting multiple targets</td>
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<td>Jennifer J Adibi, MPH, ScD</td>
<td>Reproductive System</td>
<td>Placental human choric gonadotropin is associated with sex-specific development and the response to the endocrine disruptor mono-n-butyl phthalate.</td>
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<td>Michal Adir</td>
<td>Reproductive System</td>
<td>Phthalate Metabolite Levels in Follicular Fluid among Fertile and Infertile Women</td>
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<td>Jason L. Blum, PhD</td>
<td>Reproductive System</td>
<td>Inhalation of concentrated ambient particulate matter by pregnant mice leads to adverse obstetric outcomes associated with particular exposure windows</td>
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<td>Carle Breton, ScD, MPH</td>
<td>Reproductive System</td>
<td>Prenatal traffic-related air pollution influences miRNA expression in sorted cord blood</td>
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<td>Maribel Casas, PhD</td>
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<td>Maternal occupational exposure to Endocrine Disrupting Chemicals across Europe and Birth Outcomes</td>
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<td>Maribel Casas, PhD</td>
<td>Reproductive System</td>
<td>Exposure to Bisphenol A and Phthalates during Pregnancy and Fetal Growth</td>
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<td>Christine Dobson</td>
<td>Reproductive System</td>
<td>Associations of cord blood cadmium with placental gene expression &amp; fetal growth indices in a Bangladesh birth cohort</td>
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<td>Christine Dobson, SD</td>
<td>Reproductive System</td>
<td>Cord blood cadmium and fetal growth indices in a Bangladesh birth cohort</td>
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<td>Albert Donnay</td>
<td>Reproductive System</td>
<td>High odds ratios for hyperemesis gravidarum associated with exposure to carbon monoxide sources and multi-sensory sensitivity during pregnancy</td>
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<td>Rebecca Dzubow, MPH, MEM</td>
<td>Reproductive System</td>
<td>Biomonitoring Trends in Women of Childbearing Age and Potential Prenatal Programming Effects, from EPA’s America’s Children and the Environment</td>
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<td>Jennifer A Emond, PhD</td>
<td>Reproductive System</td>
<td>The influence of arsenic exposure on infant birth size by maternal weight status among a sample of women in the Northeastern United States.</td>
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<td>Kelly Ferguson</td>
<td>Reproductive System</td>
<td>Urinary phthalate metabolites and bisphenol-A in association with circulating biomarkers of placental function across pregnancy</td>
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<td>Jennifer L Freeman, PhD</td>
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<td>A developmental origin of adult reproductive dysfunction in the zebrafish associated with an embryonic exposure to the herbicide atrazine.</td>
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<td>Thorhallur Ingi Halldorsson, PhD</td>
<td>Reproductive System</td>
<td>Does variation in fetal growth rate affect maternal concentrations of perfluorooalkyl acids during pregnancy?</td>
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<td>Molly Kile</td>
<td>Reproductive System</td>
<td>Using structural equation models to examine the association between prenatal arsenic exposure, maternal health, and birth weight</td>
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<td>Birgitte Lindeman, PhD</td>
<td>Reproductive System</td>
<td>Diet-induced obesity increases the spermatozoal toxicity of acrylamide in the absence of oxidative stress</td>
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<td>Anderson J Martino-Andrade</td>
<td>Reproductive System</td>
<td>Manipulation of pre- and postnatal androgen environments and male anogenital distance in rats</td>
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<td>Maria Skiatum Pellersen, MSC, PhD</td>
<td>Reproductive System</td>
<td>Spermatogenic capacity in fertile men with high exposure to polychlorinated biphenyls</td>
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<td>Rick Pilsker, PhD, MPH</td>
<td>Reproductive System</td>
<td>Rapid Method of Sperm DNA Extraction for Epigenetic and Genetic Studies</td>
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<td>Anna Z Pollack, PhD, MPH</td>
<td>Reproductive System</td>
<td>Urinary paraben exposure, reproducibility, and reproductive hormones in premenopausal women</td>
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<td>Christy Porucznik, PhD, MSPH</td>
<td>Reproductive System</td>
<td>The Home Observation for Periconceptional Exposures (HOPE) Study—a Prospective, Pre-conception Cohort</td>
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<td>Tracy Punshon, PhD</td>
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<td>Placental arsenic concentrations in relation to both maternal and infant biomarkers of exposure in a US cohort</td>
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<td>Pherusu Tarapore, PhD</td>
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<td>High fat olive oil, not butter, has a protective role in bisphenol A-induced impaired spermatogenesis</td>
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<td>Hanna M Vesterven, PhD, MPH</td>
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<td>Fetal growth and maternal glomerular filtration rate: a systematic review</td>
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<td>Deborah Watkins, PhD, MPH</td>
<td>Reproductive System</td>
<td>Associations between urinary phent and paraben concentrations and markers of oxidative stress and inflammation among pregnant women in Puerto Rico</td>
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<td>Abby G Wenzel, BS, MS</td>
<td>Reproductive System</td>
<td>Assessing the prevalence of phthalate metabolites in a population of pregnant women</td>
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<td>Marya G. Zatkiew, MD, MMS</td>
<td>Reproductive System</td>
<td>Reproductive Environmental Health Education for OB/GYN Specialists</td>
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<td>Caroline Serrano-Nascimento</td>
<td>Thyroid</td>
<td>Maternal exposure to iodine excess throughout pregnancy &amp; lactation induces hypothyroidism in adult male rat offspring</td>
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<td>Vinicus Careira, DVM, DACVP</td>
<td>Cardiovascular System</td>
<td>Cardiomyocyte-specific ablation of the aryl hydrocarbon receptor rescues the Nio2-5 haploinsufficiency cardiac phenotype</td>
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<td>Leda Chatzi</td>
<td>Cardiovascular System</td>
<td>Association of prenatal exposure to persistent organic pollutants with cardiometabolic traits in early childhood</td>
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<td>Susan L Whitemore, PhD</td>
<td>Cardiovascular System</td>
<td>Early PAH Exposure Impacts Cardiac Function in Xenopus laevis</td>
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<td>Changcheng Zhou, PhD</td>
<td>Cardiovascular System</td>
<td>Bisphenol A Increases Atherosclerosis Mediated by the Human PXR</td>
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<td>Kirtan Kaur, BS</td>
<td>Cardiovascular System</td>
<td>Assessing fetal size and cardiac function using ultrasound biomicroscopy- echocardiography after maternal inhalation exposure to PM2.5 in mice</td>
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<td>Rebecca N Bauer, PhD</td>
<td>Immune System</td>
<td>In Utero Arsenic and Cadmium Exposure is Associated with Altered T Lymphocyte Populations in Infant Cord Blood</td>
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<td>Libeth Boule, MS</td>
<td>Immune System</td>
<td>Developmental activation of the AHR leads to context dependent changes in CD4+ T cell responses later in life</td>
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<td>Hyunk Choi</td>
<td>Immune System</td>
<td>Airborne Benzo(a)pyrene, Lipid Peroxidation and Risk of Comorbid Condition of Asthma and Obesity in Children</td>
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<td>Hyunk Choi</td>
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<td>Modification of Ambient Benzo(a)pyrene Effects on Childhood Asthma by Single Nucleotide Polymorphisms</td>
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<td>Jessica L. Meyers, BS</td>
<td>Immune System</td>
<td>Persistent changes in dendritic cell function following developmental activation of the aryl hydrocarbon receptor</td>
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<td>Christina M Post</td>
<td>Immune System</td>
<td>Developmental exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has implications for multi- and transgenerational effects on antiviral immunity</td>
<td>MON-11</td>
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<td>Everett R Tate, BA</td>
<td>Immune System</td>
<td>Placental health is affected by Aryl hydrocarbon receptor-dependent regulation of metabolic and oxidative pathways.</td>
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<td>Philippe Grandjean</td>
<td>Immune System</td>
<td>Immunotoxic impact at age 7 years of current and long-term childhood exposure to perfluorinated compounds</td>
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<td>Thorhallur I Halldorsson</td>
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<td>Maternal concentrations of persistent organochlorine pollutants and airway obstruction in the offspring at 20 years of age</td>
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<td>carsten Helmann, MD, DMSc</td>
<td>Immune System</td>
<td>Possible mechanism for perfluorinated compound-induced inhibition of antibody production in children: Reduction of NFκB activity and IkB degradation.</td>
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<td>Margaret R Karagas, PhD</td>
<td>Immune System</td>
<td>Early childhood infections and symptoms of allergy and atopy in relation to in utero arsenic exposure in a US pregnancy cohort</td>
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<td>Amalie Timmermann, MSc</td>
<td>Immune System</td>
<td>Association between children’s exposure to perfluorinated compounds and an asthma risk modified by MMR vaccination</td>
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<td>Masakazu Umezawa, PhD</td>
<td>Immune System</td>
<td>Effect of maternal exposure to carbon black nanoparticle during early gestation on the thymus and spleen of neonatal mouse</td>
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<td>Ann Z. Bauer, MS</td>
<td>Nervous System</td>
<td>Paracetamol/Acetaminophen Exposure and Autism Spectrum Disorder-An Epigenetic Link?</td>
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<tr>
<td>Ann Z Bauer, MS, BS</td>
<td>Nervous System</td>
<td>Is Paracetamol/Acetaminophen a causal factor in the Etiology of Autism Spectrum Disorder? A review and research synthesis.</td>
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<td>Jacy Bravo</td>
<td>Nervous System</td>
<td>The role of prenatal exposures in modulation of neurodevelopment using the SHANK3e4-9/+ mutant mouse model</td>
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<td>Mary C Catanese</td>
<td>Nervous System</td>
<td>Beyond a means of exposure: an integrated view of maternal behavior and brain for toxicology research</td>
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<td>Stephanie Donauer, PhD, MS</td>
<td>Nervous System</td>
<td>An observational study measuring the impact of low-level gestational exposure to organophosphate pesticides on cognition during early childhood</td>
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<td>Virmi Dookhrun, MSc</td>
<td>Nervous System</td>
<td>Assessing environmental risk associated with mercury in Mauritius</td>
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<td>Lilah Glazer, PhD</td>
<td>Nervous System</td>
<td>Delayed effects of embryonic exposure to low levels of PCB-126 on adult zebrafish behavior</td>
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<td>Shotaro Kawaoze</td>
<td>Nervous System</td>
<td>Effects of prenatal exposure to titanium dioxide nanoparticle on DNA methylation and gene expression profile in the brain of mouse</td>
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<td>Byungmi Kim</td>
<td>Nervous System</td>
<td>Selenium alters the reproductive and developmental neurotoxicity of mercury : MOCEH (Mothers and Children’s Environmental Health) study</td>
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<td>Jinyoung Lee, MPH</td>
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<td>Sex-specific expression patterns of genes associated with Alzheimer’s disease during normal aging and with a developmental lead exposure in zebrafish</td>
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<td>Ana Maria Mora, MD, PhD</td>
<td>Nervous System</td>
<td>Prenatal exposure to manganese and neurodevelopment at 12 months of age in the ISA study</td>
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<td>Alison G Paquette</td>
<td>Nervous System</td>
<td>Placental epigenetic patterning of cortisol response genes is associated with infant neurodevelopmental outcomes and maternal environmental</td>
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<td>Zana Percy</td>
<td>Nervous System</td>
<td>Gestational Exposure to Phthalates and Gender-Related Play Behaviors in Typically Developing 7.5-9 Year Old Children</td>
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<td>Kayla M Quinnies</td>
<td>Nervous System</td>
<td>Dose-response study of di-(2ethylhexyl) phthalate (DEHP): androgenic and anti-androgenic actions</td>
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<td>Michael J Rudy, BS, MS</td>
<td>Nervous System</td>
<td>Embryonic iron deficiency alters adult neural structure</td>
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<td>Sara E Wirbsky</td>
<td>Nervous System</td>
<td>Developmental origins of neurotransmitter and transcriptome alterations in adult female zebrafish exposed to atrazine during embryogenesis</td>
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<td>Helle R Andersen</td>
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<td>Occupational pesticide exposure in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age</td>
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<td>Stephan Boeseoreilly</td>
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<td>Inorganic mercury as a potential neurodevelopmental toxin - exposure of breast fed infants in a small-scale gold mining area in Zimbabwe</td>
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<td>Rebecca M Nachman, PhD, MPH</td>
<td>Other: Endocrine Disrupting Compounds</td>
<td>Bisphenol A Exposure and Metabolism in Healthy Full-Term Neonates in Baltimore, Maryland</td>
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<td>Peter Y Bai, BSc, MSc</td>
<td>Other: Endocrine Disruptive Chemicals</td>
<td>The association of socio-demographic status, lifestyle factors and dietary patterns with fetal urinary phthalates in Australian men</td>
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<td>Caterina Vacchi-Suzzi</td>
<td>Other: Environmental Exposure</td>
<td>Temporal variability of cadmium in urine of prospective parents from the HOPE Study (UT)</td>
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<td>Flemming Nielsen, MSc, PhD</td>
<td>Other: Environmental toxicants</td>
<td>Distribution of perfluorinated compounds in blood compartments during prenatal exposure</td>
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<td>Andres Cardenas</td>
<td>Other: Epigenetics</td>
<td>In Utero Arsenic Exposure and Epigenome-Wide Association in Placenta, Artery and HUVEC</td>
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<td>Katherine E King, PhD, MA</td>
<td>Other: epigenetics</td>
<td>Air Pollutants Predict both DNA Methylation of Fetal Growth Genes and Birth Outcomes</td>
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<td>Karin B. Michels, ScD, PhD</td>
<td>Other: Epigenetics</td>
<td>Sexually Dimorphic Influence of Phthalates and Phenols on the Regulation of Genes Implicated in Neurodevelopment</td>
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<td>Stephan Bose-O'Reilly</td>
<td>Other: Exposome research</td>
<td>From chromosome to exposome - the HEALS approach to health and environment-wide associations</td>
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<td>Shoheh F Farzan, PhD</td>
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<td>Association between maternal urinary arsenic and infant cord blood inflammatory marker levels in New Hampshire</td>
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<td>Howard Walter Mielke</td>
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<td>Soil Mielke as a Reservoir of Environmental Stressors that influence Clinical Health, Human Diseases, and Preeclampsia/Eclampsia</td>
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<td>Christopher Kassolis</td>
<td>Other: Mixture Effects</td>
<td>Endocrine Disrupting Activity of Hydraulic Fracturing Chemicals and Health Outcomes Following Prenatal Exposure in Mice</td>
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<td>Thomas F Webster, DSc</td>
<td>Other: Mixtures of endocrine disruptors</td>
<td>Biological effects of mixtures of endocrine disruptors: The “synergy” of new developments in toxicology, epidemiology and exposure science</td>
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<td>Carl F. Crano, PhD, MSL</td>
<td>Other: Policy research/public health</td>
<td>Dimensions of Injustice in the Developmental Origins of Disease</td>
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<td>Susan Makris</td>
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<td>Are Standard Testing Guidelines Adequate to Screen Chemicals for Prenatal Programming of Toxicological Response?</td>
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<td>Sasha Adkins, MPH</td>
<td>Other: Risk perception</td>
<td>Perceptions of risk of in utero exposure to bisphenol-A</td>
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<td>Search for the signaling pathways involved in the hepatic tumor increase in the F2 male C3H mice born to gestationally arsenite-exposed F0 females</td>
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<td>Joshua F Gilens, BS</td>
<td>Diabetes &amp; Metabolism</td>
<td>Effects of Developmental Exposure to Nonylphenol and alpha-Zeaxanopil on Adult Energy and Glucose Homeostasis</td>
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<td>Nathaniel W Snyder, PhD, MPH</td>
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<td>Christine Dalgaard, PhD, MSc</td>
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<td>Low prenatal vitamin D exposure associated with increased risk of prediabetes in Faroese adolescents</td>
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<td>Vasanthi Padmanabhan</td>
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<td>Alexander Suworov, PhD</td>
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Cardiomyocyte-specific ablation of the aryl hydrocarbon receptor rescues the Nkx2-5 haploinsufficiency cardiac phenotype

Vinicius Carreira, DVM, DACVP, University of Cincinnati; Hisaka Kurita, PhD, Gifu Pharmaceutical University, Japan; Yunxia Fan, MS, University of Cincinnati, US; Min Jang, University of Cincinnati, US; Sheryl E Koch, University of Cincinnati, US; Mindi Naticchioni, University of Cincinnati, US; Jack Rubinstein, MD, University of Cincinnati, US; Alvaro Puga, PhD, University of Cincinnati, US

The Theory of the Developmental Origins of Health and Disease proposes that the environment encountered during fetal life shapes the organism's structure, function and metabolism. Accordingly, damage resulting from environmental stress, such as exposure to pollutants during fetal life, may be at the heart of congenital and adult onset diseases. Infants born to mothers exposed to dioxin-like compounds, which exert their effects by binding to the aryl-hydrocarbon receptor (AHR), exhibit a higher incidence of congenital heart disease, the most common type of human birth defect, the leading cause of neonatal/infant mortality, and a major source of adult cardiac insufficiency. In humans and mice, loss-of-function Nkx2-5 mutations lead to protein haploinsufficiency, an established etiology of human congenital heart defects and cardiomyopathies. We find that full-body ablation of the Ahr gene in mice or exposure to dioxin in utero cause a decreased of cardiac Ahr and Nkx2-5 expression and altered transcriptome in the developing heart, as well as mitochondrial dysfunction, abnormal myocardial structure, pathological cardiac hypertrophy, abnormal echocardiographic and blood pressure parameters, and cardiovascular challenge intolerance in the adult. Knock-in of the cre recombinase gene into an Nkx2-5 allele produces hemizygosity with resulting variably penetrant progressive cardiomyopathy due to haploinsufficiency. To determine the role of AHR in the penetrance of the pathological Nkx2-5 haploinsufficiency phenotype we used Nkx2-5+/cre mice to generate Nkx2-5+/creAhrfx/fx mice with a resulting cardiomyocyte-specific deletion of the Ahr gene. Echosonographic analyses of these mice, performed at regular intervals up to 9 months of age, revealed age-dependent decreases of ejection fraction and other critical indices of cardiac function, with increased left ventricular mass and increased systolic and diastolic volumes in haploinsufficient Nkx2-5+/creAhr+/+ mice, harboring a diploid complement of the wild type Ahr+ allele, but not in Nkx2-5+/creAhrfx/fx, in which both copies of the Ahr had been deleted in cardiomyocytes. Our data show that cardiomyocyte-specific deletion of the Ahr gene in this model rescues the abnormal cardiac function due to Nkx2-5 haploinsufficiency, suggesting that this pathological phenotype is a result of AHR-NKX2-5 interplay. These findings establish AHR-NKX2-5 gene-gene-environment interactions as potential targets of perinatal environmental exposures, underscoring significant implications to human health and disease. Supported by NIEHS R01006273.

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**Abstract type:** Population Research  
**Category:** Cardiovascular System  
**Keywords:** Birth Cohort, Epidemiology, Prenatal

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**Association of prenatal exposure to persistent organic pollutants with cardiometabolic traits in early childhood**  
**Leda Chatzi, University of Crete, School of Medicine**;  
**Marina Vafeiadi, Department of Social Medicine, Faculty of Medicine, University of Crete, Greece**

**Background:** Prenatal exposure to endocrine disrupting chemicals such as persistent organic pollutants (POPs) may increase risk of obesity later in life. In adults, exposure to these environmental chemicals has also been associated with other cardiovascular traits such as higher blood pressure and high serum lipid levels. However, there are no studies so far on the effect of prenatal POP exposure on offspring cardiovascular traits other than BMI.

**Aims:** We examined whether in utero exposure to current low levels of different POPs is associated with offspring cardiometabolic risk at 4 years in the RHEA mother-child cohort in Crete, Greece.

**Methods:** We included 689 mothers and their children from the Rhea study. Mothers were interviewed and blood samples collected during the first trimester of pregnancy. Concentrations of several polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethene (DDE), and hexachlorobenzene (HCB) were determined in first trimester maternal serum by triple quadrupole mass spectrometry. Systolic (SBP) and diastolic (DBP) blood pressure levels were measured on the right arm using an automatic oscillometric device at 4 years of age. Child lipids (total cholesterol and high-density lipoprotein cholesterol [HDL-C]), leptin, adiponectin and C-reactive protein (CRP) levels were measured in non-fasting blood samples.

**Results:** Geometric mean HCB, DDE and PCBs serum concentrations in pregnant women were 89, 2036 and 319 pg/ml respectively. On multivariable regression analyses, a 10-fold increase in maternal HCB serum levels was associated with higher systolic blood pressure at 4 years of age (adj. β = 4.34 mmHg; 95% CI: 0.63, 8.05). Increasing levels of DDE were also associated with higher offspring systolic blood pressure (adj. β = 2.31 mmHg; 95% CI: -0.07, 4.69), though confidence intervals included the null. Prenatal HCB and DDE serum levels were positively associated with child blood leptin concentrations (adj. β = 2.15 ng/ml; 95% CI: 0.42, 3.89; adj. β = 1.21 ng/ml; 95% CI: 0.16, 2.27 respectively), though no significant associations were observed with offspring serum lipid levels.

**Conclusions:** Prenatal exposure to DDE and HCB may be associated with increased blood pressure levels in early childhood. Further studies are needed to replicate these results and to evaluate potential biological mechanisms underlying the observed associations.

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**Source(s) of support:**  
**Reference(s):**
Early PAH Exposure Impacts Cardiac Function in Xenopus laevis
Susan L Whittemore, PhD, Keene State College; Julia Pinette, Keene State College, US; Madison Sestak, Keene State College, US

The common polyaromatic hydrocarbons (PAHs) phenanthrene (PHE), fluoranthene (FLA), and pyrene (PYR) result from the incomplete combustion of organic matter, including fossil fuels, and are designated as priority pollutants due to their abundance and persistence in the environment. All three PAHs have been detected in significant amounts in human milk and cord blood. A large proportion of the human population, including fetuses, infants, and young children, are being exposed daily to these poorly-studied, highly abundant PAHs, underscoring the need to gain a better understanding of their potential for developmental toxicity.

Using Xenopus laevis, a well-established model system for vertebrate heart development, we assessed the impact of PHE, PYR, and FLA as single compounds, at 0.25, 2.5, and 25 μM, on heart rate (HR, in beats/min), interbeat variability (IBV, in sec) and incidence of atrioventricular (A:V) block at four developmental stages covering the period of heart development and compared effects with those of the well-characterized PAH benzo(a)pyrene (BaP, at 0.5 and 5 μM) and with DMSO (vehicle) controls. Data were analyzed using one-way ANOVA and Bonferroni’s multiple comparisons tests (n = 20-53/treatment/stage).

The lower dose of BaP had no effect on any cardiac measure at any time. At stage 37, at the end of cardiac looping and after a 48-hr exposure, FLA (at 25 μM) was the only PAH to alter HR, with a 30% increase over control levels (p ≤ 0.001). In contrast, during valve formation (stage 42), a 72-hr exposure was associated with tachycardia for all PAHs at all doses (increases in HR ranged from 20-35% with p values from ≤ 0.05-0.001). PAH-induced tachycardia persisted in stage 45 animals (during atrial partitioning; 96-hr exposure) for all PAHs except the highest doses of PHE and FLA. By 120 hr, in stage 46/47 animals with a mature heart phenotype, the highest doses of FLA and PHE were associated with bradycardia (14% and 17% decrease in HR and p ≤ 0.05, 0.01, respectively).

In general, PAH exposure did not alter IBV, an indicator of ventricular arrhythmia. However, FLA and PHE treatment did appear to impact cardiac conduction. The incidence of A:V block in FLA-exposed animals, at stages 45-47, was 40% at 25 μM, 8% at 2.5 μM, and 2% at 0.25 μM, with 5 larvae exhibiting complete block. Similar, but less dramatic, responses were observed in PHE-exposed animals with 15% and 8% incidence for 25 and 2.5 μM. However, defects in coordination between atrial and ventricular contractions were noted for 9 additional PHE-exposed animals. None of the DMSO or 0.5 μM BaP-treated animals exhibited A:V block, with 5% for 5 μM BaP.

The embryonic heart is critical for generating the hemodynamic forces necessary for the development of circulatory system. These results suggest that early exposure to FLA and PHE compromises cardiac function and may potentially impact circulatory development.

Source(s) of support: This work was supported by the New Hampshire IDeA Network of Biomedical Research Excellence (NH-INBRE) with an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health: Grant number P20GM103506.

Reference(s):
Bisphenol A Increases Atherosclerosis Mediated by the Human PXR
Changcheng Zhou, PhD, University of Kentucky

Objective: Bisphenol A (BPA) is a base chemical used extensively in many consumer products. BPA has recently been associated with increased risk of cardiovascular disease (CVD) in multiple large-scale human population studies but the underlying mechanisms remain elusive. We previously reported that BPA activates the pregnane X receptor (PXR) which acts as a xenobiotic sensor to regulate xenobiotic metabolism and has pro-atherogenic effects in animal models upon activation. BPA is a potent agonist of human PXR but has no effects on mouse or rat PXR activity, which confounds the use of rodent models to evaluate mechanisms of BPA-mediated CVD risk. This study aims to investigate the atherogenic mechanism of BPA using a novel PXR-humanized mouse model.

Approach and Results: We generated PXR-humanized ApoE deficient (huPXR•ApoE/-) mice that respond to human PXR ligands and therefore constitute a model to study the atherogenic effects of BPA. Feeding studies were performed to determine the effects of BPA exposure on atherosclerosis development. We found that exposure to BPA increased atherosclerosis in huPXR•ApoE/- mice but not their control littermates. BPA exposure did not affect plasma lipid levels but increased CD36 expression and lipid accumulation in macrophages of huPXR•ApoE/- mice.

Conclusions: Our findings provide a molecular mechanism linking BPA exposure to increased risk of CVD in exposed individuals. PXR is therefore a relevant target for future risk assessment of BPA and related environmental chemicals in humans.

Source(s) of support: NIH R21ES022745.
Reference(s):
Assessing fetal size and cardiac function using ultrasound biomicroscopy- echocardiography after maternal inhalation exposure to PM2.5 in mice

Kirtan Kaur, BS, NY; Sarah E. Attreed, BS, NYU School of Medicine, US; Shannon Doherty-Lyons, MS, NYU School of Medicine, US; Carol Hoffman, BS, NYU School of Medicine, US; Pamela B. Tijerina, NYU School of Medicine, US; Arthur Nadas, PhD, NYU School of Medicine, US; Jason L. Blum, NYU School of Medicine, US; Colin K.L. Phoon, MD, NYU School of Medicine, US; Judith T. Zelikoff, PhD, NYU School of Medicine, US

Over the past decade, research has shown a causal link between air pollution exposure and cardiovascular disease. Ambient air pollution is composed of many constituents, but particulate matter <2.5μm (PM2.5) has been shown to have the greatest effect on human health. In particular, cardiovascular health is influenced by inhalation exposure to PM2.5. Although substantial epidemiologic research exists on the health effects of PM2.5, exposure to PM2.5 during gestation and ensuing adverse health outcomes on the fetus/offspring are less explored. The aim of this study was to determine whether PM exposure during different gestational “windows” impacts fetal size/length and cardiac function. Pregnant B6C3F1 mice were exposed to either concentrated ambient PM (CAPs) or filtered air (FA) throughout gestation or specifically during organogenesis/placentogenesis. The purpose of using these two different gestational windows was to investigate the effects of maternal PM exposure during time points critical for embryonic and fetal development. The normal gestational length of B6C3F1 mice is ~18.5 days. For this study, gestational day (GD) 0.5 was considered the first day of gestation after the seminal plug was observed. Dams from both FA and CAPs were exposed daily for six hours from GD6.5-14.5 (i.e., “Window” 1) or “Window 2” daily from GD0.5-16.5. Window 1 targeted the developing embryos during organogenesis/placentogenesis, whereas exposure during Window 2 exposed the fetus across in utero development similar to human exposures, which would typically extend through the full term of pregnancy. On GD12.5 each dam was prepared for ultrasound biomicroscopy (UBM) to analyze in utero fetal cardiac effects of maternal CAPs vs. FA exposure using a VisualSonics Vevo 770 High-Resolution In Vivo Micro-Imaging System. Three different embryos from each dam were imaged, and for each the crown-to-rump length (CRL), heart echocardiogram, and fractional area change (FAC) of the ventricles (i.e., during refilling and emptying), umbilical cord blood flow, and heart blood flow were measured. UBM data were analyzed using Vevo 770 software and results demonstrate that FAC (diastole – systole / diastole) was significantly reduced in fetuses exposed throughout gestation (Window 2) indicating reduced ventricular emptying and thus cardiac inefficiency. In addition, CRL was reduced in fetuses born to mothers exposed to CAPs during Window 1 by 17%. Additionally, another set of dams from each treatment group and Exposure Window was sacrificed on GD17.5. Placentas and fetuses were collected from each dam keeping them in the same orientation as in utero. Fetal and placental weights for the CAPs-exposed mice were smaller in Window 2 compared to the control groups. These studies suggest that some cardiovascular ailments epidemiologically-linked with PM exposure in adults, may actually begin in utero. Research supported by March of Dimes and NYU NIEHS Center Grant (ES00260).

Source(s) of support:
Reference(s):
In Utero Arsenic and Cadmium Exposure is Associated with Altered T lymphocyte Populations in Infant Cord Blood
Rebecca N Bauer, PhD, Stanford University; Zhigang Li, Dartmouth University, US; Unni C Nygaard, Norwegian Institute of Public Health, Norway; Melanie Subbiah, Dartmouth University, US; Shohreh Farzan, Dartmouth University, US; Meena Malipatlolla, Stanford University, US; Holden Maecker, Stanford University, US; Margaret R Karagas, Dartmouth University, US; Kari C Nadeau, Stanford University, US

Gestation is a critical time period for immune development, and prenatal exposure to heavy metals such as arsenic and cadmium has been suggested to affect immune development. In utero exposure to the common environmental toxicant and carcinogen arsenic via drinking water is associated with increased risk of early life respiratory and gastrointestinal infections in humans, suggesting that exposure to arsenic during gestation alters immune development and function. Relatively few studies have investigated the immunomodulatory effects of cadmium, a toxicant highly present in tobacco smoke and contaminated food and water, though rodent studies suggest prenatal cadmium exposure is associated with altered lymphocyte development. We hypothesized that exposure to arsenic or cadmium during pregnancy alters T lymphocyte differentiation, which may increase susceptibility to infections. Cord blood was obtained from 52 newborns participating in a New Hampshire pregnancy cohort in which the concentration of arsenic in well water ranged from <0.01 to over 100ug/L, with over 10% of exposures exceeding the U.S. EPA standard of 10ug/L arsenic in water. Drinking water and urine was assessed for arsenic, and maternal post-partum toenail cadmium were analyzed using inductively coupled plasma mass spectrometry (ICP-MS). Peripheral blood mononuclear cells were isolated from the cord blood and lymphocyte subsets were characterized by immunostaining and flow cytometry. Arsenic exposure was inversely associated with the percentage of type 2 helper T lymphocytes (CD3+ CD4+ CD294+) out of all CD3+ CD4+ lymphocytes in the cord blood (β1 coefficient = -0.06 [95% CI = -0.11, -0.00]). For cadmium, we found a positive association between cadmium and the percentages of both induced regulatory T cells (CD3+ CD4+ CD45RO+ CD127- CD25+; β1 coefficient = 1159.08 [95% CI = 411.377, 1906.78]) and natural regulatory T cells (CD3+ CD4+ CD45RO- CD127- CD25+; β1 coefficient = 90.38 [95% CI = 11.93, 168.83]) in the cord blood. Our results suggest that in utero exposure to arsenic and cadmium may modify T cell populations in newborn cord blood. Future assessment of infant infections and antibody response to vaccination at 1 year of age will help to determine the association between arsenic-related alterations in T lymphocyte development and overall immune function.

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**Developmental activation of the AHR leads to context dependent changes in CD4+ T cell responses later in life**  
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Early life exposures have been shown to alter immune-mediated processes, yet the mechanism by which this occurs is unknown. In fact, in most cases it is unclear which cell types and molecular machinery are affected. Many studies have examined developmental exposures to chemicals that activate the aryl hydrocarbon receptor (AHR). Cells of the immune system express this receptor, and AHR activation in the fully mature immune system (i.e., non-developmental exposure) alters CD4+ T cell-dependent immune responses and autoimmune disease onset. However, little is known about how activation of the AHR during development changes the function of CD4+ T cells in adult offspring. Therefore, using two mouse model systems that closely mirror different human diseases, we examined CD4+ T cell responses in adult offspring that were developmentally exposed to the prototypical AHR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). We used the replicating human pathogen influenza A virus (IAV) to examine CD4+ T cell responses during infection, and a non-replicating but well-established immunogen (MOG peptide), which induces experimental autoimmune encephalomyelitis (EAE), a CD4+ T cell driven pathophysiology that mimics aspects of multiple sclerosis. Developmentally exposed adult mice infected with IAV had fewer conventional effector CD4+ T cells in draining lymph nodes of the lung (dLN), yet an increase in regulatory CD4+ T cells (Tregs). The lungs of these mice had an increase in all CD4+ T cell subsets. Conversely, developmentally exposed mice exhibited no difference in disease pathogenesis or effector CD4+ T cell responses after MOG immunization when compared to offspring of control-treated dams. These observations led us to test whether (1) a replicating pathogen is required to reveal developmentally-induced changes in CD4+ T cells or (2) the anatomical location influences whether CD4+ T cell function is affected by developmental exposure. After challenging mice with IAV in the peritoneal cavity, where it does not replicate, we no longer observe differences in the CD4+ T cell response in offspring of control and TCDD-treated dams. However, if CD4+ T cells from unexposed mice are adoptively transferred into developmentally exposed recipients, we recapitulate changes in CD4+ T cell responses in the lung and dLN after IAV infection. Together, these data suggest that pathogen replication and anatomical location are important considerations when examining the consequences of developmental exposures on CD4+ T cell function. Furthermore, this study emphasizes the importance of probing effects of developmental exposures on non-immune organs during an immune response, because changes in peripheral tissues may influence the totality of the impact of developmental exposure on the immune response to a particular challenge.

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Airborne Benzo[a]pyrene, Lipid Peroxidation and Risk of Comorbid Condition of Asthma and Obesity in Children

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Background: Early-life exposure to benzo[a]pyrene (B[a]P), a representative polycyclic aromatic hydrocarbon compound, is a known risk factor of asthma and obesity, respectively. Yet, its role in comorbid occurrence of asthma and obesity remains unknown.

Objective: We examined the association between ambient B[a]P with co-occurrence of clinically diagnosed asthma and obesity in 385 children and adolescents.

Methods: In a case-control study, children between the ages 7-15 years were investigated. We conducted multivariate linear and logistic regression on ambient B[a]P level and asthma-obesity comorbid condition as an outcome. Separate models were developed in order to clarify the role of the developmental stage [i.e., children (7–11 years) and adolescents (12–15 years)].

Results: Highest quartile of exposure to B[a]P was associated with a significantly higher prevalence asthma-obesity comorbid condition (P-value = 0.036). In a stratified analysis of children and adolescents, one natural log-unit increase in ambient B[a]P was associated with 130% increase in the likelihood of asthma-obesity comorbid condition (95% CI, 20–340%, p-value = 0.01) in the adolescents, but not among the children. Furthermore, same unit of increase in ambient B[a]P was associated with 10% increase in serum lipid peroxidation level among the adolescents (95% CI, 2–18%, p-value = 0.01), but not among the children.

Conclusions: Airborne B[a]P is significantly associated with asthma-obesity comorbid condition in adolescents, 12–15 years of age. This association appears to be further contributed by lipid peroxidation.

Source(s) of support:
Reference(s):
Modification of Ambient Benzo[a]pyrene Effects on Childhood Asthma by Single Nucleotide Polymorphisms

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Background: While the adjuvant role of ambient benzo[a]pyrene (B[a]P) on asthma development has been demonstrated, modification of asthma risk per unit exposure to ambient B[a]P by single nucleotide polymorphisms (SNPs) remains unknown.

Objectives: to examine the modification of ambient B[a]P effect on current asthma diagnosis by 621 SNPs in 95 genes.

Methods: Clinically validated cases of asthmatic (n=191) and healthy control (n=194) children between 7-15 years in age were investigated during November 2008. We used a semi-agnostic search for SNPs in which the initial set of 621 candidate SNPs were reduced to nine SNPs in two-stage screening process. Significantly modified the risk of ambient B[a]P on asthma was modeled in multivariate logistic regression model per interquartile range increase in B[a]P. We compared the likelihood of the outcome between those with native versus those with variant genotype.

Results: Three SNPs located within Cytotoxic T-Lymphocyte Antigen (CTLA4: rs11571315, rs11571316, and rs11571319), two SNPs (rs2229090 and rs2607775) within xeroderma pigmentosum group C (XPC), rs1031509 on signal transducer and activator of transcription 4 (STAT4), rs703817 on signal transducer and activator of transcription 6 (STAT6), rs2070673 on Cytochrome P450 2E1 (CYP2E1), and rs7208693 on Myeloperoxidase (MPO) were associated with significantly modification of B[a]P—asthma association in children. In particular, an interquartile increase in B[a]P (2.27 to 8.64 ng/m3) was associated with five-times greater likelihood of current asthma diagnosis (95% confidence interval, 3.92-34.65) among those with variant genotype in CYP2E1 gene compared to those with native one. Model adjusted for obesity, serum cotinine, and the history of allergic rhinitis with the past 12 months

Conclusions: The children with variability immune response, detoxification enzymes, oxidative damage repair, and DNA repair SNPs appear to have greater susceptibility to B[a]P exposure on asthma.

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Reference(s):
Persistent changes in dendritic cell function following developmental activation of the aryl hydrocarbon receptor
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Due to its long period of development, which extends into early postnatal life, the immune system is especially sensitive to early life environmental insults, potentially leading to altered immune function later in life. The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that influences the development and function of the immune system. Furthermore, AHR binds a variety of ligands, including dioxins and polychlorinated biphenyls (PCBs), pollutants to which humans are regularly exposed. Epidemiological studies and work in animal models indicate that early life exposure to AHR-binding pollutants alters immune function later in life, supporting the idea that inappropriate activation of AHR influences the developing immune system. To further understand the consequences of developmental exposure to AHR agonists, we used the prototypical AHR ligand, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Adult C57Bl/6 mice exposed to TCDD during development exhibit persistent alterations in the response of CD4+ and CD8+ T cells upon primary acute infection with influenza A virus (IAV). However, the mechanism by which early life activation of AHR alters T lymphocyte function is not known. Naïve T cell activation following infection requires cognate interaction with and proper stimulation by professional antigen presenting cells (APCs), such as dendritic cells (DCs). During IAV infection, DCs take up antigen in the lung and migrate to lymphoid tissues, where they activate naïve T cells. We therefore investigated whether developmental exposure impairs the ability of DCs to activate naïve T cells by enriching DCs isolated from developmentally exposed mice and using a sensitive and antigen-specific ex vivo assay system. AHR activation during development reduced DC function, as evidenced by an approximately two-fold poorer capacity to stimulate the proliferation and differentiation of naïve CD4+ and CD8+ T cells. Thus, early life activation of AHR decreases the number of DCs following IAV infection, and diminishes their ability to activate naïve T lymphocytes. These observations suggest that disruption of DC number and function following infection is one factor that may contribute to altered T cell responses observed as a consequence of developmental activation of AHR.

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Placental health is affected by Aryl hydrocarbon receptor-dependent regulation of metabolic and oxidative pathways.

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Placental regulation of nutrient availability is required for proper fetal development and perturbations during the developmental process can increase susceptibility to multiple later-life pathologies, including those of the blood system. Hematopoietic stem cells (HSCs) are the precursors for all blood cells throughout the life of the organism and emerge in the fetus and placenta at a point where the intrauterine environment is shifting from glycolytic to oxidative metabolism. The increasing energy demands and growth of the fetus coincide with increased placentation and regulation of fetal nutrient availability. Disturbances in nutrient and oxygen availability affect the unique metabolic and oxidative requirements of HSCs and can alter multi-potency and self-renewal, potentially leading to spectrum of diseases from stem-cell exhaustion to hematological malignancies. Adult 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD) exposures have been shown in numerous studies to disturb energy balance regulation, including fatty acid metabolism, insulin resistance, and cholesterol synthesis. In comparison, developmental exposure models using TCDD or AHR null mice show vascular and hematologic irregularities. We hypothesized that the placental energy regulatory systems would be altered by developmental TCDD exposure, which would consequently affect both fetal health and HSCs. To test this, we exposed pregnant C57Bl/6 mice to 3ug/kg TCDD or vehicle control throughout pregnancy and collected fetal and placental hematopoietic cells mid-gestation. We found TCDD significant increased ROS production by 1.6-fold in fetal hematopoietic cells, and 2.6 fold in the placental hematopoietic cells. Furthermore, placental weights of TCDD exposed fetuses were 80% of vehicle exposed (p<.0001). Placental HSCs showed significant TCDD-induced changes in genes related to metabolic regulation (14 and 7 fold induction Tsc1 and Lkb1 respectively), redox status (>9 fold induction Sod2), fatty acid metabolism (>5 fold induction Cpt2), and nitric oxide synthesis (>4 fold induction Gtpch). Taken together, developmentally exposed mice show decreased placental weight, increased oxidative stress, and gene expression changes related to glycolytic, redox, and fatty acid metabolism at a time when the fetus has increased need for oxygen and glucose. Our results add to the knowledge that placental health is key regulator of fetal development and programming, and these changes in the metabolic and oxidative state of HSCs may be an important part for understanding the role of toxicological insults during development and the fetal origins of adult health and disease.

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Immunotoxic impact at age 7 years of current and long-term childhood exposure to perflourinated compounds

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Serum concentrations of specific antibodies against certain childhood vaccines tend to decrease at elevated exposures to perfluorinated compounds (PFCs). We explored the immunotoxic impacts of three major PFCs in a Faroese birth cohort of 656 children. A total of 587 children contributed with blood samples to assess the serum concentration of the PFCs and of antibodies against diphtheria and tetanus at ages 5 and 7 years. In addition, maternal pregnancy serum was analyzed to assess prenatal exposures. We utilized structural equation models to take into consideration that serum PFC concentrations are likely to be imprecise indicators of the causative exposures. Concentrations of all three PFC concentrations at age 7 were individually associated to a decrease in the 7-year concentrations of antibodies, but it was not possible to attribute causality to any single PFC concentration. When combining the three PFC concentrations into a joint, latent exposure variable, a 2-fold increase in exposure was associated with a decrease by 54.4% (95% CI: 22.0%, 73.3%) in the antibody concentration. If considering both the age-5 and age-7 concentrations of the three major PFCs showed a slightly greater loss. Prenatal exposure to the PFCs had no impact on the outcomes. These analyses strengthen the evidence of human PFC immunotoxicity at current exposure levels and reflect the usefulness of structural equation models.

Source(s) of support:

Reference(s):
Maternal concentrations of persistent organochlorine pollutants and airway obstruction in the offspring at 20 years of age
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Authors:

Background: In a registry based study of ~900 women giving birth in Denmark in 1988-89 we observed positive associations between maternal concentrations of certain organochlorine pollutants and offspring use of asthma medication with 20 of follow-up (EHP, 2014; 122(1): 93–99). Use of asthma medications as an outcome does, however, provide limited information on asthma phenotype.

Objective: To examine the relation between prenatal exposures to persistent organochlorine pollutants and biomarkers of allergic airway disease, obtained during a clinical examination, among a sub-set of offspring at 20 years.

Methods: Six PCB congeners, hexachlorobenzen (HCB) and dichlorodiphenyldichloroethylene (p,p’-DDE) were quantified in maternal serum from week 30 of gestation. In 2007-2008 416 offspring (45% of those invited) attended a clinical examination and serum eosinophil cationic protein (ECP), total immunoglobulin E (IgE), and 12 allergen-specific IgE (ImmunoCAP) levels were quantified. Airway obstruction was defined as the ratio of the forced expiratory volume in the first second (FEV1) of the forced vital capacity (FVC) below 0.75.

Results: In line with our previous findings maternal dioxin-like PCBs (sum of congeners 118 and 156) and HCB concentrations were positively associated (p<0.05) with offspring use of asthma medication in our sub-set of participants. Offspring whose mother had concentrations above compared to below the median for the dioxin-like PCBs (0.3 ng/mL) had 2.4 (95% confidence interval: 1.1-5.0) increased odds of airway obstruction. A direct association was also observed when PCBs were modeled as continuous (p=0.01). Similar results were observed for HCB. None of the organochlorine pollutants were associated with serum ECP, total IgE or allergen-specific IgE levels in the offspring.

Conclusion
Prenatal exposure to certain organochlorine pollutants may be associated with airway obstruction but not with IgE-mediated outcomes.

Source(s) of support:
Reference(s):
Possible mechanism for perfluorinated compound-induced inhibition of antibody production in children: Reduction of NFKB activity and IKB degradation.

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Animal studies of perfluorinated compounds (PFC) have shown that these substances have immunotoxicity effects. Furthermore, in vitro studies on human cells have suggested (1,2) that PFCs may reduce LPS induced NFκB activation in lymphocytes. Since especially PFOA and PFOS are widespread organic compounds with the ability to bioaccumulate and with a relative long body half-life in humans, we found it of interest to investigate if these two compounds had an influence on a T-lymphocyte simulating activation of B lymphocytes by stimulation with CD40 ligand (CD40L).

Methods: Peripheral blood mononuclear cells (PBMCs) where collected from 19 healthy adult donors and cryo-preserved until use. The cells were thawed and incubated overnight with PFOS or PFOA at a concentration of 10 μg/ml. Next day, the cells were stimulated with recombinant soluble CD40L for 10 minutes to activate B cells. The PBMCs were fixed by Fix Buffer and stained with antibodies against CD19. Then PBMCs were permeabilized by Perm Buffer III and stained with mouse anti-NFκB and mouse anti-IκB antibodies. Cells were analyzed on a FACS Canto flow cytometer the same day. CD19 positive B lymphocytes were analyzed for up-regulation of NFκB and degradation of IκB upon CD40L stimulation.

Results: Reduced NFκB activation was observed when B lymphocytes activated with CD40L were exposed overnight either to PFOS or to PFOA, however the reduction was only borderline significant. However, a significant reduction in IκB degradation was observed when B lymphocytes were exposed to PFOA.

Conclusion: Treatment of B lymphocytes, with PFOA or PFOS over-night at concentrations similar to very high in vivo exposure levels of these toxicants, caused a reduction in NFκB activation upon induction with CD40L and similarly a reduced degradation of IκB. Although most westerners are exposed to concentrations of PFCs that are < 0.1μg/ml it could be speculated that the combination of exposures to many PFCs in conjunction for several years could influence negatively the ability of B lymphocytes to produce antibodies upon stimulation by T lymphocytes i.e. in relation with immunization.

Source(s) of support:
Reference(s):
Early childhood infections and symptoms of allergy and atopy in relation to in utero arsenic exposure in a US pregnancy cohort

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Early childhood infections and symptoms of allergy and atopy in relation to in utero arsenic exposure in a US pregnancy cohort

Infectious diseases, led by lower respiratory tract infections and diarrhea, remain the leading cause of early childhood mortality worldwide and an important cause of morbidity in US children. In addition, the prevalence of atopy and allergic diseases have increased dramatically in recent years, for reasons as yet unknown. In animal models, arsenic (As) exacerbates morbidity and viral titers of an H1N1 infection, and epidemiologic studies from Bangladesh, Mexico and Chile report clinical manifestations of altered immune response including increased risk of infection associated with high As exposure. As part of a pregnancy cohort study from New Hampshire we investigated whether in utero arsenic exposure relates to risk of childhood infections and symptoms of allergy and atopy. The cohort enrolled over 1,250 maternal-infant dyads who used a private, unregulated water system at their home. A telephone interview was conducted every four months during the child’s first year of life, and every six months thereafter to ascertain information on recent infections and symptoms. Initial findings suggested higher maternal (~24-28 week gestational) urinary arsenic concentrates related to a greater number of infections involving a physician visit or prescription medicine in the first four months of life. Specifically, we observed an increased risk of lower respiratory infections and diarrhea. Assessment of infections over the entire first year of life were consistent with these results, and also indicated a heightened risk of wheezing. Follow-up to age 5 years is now underway. Thus, our findings to date parallel those from more highly exposed populations and suggest that in utero arsenic exposure may raise children’s susceptibility to infection in the US. The possibility that arsenic may enhance risk of allergy and atopic disease will require longer-term follow-up.

Source(s) of support:
Reference(s):
Association between children's exposure to perfluorinated compounds and an asthma risk modified by MMR vaccination

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Introduction

Perfluorinated compounds (PFCs) have been associated with increased odds of asthma in a Taiwanese study, while a recent US study showed inconsistent results. Measles mumps and rubella (MMR) vaccination might cause a reduced risk of developing asthma or asthma symptoms, a tendency that we have confirmed in a Faroese birth cohort (unpublished results). We therefore aim to examine if MMR vaccination modifies the possible association between PFC exposure and asthma risk.

Methods

Five PFCs; perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were measured in blood samples from 544 5-year-old Faroese children. At both age 5 and age 13 years, the parents answered a health-related questionnaire, including a question on whether the child had asthma. MMR vaccination was administered at age 15 months, and at the 5-year examination, the child’s vaccination card was inspected to verify if the child had been vaccinated.

Logistic regression models were performed to determine the association between serum concentrations of each of the PFCs and asthma at age 5 and 13 years. The analyses were adjusted for sex and maternal smoking during pregnancy, and an interaction term was included between each of the PFCs and MMR vaccination.

Results

At age 5, 72 children (14% of 513) had asthma, and 20 had not been MMR vaccinated. At age 13, 77 children (17% of 463) had asthma, and 17 had not been MMR vaccinated before age 5. Among MMR vaccinated children, increased serum-PFC concentrations were associated with reduced odds of asthma at age 5 and 13 years, but the associations had a p-value >0.05. Among the MMR-unvaccinated children, increased PFC concentrations were associated with increased odds of asthma. A doubling of the PFOA level was associated with an eight-fold increased odds of having asthma at age 5 (OR: 8.01, 95% CI 1.00; 64.09). All other associations were in the same direction, but did not reach statistical significance. MMR vaccination significantly interacted with PFOA, PFHxS, PFNA and PFDA in relation to asthma risk at age 5, and with PFOA in relation to asthma risk at age 13.

Discussion

PFC exposure in unvaccinated children was associated with increased odds of asthma, but the association was reversed by MMR vaccination. Although the same tendencies were seen in all of the analyses, only a few results were statistically significant. Given the small number of unvaccinated children, the results should be interpreted with caution.

Source(s) of support:
Reference(s):
**Effect of maternal exposure to carbon black nanoparticle during early gestation on the thymus and spleen of neonatal mouse**

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Maternal exposure to environmental factors is implicated as a major factor in the development of the immune system in newborns. Newborns are more susceptible to microbial infection because their immune system is immature. Development of lymphocytes reflects an innate program of lymphocyte proliferation. The aim of this study was to investigate the effects of maternal exposure to carbon black nanoparticle (CB-NP) during early gestation on the development of lymphoid tissues in infantile mice.

Pregnant ICR mice were treated with a suspension of CB-NP (95 µg/kg/time) by intranasal instillation on gestational day 5 and 9. Spleen tissues were collected from offspring mice at 1, 3, 5, and 14 days post-partum. Splenocyte phenotypes were examined by investigating the pattern of surface molecules using flow cytometry. Gene expression was examined by SurePrint G3 Mouse GE 8x60K microarray (Agilent Technologies) and functionally analyzed by gene annotation with related transcription factors.

CD3+ (T), CD4+ and CD8+ cells were decreased in the spleen of 1−5-day-old offspring in the treated group. The decrease in splenic T cells in the treated group recovered at 14 days after birth. Expression level of IL-15 was significantly increased in the spleen of newborn male offspring, and Ccr7 and Ccl19 were increased in the spleen of female offspring in the CB-NP group. Microarray data showed that the genes differentially expressed by prenatal CB-NP treatment in the spleen of both male and female offspring were enriched in a transcription factor GATA1. Regarding the effect on thymus, the genes differentially expressed by prenatal CB-NP treatment in the thymus of both male and female offspring (5 days post-partum) were enriched in transcription factors NF1 (neurofibromin 1), STAT4, and GFI1, which are closely associated with thymocyte development. NF1 and GFI1 were also extracted from the group of genes differentially expressed in 1-day-old offspring. Most of genes related to NF1 and GFI1 were downregulated in offspring mouse, especially 1-day-old offspring, by prenatal CB-NP exposure. Interestingly, previous studies showed that NF1 deficiency reduced T-cell receptor and interleukin-2 receptor-mediated proliferation of thymocytes and mature T cells. A role of GFI1 in the T-cell differentiation, selection, and maturation was also reported. Information of TF enriched in the present study may give us clues as to the mechanisms that underlie the effect of prenatal CB-NP exposure on the neonatal immune system.

This article concluded that exposure of pregnant mothers to CB-NP partially suppressed the development of the immune system of offspring mice. The effect of nanoparticles on the neonatal immune system supports a creative approach to the development of such nanotechnology, particularly nanomedicine employing inorganic nano-sized carbon material, and also provides a method for hazard assessment of nanoparticle exposure during early pregnancy.

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**Reference(s):**
Paracetamol/Acetaminophen Exposure and Autism Spectrum Disorder-An Epigenetic Link?  

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Autism Spectrum Disorder (ASD) is a disorder of social and communication deficits, repetitive behaviors and fixated interests that appear in early childhood with the etiology proposed to involve both genetic and environmental factors. ASD-related mutations are rare, with the vast majority accounting for less than 1% of affected individual. This has shifted focus to epigenetic mechanisms. These mechanisms involve modifications of nucleotides or chromosomes without altering the genetic sequence, which can cause modifications in gene expression that may increase the likelihood of developing disease. The epigenetic mechanism, miRNA is a class of small non-coding RNA which regulates post-transcriptional gene expression by repressing and fine-tuning the majority of protein coding genes, mainly via sequence-specific binding within the 3’ untranslated region of mRNA transcripts. MiRNA’s have been shown to be important for neurogenesis, brain development and differentiation. Studies suggest that environment toxins can alter miRNA expression leading to susceptibility to disease. Beginning with the hypothesis that paracetamol/ acetaminophen (APAP) exposure is a biologically plausible causal factor in ASD, this investigation will identify ASD implicated genes that are targets of the same miRNA in which expression is changed by APAP exposure.

METHODS: The conserved miRNA that target each of 330 implicated ASD gene were identified using TargetScan Human 6.2. A PubMed search identified 8 studies of plasma miRNA and APAP. The miRNA’s whose expression was altered by APAP exposure were cross referenced to the conserved miRNA of the ASD genes to identify commonalities.

RESULTS: 29 common ASD genes involved in both immune and synaptic functions were identified. Four sets of APAP miRNA had consistently altered expression across studies. The first, hsa-miR-19a and 19b were shown to be up-regulated by APAP in humans at low doses(1). These miRNA may target ASD genes CACNAIC, TNF, SLC9A6, ATP10A, TBR1, HOMER1, PCDH10, GRIN2A, MBD4, MID1, PITX1, DCUN1D1, DLX1, ATRX. The second set, hsa-miR 29c, 29b and 29a showed consistency, with 29c up-regulated at low doses in humans(1), and were conserved for HDAC4, GRIP1, OXTR, ADA, DCX. The third, hsa-miR-218, a brain enriched miRNA, was found to be significantly elevated in humans during APAP induced liver injury (AILI)(2)and may target NRXN1, CNTNAP2, HOXA1, GRK2, MYO16, NBEA, PDZD4, KCND2, DPP6. The fourth APAP miRNA, hsa-miR-122, may target NLGN3, and has consistently been shown to be the most upregulated miRNA during AILI and is being tested as a clinical biomarker. Hsa-miR-122 was shown to be the second highest in expression(of 835)in the human embryonic brain during weeks 4-6(3).

CONCLUSIONS: This hypothesis generating investigation identified ASD implicated genes that have the potential to have their expression modified via miRNA altered by APAP exposure. Further studies are needed to directly test this hypothesis.

Source(s) of support:

Reference(s):
(2) Starkey Lewis PJ, Dear J, Platt V, et al. Circulating microRNAs
Is Paracetamol/Acetaminophen a causal factor in the Etiology of Autism Spectrum Disorder? A review and research synthesis.

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Autism Spectrum Disorder (ASD) is a disorder of social and communication deficits, repetitive behaviors and fixated interests that appear in early childhood(1). Both genetic and environmental factors appear to play a role in the etiology(2,3). One environmental exposure that may be involved is the use of paracetamol/acetaminophen(APAP). APAP is the most commonly used medication during pregnancy and for young children(4,5). It crosses the placenta and blood brain barrier(6-8). The FDA has reported that APAP’s narrow therapeutic index causes many users to receive a toxic dose in the course of normal use 9.

OBJECTIVE: To present a research synthesis of the parallels between ASD and APAP within the causal framework of the Hill Criteria. 

RESULTS: Strength, Biologic Gradient and Specificity: Two prospective cohort studies have investigated APAP exposure and neurodevelopment. The first study found that children exposed prenatally to APAP for more than 28 days had, at 3 years old, poorer gross motor development(β 0.24, 95% CI 0.12-0.51)(≈RR 1.67), communication(β 0.20, 95% CI 0.01-0.39)(≈RR 1.51), externalizing behaviors(β 0.28, 95% CI 0.15-0.42)(≈RR 1.69), internalizing behaviors(β 0.14, 95% CI 0.01-0.28)(≈RR 1.40) and hyperactivity(β 0.24, 95% CI 0.11-0.38)(≈RR 1.67). Children exposed shorter-term had a smaller elevation in risk. No association found to Ibuprofen(10). The second study found that 7 year old children prenatally exposed to APAP were at higher risk of a diagnosis of hyperkinetic disorders(HR 1.37 95% CI 1.19-1.59), use of ADHD medication(HR 1.29 95% CI 1.15-1.44) or ADHD behavior(HR 1.13 95% CI 1.01-1.27). All outcomes exhibited dose-response. Use of ibuprofen and aspirin did not modify risk(11).

Biologic Plausibility: Similarities in 1) Immune system dysregulation(12-14) altered cytokine levels(15-26) inflammation and oxidative stress(27-31). 2) Endocrine disruption(32-39) 3) Mitochondrial dysregulation(13,40,41) 4) Metabolic dysregulation including glutathione(42-46) and sulfate depletion(46-49), perturbation of endocannibinoid(50-53), Cox-2(54,55) and serotonin pathways(56-60). 5) Brain pathology including loss of Purkinje neurons(54,61,62), altered amino acid profiles(63,64), neurotoxicity(31,41,65-67), and excitotoxicity(27,63,68) 6) Gut microbiota alterations(47,69-73) 7) Epigenetics(30,49,52,74-80) 8) Impaired topoisomerases(81,82) Temporality: Autism prevalence increased with APAP usage rate timelines(83-87). Coherence: Higher males susceptibility (87-90) Analogy 1) Other prenatal medications increase risk of ASD-thalidomide, valproate, SSRI’s, misoprostol(91-99) 2) APAP may increase risk of asthma, allergies, cryptorchidism, ADHD(11,23-39,100-107): all comorbidities in autism(108-117). CONCLUSIONS: The limited evidence supports the plausibility of a relationship between APAP use and ASD. Further ASD specific studies are urgently needed. Given the widespread use of APAP, a determination of causality would have a significant public health impact.

Source(s) of support: none
Reference(s):
THE ROLE OF PRENATAL EXPOSURES IN MODULATION OF NEURODEVELOPMENT USING THE SHANK3e4-9/+ MUTANT MOUSE MODEL

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Autism spectrum disorder (ASD) comprises a set of neurodevelopmental conditions manifesting as repetitive behaviors and social and communication impairments. Genes affecting synaptic function have been found to be causative in a subset of ASD patients. Early exposure to environmental factors either by themselves or in conjunction with genetic factors has also been implicated in ASD, and in combination may play a role in ASD penetrance. To minimize confounding factors, our lab uses mouse models to answer this question. The overall goal of my project is to investigate how gene and prenatal environment interact (GxE) to influence ASD-like behavior in a Shank3 mutant mouse model. I chose the Shank3 null mice based on their ASD-like behaviors. Furthermore, deletions in SHANK3 cause Phelan-McDermid Syndrome, whereas mutations cause isolated ASD. Our overarching hypothesis is that ASD-associated risk alleles combined with certain common prenatal exposures can modulate neurodevelopment, altering maternal care and resulting in offspring behavior disturbances. This combination might cause an individual to reach a “phenotypic threshold” resulting in increased ASD penetrance. I will address this hypothesis through two specific aims. SPECIFIC AIM 1: To assess the effects of prenatal CUMS exposure on maternal care in Shank3 mutant dams. Preliminary data from our lab indicates that mutant male offspring of HET Shank3 dams exposed to gestational chronic unpredictable mild stressors (CUMS) exhibit an atypical response when compared to non-stressed gender and genotype-matched littermates in the three-chamber social behavior test. Because studies indicate that gestational stress can alter postpartum maternal care and offspring development, I am examining the effects of gestational stress on maternal care in WT and mutant Shank3 dams. Proposed experiments will likely answer how stress combined with genetic susceptibility contributes to observed phenotypes. SPECIFIC AIM 2: To assess the effects of prenatal FLX exposure of Shank3 HET dams on offspring neurodevelopment. For the second aim, I am investigating if other prenatal stressor-genotype combinations will result in altered social behavior in offspring. I am focusing on Fluoxetine (FLX), a Selective Serotonin Reuptake Inhibitor, regularly prescribed during pregnancy, and because maternal intake of (FLX) in the first trimester is associated with increased incidence of ASD. Therefore, I will examine whether FLX exposure in Shank3-mutant dams affects penetrance of ASD features in offspring through behavioral assessments. Post-battery, offspring brains are being harvested and processed for brain morphology, histology, gene and protein expression. In doing so, we will be assessing whether these factors exhibit additive defects. Proposed experiments will likely answer whether prenatal drug exposure combined with genetic susceptibility can play a role in ASD penetrance.

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Reference(s):
Beyond a means of exposure: an integrated view of maternal behavior and brain for toxicology research

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Toxicological studies generally view the pregnant mammal as a vessel of gestational exposure to chemicals in order to test potential developmental effects in offspring. Endocrine disrupting chemicals (EDCs) interfere with hormonal signaling and have demonstrated profound effects when exposures occur during development. There is mounting evidence that the traditional approaches to assessing EDCs on health, using test guidelines, are not sufficiently sensitive or comprehensive to fully appraise potential effects. Our work is focused on the potential effects of EDCs on more complex, integrated endpoints than those traditionally assessed (i.e. organ weight, histopathology and lethality). We present evidence that EDCs interfere with the expression of maternal behavior and induce related alterations in the maternal brain. The behavioral assays that we have used are relatively simple to perform and quantify for the assessment of the effects of environmental chemicals on maternal behaviors. We have also conducted a molecular investigation of the medial preoptic area (MPOA) of the hypothalamus, considered to be a critical neural region for maternal responsiveness. We show preliminary data, which suggests that bisphenol S, a widely used bisphenol A replacement, interferes with maternal behavior and expression of estrogen receptor in the MPOA. We propose that studies of emerging chemicals of concern should include maternal behavior in developmental toxicity tests; if behavioral changes are observed, the maternal brain should also be examined. There is more than sufficient evidence to conclude that the mother serves not only as a route of exposure, but also that the quality of maternal care can directly affect the health and behavior of a mother’s offspring.

Source(s) of support:
Reference(s):
An observational study measuring the impact of low-level gestational exposure to organophosphate pesticides on cognition during early childhood

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Background: Exposure to organophosphate pesticides (OPs) during pregnancy is widespread, and has been associated with neurodevelopmental deficits in children.

Methods: We examined the association between gestational OP exposure and neurodevelopmental outcome in 327 singleton mother/infant pairs enrolled in an ongoing prospective birth cohort study. We collected spot urine samples from mothers at 16±4 and 26±4 weeks gestation. Six common metabolites of OPs were measured and then summed to obtain aggregated concentrations of diethyl phosphates (∑DE), dimethyl phosphates (∑DM), and total dialkyl phosphates (∑DAP). OP concentrations were creatinine corrected, and the means of log-transformed gestational OP concentrations were calculated. Neurodevelopmental examinations included the Bayley II Mental Development Index (Bayley II-MDI) and Bayley II Psychomotor Development Index performed at ages 1, 2 and 3 years; the Clinical Evaluation of Language Fundamentals-Preschool, Second Edition (CELF-P-2) at age 4, and the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) at age 5.

Multiple linear regression was used for analysis.

Results: Mothers with higher OP concentrations had higher education levels, were more likely to be employed, and reported greater fresh fruit and vegetable consumption. In unadjusted analyses, higher urinary concentrations of ∑DM and ∑DAP were significantly associated with higher Bayley II-MDI at age 2 years (β=0.939, SE=0.433 and β=1.077, SE=0.493, respectively), and 3 years (β=1.204, SE=0.433 and β=1.612, SE=0.489, respectively). However, these relationships were not significant in multivariable analyses after accounting for socio-demographic factors. At age 4, there were no significant relationships between mean OP exposure and any of the child language index measures. At age 5, in unadjusted analyses, higher urinary measures of ∑DM were significantly associated with higher Full-Scale IQ (β=1.581, SE=0.538), Performance IQ (β=1.451 SE=0.564), and Verbal IQ (β=1.652, SE=0.538), as measured by the WPPSI-III. Similarly, higher urinary measures of ∑DAP were significantly associated with higher Full-Scale IQ (β=1.970, SE=0.603), Performance IQ (β=1.682, SE=0.635), and Verbal IQ (β=2.081, SE=0.602). These associations at age 5 were not significant in multivariable analyses.

Conclusions: Mothers in the HOME Study cohort who had higher urinary dialkyl phosphate concentrations were better educated, more likely to be employed, and reported a higher fresh fruit and vegetable intake, thus, it is possible, that a higher level of SES and a healthier diet during pregnancy may provide additional protection to the fetus from the potential adverse effects of gestational OP exposure. Our results contrast with other prospective birth cohort studies, but this may be a result of confounding by socioeconomic status and nutritional factors or reliance on non-specific metabolites to measure exposures to parent pesticides.

Source(s) of support:
Reference(s):
Assessing environmental risk associated with mercury in Mauritius

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Considering the varying pattern of an island development like Mauritius, the management of risks posed by anthropogenic releases of mercury is seen as an integral component of sustainable development. Despite that diabetes is often linked with lifestyle and genetic factors, epidemiological studies indicate that presence of endocrine disrupting chemicals in the environment can also contribute to the incidence of metabolic diseases. A local non-communicable disease survey conducted in 2009 revealed that 21.3% of the Mauritian population aged between 20-74 years had type 2 diabetes. While research on endocrine effects of Hg is ongoing, quantifying the amount of Hg that enters the body via consumption of fish of higher trophic levels, in such an island can be an important lead to further research in this field. Mauritius, being heavily reliant on coastal and marine resources, signed the Minamata Convention in October 2013. Sustainable catch of fish for Mauritius stand at 200 tons/yr, with a local consumption pattern of 21 kg/yr per capita. However, artisanal catches of up to 1043 tons in 2004 were reported by FAO, of which 90% were consumed locally. White albacore and yellow tuna are important sources of protein in the local diet. At present export earnings for canned tuna fish is higher compared to the cost of these imported products, but this positive balance in trade can alter with its rapidly increasing demand. Research conducted by the Zero Mercury Working Group showed that 36% of the samples of hair tested for women of child-bearing age in this small island, exceeded the U.S. Environmental Protection Agency guideline of 1 micrograms per gram of hair. This paper presents findings of an environmental risk assessment of Hg conducted in Mauritius. The aim of the study is to assess the risks posed by anthropogenic mercury releases to the environment and to investigate human intake of mercury via ingestion and inhalation routes. A material flow analysis approach is used to estimate mercury emissions from industrial, non-industrial processes and consumer products to air, water and soil. The coal-fired power plants for electricity production are among the highest emitters of mercury to air (140 kg Hg/yr) and other forms of emissions identified are from sanitary landfills, consumer products such as compact fluorescent lamps and dental amalgam. Following its mobilization, Hg compounds may follow different distribution pathways before entering the environment. The source and receptor pathways were mapped in order to establish relationship of mercury sources to a set of selected environmental compartments (including water, land and sediment) and to humans. A multimedia transport model is used to study the mercury speciation. Exposure parameters with respect to population density, estimated mean body weight, fish consumption pattern, fraction of drinking water derived from surface water and groundwater respectively were considered in the model.
Delayed effects of embryonic exposure to low levels of PCB-126 on adult zebrafish behavior

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Over the past several years there has been increased recognition that the early-life environment can strongly influence the trajectory of developmental pathways, and that perturbations at critical stages of development can have persistent or delayed functional consequences in later life stages. Human exposure to anthropogenic environmental contaminants such as dioxin-like compounds has been documented worldwide and is a cause for concern. PCB-126 (3,3’,4,4’,5-pentachlorobiphenyl) is the most toxic dioxin-like PCB congener, causing toxicity through the aryl hydrocarbon receptor (AHR) pathway for which there is detailed understanding of the effects and the associated mechanisms following acute exposure of adults as well as embryos. However, when considering the developing embryo, the levels of chemical exposure leading to delayed effects can be below those causing overt effects. Yet, the full potential for later-life health effects that result from early-life low level exposure to dioxin-like compounds is not well understood. Epidemiological studies, performed in many contaminated locations worldwide, provide strong evidence supporting an association between prenatal and lactational exposure to PCB mixtures, including PCB-126 and other dioxin-like compounds, and neurodevelopmental deficits in children. The use of animal models provides experimental platforms for more thorough evaluation of behavioral phenotypes and for mechanistic studies as well as for the study of chemical-specific congeners in order to determine their individual roles in mediating the observed outcomes. In addition, animal models facilitate the continuation of studies from early life stages through adulthood. Zebrafish are excellent tools for studying later life effects of embryonic exposure for several reasons; their short generation time is ideal for performing full embryo-to-adult experiments in relevant time-scales, their ex utero development and optically transparent embryos allow for easy evaluation of exposure levels that do not cause immediate overt effects, their easy maintenance and breeding and high fecundity allow high throughput experimentation with many biological replicates. We exposed zebrafish embryos to either DMSO (vehicle control) or a low concentration of PCB-126 (0.3 nM) starting from 4-5 hours post fertilization (hpf) until 24 hpf, and reared them to adulthood (3 months). We compared the behavior of DMSO- and PCB-126-exposed fish at the juvenile stages (6, 7 and 14 days post fertilization) and after reaching adulthood. Juvenile behavior assays included activity analysis during dark/light transitions, and adult assays included anxiety testing such as the novel-tank assay. Our study shows that early, embryonic exposure to PCB-126 causes adult behavioral changes that are not apparent at the juvenile stages.

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Reference(s):
Effects of prenatal exposure to titanium dioxide nanoparticle on DNA methylation and gene expression profile in the brain of mouse

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Background: Titanium dioxide nanoparticle (TiO2-NP) is an important material used in paints, cosmetics, food additives and implanted biomaterials. Health effect of TiO2-NP exposure is concerned. Previous studies suggested that exposure of pregnant body to TiO2-NP affects the development of the central nervous system of mouse offspring; however, the mechanism underlying the effect has yet to be elucidated. In the present study, we investigated the effect of prenatal TiO2-NP exposure on the global DNA methylation and mRNA expression patterns in the brain of mice. The effects on DNA methylation in the promoter regions were especially focused.

Methods: Pregnant C57BL/6J mice were treated with TiO2 suspension (100 micro g/mouse, rutile : anatase = 20 : 80, <150 nm particle size [DLS], primary particle size of starting nanopowder : 21 nm; Sigma-Aldrich Japan) by intrapulmonary administration on gestational day 10.5 and, after childbearing, the brains were collected from their male and female offspring 1-day post-partum. After extraction of methylated DNA by MeDIP, methylation profile in the promoter region was analysis using Mouse CpG Island Microarray (Agilent technologies). Total RNA was also obtained, and mRNA expression profile was comprehensively analyzed using SurePrint G3 Mouse GE 8x60K microarray (Agilent Technologies). To better understand the biological meanings of the microarray results, functional analysis were performed using gene annotation by enrichment analysis using Gene Ontology (GO) and brain region information from Medical Subject Headings (MeSH). Quantitative RT-PCR was also performed.

Results: Methylated region of TiO2-exposed group was significantly and globally decreased. 22885 methylated region in male and 23481 methylated region in female were decreased. Microarray analysis showed that 299 (in male) and 244 (in female) genes were differentially expressed (fold change >2 or <0.5) in the TiO2-NP-exposed group. The mRNAs differentially expressed by prenatal TiO2-NP exposure were enriched in some GO categories related to sensory perception and a MeSH “Mesencephalon”.

Conclusion: The present study suggests that prenatal TiO2-NP exposure may globally decrease DNA methylation in promoter region and increase expression of some mRNAs related to the function of sensory system and midbrain during the perinatal period.

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Reference(s):
Selenium altered the reproductive and developmental neurotoxicity of mercury: MOCEH (MOthers and Children’s Environmental Health) study

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Background and aims:

Previous studies suggested that mercury (Hg) exposure and selenium (Se) level during pregnancy may influence on the early-childhood neurodevelopment, but the results remain unclear. Therefore, we aimed to evaluate whether increased Se level were associated with decreased mercury-related neuropsychological dysfunctions.

Methods:

The prospective cohort study of Mothers and Children’s Environmental Health (MOCEH) have been built up in 2006 and we enrolled 1,751 women before second trimester of their pregnancy and their partners in 2006-2010. Participants visited research center at 6, 12, 24 and 36 months. We used the atomic absorption spectrophotometer to measure Hg and Se in blood. Questionnaires about infantile environment and health conditions were answered and anthropometric factors including body weight and height were measured, and neurobehavioral test (Bayley) were conducted by certificated investigators. We performed multiple linear regression models for statistical analyses (SAS 9.3).

Results: The GMs of mercury concentration were 3.21 μg/L in maternal blood and 4.82 μg/L in cord blood. The GMs of the Se concentration were 9.6 μg/dL during midpregnancy. The mercury level in maternal and cord blood negatively correlated with the maternal Se level on infants during the first 3 years. Mercury level of cord blood in the infants during the first 3 years was significantly decreased the bayley test cognitive scores at 36 months in group of less than median value in maternal Se level (9.13 ng/ml) adjusted for potential confounders (maternal blood at late pregnancy: β=-16.64, p=0.02, cord blood: β=-18.73, p=0.04).

Conclusions: Mercury exposure adversely affects neurodevelopment on infants during the first 3 years. Also, Se maybe explain the protective effect against mercury neurotoxicity.

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Reference(s):
Sex-specific expression patterns of genes associated with Alzheimer’s disease during normal aging and with a developmental lead exposure in zebrafish

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Aging and environmental chemical exposures are risk factors for neurodegenerative diseases such as Alzheimer’s disease (AD). Among many factors, environmental lead (Pb) exposure is suggested as a trigger for AD due to the adverse effects on neurological functions in adults and children. Recent studies also suggest a potential role of a developmental Pb exposure in the pathogenesis of AD with the presence of pathological hallmarks of AD and expression alterations in genes related to amyloid beta production in aged rodent and non-human primate brains. To further investigate the association between early-life Pb exposure and AD pathogenesis, sex-specific spatial and quantitative expression of six genes associated with AD: amyloid beta precursor protein (appa and appb), presenilin (psen1 and psen2), and apolipoprotein E (apoeea and apoeb) was first compared in zebrafish aged 3 months (young) and 12 months (aged) to assess gene expression changes during normal aging. In situ hybridization revealed spatial expression of appa, appb, psen1, and apoeea genes throughout the brain, exhibiting weak to extensive staining restricted to some areas including the hypothalamus, torus semicircularis, and/or optic tectum regions. However, location of expression was not different between sexes or ages. Quantitative polymerase chain reaction analysis revealed a significant increase in appa, appb, and psen1 expression in aged females compared to the young female zebrafish. Moreover, a significant down-regulation of apoeea and apoeb was also detected in the aged females compared to the young females. However, expression of the genes in males was not significantly influenced by normal aging. In the second set of analyses, zebrafish embryos at 1 hour post fertilization were collected and exposed to a control treatment or 100 ppb of Pb through the end of embryogenesis (72 hpf). Larvae were then rinsed and reared under normal laboratory conditions until they reached the age of 3 months (young) or 12 months (aged) for sex- and age-specific gene expression analyses using brains of zebrafish with or without developmental Pb treatment. No significant spatial or quantitative differences were exhibited in any Pb treated groups analyzed. Overall while a significant difference in expression was observed for most AD-associated genes tested in female zebrafish during the natural aging process, no significant differences in gene expression was observed in males indicating that sex-specific alterations of genes associated with AD occur during normal brain senescence. In addition, while no differences were observed in fish exposed to Pb during embryogenesis for this specific set of genes, further work is needed to assess involvement of other genes associated with neurodegeneration to understand the impacts of a developmental Pb exposure on neurodegenerative disease pathogenesis.
Prenatal exposure to manganese and neurodevelopment at 12 months of age in the ISA study

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Background: Manganese (Mn) is an essential nutrient, but also a neurotoxicant at high concentrations. Previous studies have examined the association between prenatal Mn exposure and neurodevelopment in children, but few studies have measured Mn concentrations at more than one time point during pregnancy.

Methods: We conducted a birth cohort study (Infants’ Environmental Health Study, ISA) among families living near banana plantations aerially sprayed with Mn-containing fungicide mancozeb in Costa Rica. We measured Mn concentrations in maternal hair and blood samples collected at different times during pregnancy. We assessed cognitive, language, motor, and social-emotional development in 344 children at 12 months of age using Bayley Scales of Infant Development-III. We tested for linear and nonlinear relationships and also assessed if these associations were different for boys and girls. We adjusted multivariable regression models for maternal education, parity, gestational age, and child’s age and sex.

Results: Geometric mean (GSD) Mn concentration in hair was 1.9 (2.9) μg/g; mean (SD) Mn concentration in maternal blood was 24.4 (6.2) μg/L. We observed that higher mean maternal hair Mn concentrations during pregnancy were associated with poorer social-emotional development in boys (β for 10-fold increase = -5.7; 95% CI: -9.4, -2.0), but not in girls (β = -1.4; 95% CI: -5.6, 2.7; p int = 0.11). However, we did not find linear or nonlinear associations of maternal blood Mn concentrations during pregnancy with cognitive, language, motor, and social-emotional development at 12 months.

Conclusions: Our preliminary results suggest that Mn may be adversely related to social-emotional development of boys. Next steps will include examining associations of maternal hair and blood Mn concentrations by trimester/half of pregnancy with neurodevelopmental outcomes at 12 months.

Source(s) of support:

Reference(s):
Placental epigenetic patterning of cortisol response genes is associated with infant neurodevelopmental outcomes and maternal environment

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Epigenetic variation of stress response genes has been linked to behavioral and psychiatric outcomes in infants and adults, and this variation may be related to fetal programming by maternal environmental exposures and stress. The placenta regulates fetal cortisol exposure and response, by expressing genes involved in cortisol response. Rodent and our own human data suggest a role for epigenetic variation of these genes individually contributing to behavioral development, but an appreciation of the broader pathway and its coordinated role is needed. We hypothesized that the epigenetic patterning of cortisol response genes in the placenta is associated with infant neurodevelopment and this patterning is influenced by environmental and maternal factors. In 537 infants enrolled in the Rhode Island Child health study, placental DNA methylation of key regulatory regions of cortisol response genes NR3C1, HSD11B2, FKBP5 and ADCYAP1R1 was quantified using bisulfite pyrosequencing, and exploratory factor analysis was used to reduce the dimensionality of the methylation data. Infant neurobehavioral outcomes were defined using the validated Neonatal Intensive Care Unit Network Neurobehavioral Scales (NNNS). Relationships between the factor scores and NNNS outcomes, dichotomized at the upper or lower 10th percentile as appropriate, were examined using logistic regression models adjusted for confounding variables, while the relationships between infant and maternal clinical covariates, maternal toenail metal concentrations and the factor scores were examined using linear regression models. Factor 1 explained 23% of the methylation variation and was significantly loaded by methylation of NR3C1 exon 1F, CpGs 3 and 6-13, a promoter of the glucocorticoid receptor gene. A one unit increase in the NR3C1 methylation factor was associated with increased odds of membership in the top 10th percentile of stress abstinence scores (OR 1.63, CI 1.27-2.1), as well as with increased odds of membership in the top 10th percentile of attention scores (OR=1.33, CI 0.95-1.85). This NR3C1 methylation factor was positively associated with maternal toenail mercury concentration (P=0.03). Factor 3, which explained 12% of the variation in methylation, was significantly loaded by methylation of ADCYAP1R1, a gene whose product regulates release of neuroactive peptide hormones. A one unit increase in ADCYAP1R1 methylation factor was associated with decreased odds of membership in the 90th percentile of infant arousal (OR 0.76, CI 0.58-1) and was positively associated with maternal obesity (P=0.01). These results suggest that coordinated epigenetic regulation of cortisol pathway genes independently influences different domains of newborn neurobehavior and environmental influences including exposure to exogenous toxicants or maternal metabolic condition can alter this regulation and potentially influence infant programming.

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Reference(s):
Gestational Exposure to Phthalates and Gender-Related Play Behaviors in Typically Developing 7.5-9 Year Old Children

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Phthalates, a class of chemical additives used in polyvinyl chloride plastics and personal care products, are prevalent, and their metabolites are detectable in urine samples of nearly 100% of the U.S. population. Clinical studies have demonstrated sex-differentiated effects of phthalate exposure on the reproductive systems of infants, children, and adults, postulated to be caused by the chemicals’ endocrine disrupting properties. This has led to concern in the scientific and lay communities about the long-term consequences of phthalate exposure, particularly in children. We investigated the effects of gestational phthalate exposure on gender-related play behaviors using data available from the Health Outcomes and Measures of the Environment (HOME) Study, an on-going prospective pregnancy cohort study conducted in Cincinnati, Ohio. The HOME study enrolled pregnant women from 2003 and 2006 and followed their children through 7.5-9 years. The cohort consists of mothers and their typically-developing children with diverse demographic and socio-economic backgrounds. We measured phthalate metabolite concentrations in maternal urine samples collected at approximately 16 and 26 weeks gestation. Concentrations were corrected for creatinine and log transformed. These concentrations were then summed by the parent compounds di-2-ethylhexly (DEHP) and di-butyl (DBP) phthalates, which represent phthalates with high and low molecular weights, respectively. Gender-related play behaviors were measured in the 7.5-9 year old children using the parent-completed Gender Identity Questionnaire (GIQ) and the child-completed Playmate and Playstyle Preferences Structured Interview (PPPSI). Children who had complete exposure and play data were included in the analyses (n=221). The associations between gestational exposure to phthalates and GIQ and PPPSI scores were assessed using multivariable linear regression models. Covariates tested included child sex, race, gestational age, older sibling sex, income, and Parenting Relationship Questionnaire t-scores. Concentrations of DEHPs and DBPs measured in women in this cohort were slightly higher than those reported by the Centers for Disease Control and Prevention for U.S. women tested around the same time period. We found no statistically significant associations between maternal phthalate concentrations and child gender-related play behaviors (GIQ: DEHP β=0.03 (95% CI: -0.01, 0.08), DBP β=0.01 (-0.05, 0.07); PPPSI z score: DEHP β=-0.04 (95% CI: -0.20, 0.11), DBP β=-0.03 (-0.25, 0.19). Although we found no associations between gestational exposure to phthalates and gender-related play behaviors, this study is, to the best of our knowledge, the first of its kind to be done wholly with typically-developing children. More research is needed to further explore possible associations with postnatal exposure to phthalates.

Source(s) of support:

Reference(s):
Dose-response study of di-(2ethylhexyl) phthalate (DEHP): androgenic and anti-androgenic actions

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Di-(2ethylhexyl) phthalate (DEHP) is a man made endocrine disrupting compound (EDC) used to produce flexible plastic products. The mechanism of action for this EDC is complex acting on both steroid receptors and steroidogenic enzymes. Much of the work on this compound has focused on the effects that high doses have on androgen-target tissues, in particular on anogenital distances (AGD). Epidemiological studies have demonstrated correlations between DEHP metabolites (mainly MEHP) in urine and a variety of behaviors in children. Interestingly one of the first reports of DEHP and childhood behavior was a correlation between less masculine play behavior in boys and more DEHP exposure in utero [1]. Furthermore, higher urinary levels of MEHP in autistic as compared with control children [2] have been reported, and more activity disorder in children whose mothers had high levels of MEHP during their pregnancies. In addition to androgens DEHP may produce alterations in lipids and cholesterol metabolism, the hypothalamic-pituitary-adrenal axis, and/or retinoic acid. Here we used three doses (5ug, 40ug, and 400ug/kg body weight/day) of DEHP, which pregnant mice consumed voluntarily throughout gestation and for the first ten days of lactation. These doses represent a range from low (within levels found in humans) to high. Others have shown that in mouse embryos the two lowest doses we used are androgenic while the highest dose is anti-androgenic as measured by AGD [3]. Our preliminary data indicate significant effects of DEHP dose on AGD in F1 and F2 mice, indicating possible multigenerational effects. We also found effects on spontaneous social behavior in juvenile mice. Females from the highest dose group and males from the two lower dose groups are more socially interactive than control animals. Importantly, we have not observed any effects of these DEHP doses on maternal behavior indicating that the behavioral results are due to DEHP exposure and not differences in rearing. This research has important implications for human social behaviors.

Source(s) of support: NIH ES022759 (EFR)

Reference(s):
Embryonic iron deficiency alters adult neural structure
Michael J Rudy, BS, MS, University of Rochester

Iron deficiency (ID) is the most common micronutrient deficiency, affecting more than nine percent of reproductive age women in the United States and over a billion women worldwide. When an iron deficient woman becomes pregnant, her body cannot provide the iron a developing fetus requires, and low iron during critical windows of development has been linked to an increased risk of psychiatric disorders, behavioral problems, and learning difficulties later in life. Despite an awareness of this risk, the mechanism linking iron availability and brain development remains largely unknown.

We established a mouse model of gestational ID where mice are placed on a diet with adequate iron to support an adult animal, but too little to support the increased iron requirement during pregnancy. As is often seen in humans, this model produces anemia during the third trimester which is then treated with postnatal iron supplementation. We found that the central nervous system of adult mice, who were gestationally iron deficient, had a significantly impaired response to both a GABA antagonist and a glycine agonist. These mice also had an increased number of inhibitory GABAergic interneurons in the cerebral cortex, with no apparent decrease in excitatory pyramidal neurons. We then examined the region which gives rise to GABAergic interneurons and found an expansion of both Nkx2.1 and Gli1 signaling: two factors which are important for appropriate specification of GABAergic interneurons. Of particular interest, these signaling changes are seen while maternal hematocrit is still in the normal range. Taken together, our data suggests that embryonic ID increases inhibitory signaling in the adult brain by expanding the region which produces inhibitory GABAergic interneurons, thereby increasing the number of inhibitory interneurons in the adult cortex.

Source(s) of support:
Reference(s):
Developmental origins of neurotransmitter and transcriptome alterations in adult female zebrafish exposed to atrazine during embryogenesis
Sara E Wirbisky, Purdue University

Atrazine is an herbicide applied to agricultural crops that is indicated to be an endocrine disrupting chemical (EDC) and a potential carcinogen. Atrazine is frequently found to contaminate potable water supplies above the maximum contaminate level (MCL) of 3 parts per billion (ppb) as defined by the Environmental Protection Agency (EPA). The developmental origin of adult disease hypothesis suggests that toxicant exposure during development can increase the risk of developing certain diseases during adulthood. However, the molecular mechanisms underlying disease progression is still unknown. In this study, zebrafish embryos were exposed to 0, 0.3, 3, or 30 ppb atrazine throughout embryogenesis [1-72 hours post fertilization (hpf)]. Following embryonic exposure larvae were allowed to mature under normal laboratory conditions with no further chemical treatment until 7 days post fertilization (dpf) or until adulthood and neurotransmitter levels assessed. While no significant alterations in dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), or gamma-aminobutyric acid (GABA) were observed at 7 dpf, a significant decrease in 5-HIAA and serotonin turnover was observed in adult female brain tissue. No significant alterations were measured in adult male brain tissue. To further investigate molecular pathways underlying the observed neurological alterations, transcriptomic analysis was completed on adult female brain tissue. Results revealed 1853, 84, and 419 genes with altered expression in females exposed to 0.3, 3, or 30 ppb atrazine during embryogenesis, respectively. There was a high level of overlap between the biological processes and molecular pathways in which the altered genes were associated in adult females from all three atrazine treatments with specific enrichment in nervous system development and function, tissue and embryonic development, and behavior. Moreover, a subset of genes was down regulated throughout the serotonergic pathway providing support of the developmental origins of neurological alterations observed in adult female zebrafish exposed to atrazine during embryogenesis.

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Reference(s):
Poster #: MON-35

Abstract type: Population Research
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Keywords: Birth Cohort, Epidemiology, Prenatal

Occupational pesticide exposure in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age

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Background: Many pesticides possess neurotoxic and endocrine disrupting properties and may adversely affect neurodevelopment, possibly in a sex-specific manner.

Methods: Pregnant women working in greenhouse horticultures were recruited in the beginning of their pregnancy. Women categorized as occupationally exposed to pesticides were moved to unexposed work functions or went on paid leave. Women without occupational pesticide exposure were considered unexposed controls. At age 6 to 11 years, their children underwent a standardized examination including a battery of neurodevelopmental tests.

Results: Maternal occupational pesticide exposure in early pregnancy was associated with prolonged brainstem auditory evoked potential latencies in the children. In girls, language and motor speed functions were significantly inversely associated with prenatal exposure, and a non-significant tendency toward decreased function was also seen for other neuropsychological outcomes. No associations between prenatal pesticide exposure and neuropsychological function were apparent for boys. A structural equation model that combined all these test results showed an overall impaired neuropsychological function in girls prenatally exposed to pesticides.

Conclusion: Our findings suggest an adverse effect of maternal occupational pesticide exposure in early pregnancy on their children’s neurodevelopment despite well regulated working conditions, where special measures to protect pregnant women were applied. Girls seem more affected than boys.

Source(s) of support: The study was supported by grants from the Danish Environmental Protection Agency
Reference(s):
Inorganic mercury as a potential neurodevelopmental toxin - exposure of breast fed infants in a small-scale gold mining area in Zimbabwe

Stephan Boeseoreilly, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine

Background and Aims: Small-scale gold miners use mercury (Hg) to extract the gold from the ore. In Kadoma (Zimbabwe) and elsewhere women are exposed to toxic, mainly inorganic mercury vapors, by living in an exposed area or worse working as miners with mercury. Infants being breast fed are loaded via contaminated milk and the wide-ranging environmental exposure. Does this exposure burden the infants or even cause any negative health effects?

Methods: 120 mother-child pairs were examined in 2006. The environmental epidemiological field study included a non-exposed control group (n=42), a medium exposed group (n=51) and a high exposed group (occupational exposure, n=27). Total mercury was analyzed in urine, hair and breast milk. Clinical and neurological data from mother and children were achieved. An assessment of motor milestone to determine the developmental stage was performed.

Results: Median (maximum) urine concentrations were (i) control group < 0.50 [µg Hg/l] (1.55), (ii) medium exposed group 1.10 (10.48), (iii) high exposed group 1.20 (24.80) (p<0.001). The levels of exposure in hair and urine are similar for mothers and infants. The correlation between the specimens is high showing that the exposure of the infant correlates with the burden of the mother and the breast milk. The daily uptake of mercury via breast milk was calculated. The reference dose of 0.3°[µg Hg/kg BW/d] was used to compare the burden of the infants. No infant from the control group, but 17.6% of the medium and 18.5% of the high exposed group were above the reference dose. Examining the children neurologically one significant difference was observed. The children in the high exposed group were more likely to be drowsy (7% versus 0% in the two other groups). The number of examined mother child pairs was not large, and the regular achievement of the developmental milestones does naturally differ between children. Nevertheless this study shows first results, that the developmental milestones of exposed children are delayed compared to lesser exposed children. Mercury is known as a neurotoxic substance. But it is a new result, that the children in gold mining areas, exposed mainly to inorganic mercury do show neurodevelopmental effects, similar to the known exposure with methylmercury via fish.

Conclusions: The levels of mercury in breast milk exceeded in a high percentage threshold limits. Interventions to reduce the exposure of infants are indispensable. Possibly inorganic mercury is a neurodevelopmental toxin. Further research is urgently needed to identify the health risks for infants in small-scale gold mining areas.

Source(s) of support: Limited funding for the field project came from a personal grant (BL). Laboratory and statistical analysis were performed as in kind contribution by the authors.

Reference(s):
(2) Bose-O’ Reilly S, McCarty KM, Steckling N, Lettmeier B: Mercury ex
**Poster #: MON-37**

**Abstract type:** Population Research  
**Category:** Other: Endocrine Disrupting Compounds  
**Keywords:** Birth Cohort, Exposure Assessment, Postnatal

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**Bisphenol A Exposure and Metabolism in Healthy Full-Term Neonates in Baltimore, Maryland**

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**Background:** Exposure to Bisphenol A (BPA) is widespread in the general population due to leaching from food packaging. BPA's known estrogenic properties have given rise to public health concerns. Neonatal glucuronidation capacity is limited compared with adults and it is hypothesized that in newborns a greater proportion of BPA remains in the unconjugated, more biologically active form, free BPA. However, metabolism of BPA during the first month of life has not been assessed fully.

**Aim:** To investigate the impact of glucuronidation capacity on BPA toxicokinetics in healthy full-term neonates using urinary BPA biomarkers.

**Methods:** Mothers and healthy full-term neonates (N=44) were recruited at the Johns Hopkins Hospital in Baltimore, Maryland from 2012 to 2013. Urine samples (N=78) were collected at ages 3-6 days and 7-28 days. Free BPA and BPA glucuronide concentrations were quantified by high performance liquid chromatography, tandem mass spectrometry with dansyl chloride derivatization (LOQ=0.1 µg/L). In addition, specific gravity was measured by refractometer (Model: PAL 10-S, Atago, Bellview, WA). Information on potential individual-level sources of BPA exposure was collected via questionnaire during well visits at the Johns Hopkins Harriet Lane Pediatric Care Clinic, and the contribution of these sources to BPA exposure was evaluated using a generalized estimating equation, accounting for correlation between measurements from the same individual.

**Results:** Only BPA glucuronide was detected in the urine samples and concentrations ranged from <0.1 µg/L to 11.21 µg/L (median: 0.27 µg/L). Free BPA concentrations levels fell below the limit of quantification of 0.1 µg/µg/L in all samples. After adjusting for specific gravity, age was negatively and significantly associated with urinary BPA glucuronide concentration, but we report no significant association for sex and type of diet.

**Conclusions:** Our results illustrate that BPA exposure is widespread in healthy full-term neonates and that these neonates are capable of efficiently conjugating BPA to its readily excretable and biologically inactive form (BPA glucuronide) as early as 3 days of age. Our results suggest that factors other than type of diet may be important contributors to BPA exposure in this population.

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**Reference(s):**

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**Keywords:** Epidemiology, Exposure Assessment, Public Health

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**The association of socio-demographic status, lifestyle factors and dietary patterns with total urinary phthalates in Australian men**

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Objective: To investigate the associations between socio-demographic status, lifestyle factors, dietary patterns and urinary total phthalate concentration in a cohort of South Australian men.

Method: We randomly selected 1527 males aged 39 to 84 from wave two of the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study. Total phthalate concentration was examined in fasting morning urine samples. Socio-demographic and lifestyle factors were assessed by questionnaire. Food intake was assessed by food frequency questionnaire (FFQ). Dietary patterns were constructed using factor analysis.

Results: Total phthalates were detected in 99.6% of the urine samples. The overall geometric mean (95% CI) of total phthalate concentration was 112.5 (107.7-117.6) ng/mL. The least square geometric means (LSGMs) of total phthalate concentration were significantly higher among people who were obese (126.2 ng/mL), consuming less than two serves fruit per day (124.7 ng/mL) and drinking more than one can (375mL) of soft drink per day (137.0 ng/mL). Two dietary patterns were identified: a prudent dietary pattern and a western dietary pattern. Both the western dietary pattern (p=0.002) and multiple lifestyle risk factors including smoking, obesity, insufficient physical activity and the highest quartile of the western dietary pattern (p<0.001), were positively associated with total phthalate levels. There was no significant relationship between total phthalate concentration and socio-demographic status.

Conclusion: Phthalate exposure is ubiquitous and positively associated with lifestyle risk factors in urban dwelling Australian men.

**Source(s) of support:**

**Reference(s):**
Temporal variability of cadmium in urine of prospective parents from the HOPE Study (UT)

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Background: The heavy metal cadmium (Cd) is a known occupational carcinogen. Low chronic exposure, via cigarette smoke and dietary sources have been linked to kidney and bone disease. At the molecular level, Cd can interfere with the natural hormonal communication (estrogen-like activity), and induce epigenetic modifications in the DNA. Importantly, potentially harmful pre-pregnancy epigenetic changes acquired by the parents could be inherited by the progeny. Hence, exposure of parents to low levels of cadmium pre-pregnancy could have untoward consequences on both pregnancy success and child development. Urinary Cd (U-Cd) level in spot urine is used as a biomarker of lifetime Cd body burden. However, age and time of day of urination can impact the toxicokinetic parameters of Cd, and hence lead to biased quantification of Cd exposure.

Objective: Clarify the temporal variability of U-Cd in healthy men and women of reproductive age who were not exposed to high levels of cadmium.

Methods: Five urine spots were collected during 2 consecutive months from 23 never-smokers (13 females and 10 males) who were trying to conceive in 2012-13. Participants collected daily first morning urines during the fertile window (males and females) with females continuing through the end of the menstrual cycle for up to two menstrual cycles. We selected four samples 2-5 days apart from the first cycles and one from the second cycles for cadmium analysis. U-Cd and creatinine were measured via ICP-MS and ELISA, respectively. General demographic and physical characteristics were also collected. Intra-class Correlation Coefficient (ICC) of creatinine-adjusted U-Cd was determined. Repeated measures ANOVA was used to identify variables that would modify the correlation.

Results: None of the participants were occupationally exposed to cadmium, 16 (73%) were Caucasian, and the average age (min.-max.) was 30.6 (26-38) years. Cadmium was detected in all of the samples with a detection limit of 0.0142 µg/L. The ICC (95% CI) across the five samples was 0.58 (0.40, 0.76). None of the demographic (age, race, education, employment, marital status, income, BMI) or technical (menstrual cycle, time of collection) parameters influenced this result (ANOVA Type III sum of squares p >0.05).

Conclusions: U-Cd concentration measured in urine spot collected a few days apart indicated some variability. Studies based on U-Cd as an exposure biomarker should consider this variability during the design and analysis phase.

Source(s) of support:
Reference(s):
Perfluorinated compounds (PFCs) are a class of persistent environmental toxicants widely used in industrial and consumer products due to their unique chemical and physical properties. Knowledge on the health effects in humans is sparse and have most often been studied only for PFOS and PFOA, but use of other PFCs are emerging, not at least after restriction of PFOS in the Stockholm Convention. Knowledge of prenatal exposure, and distribution between blood compartments for a wider range of PFCs in humans is therefore needed.

We present prenatal exposure data for 19 perfluorinated organic compounds from 100 mother and child pairs. The compounds were quantified in maternal serum as well as in umbilical cord blood and serum from the child at birth. The samples were collected between 1999-2001 at the Faroe Islands. The quantified compounds includes the two major subgroups perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonates (PFSAs) ranging from C4-C12, as well as perfluorooctane sulfonamides (FOSAs) and perfluorooctane sulfonamidoacetic acids (FOSAAs).

Maternal and fetal serum concentrations were significantly correlated for nearly all PFCs with median concentrations in cord serum ranging between 30-95% of the maternal concentration, while cord whole blood levels were lower. The only exception was FOSA that binds to erythrocytes and therefore occur at significantly higher concentration in whole blood. The apparent partition of the PFCs across the placental barrier varied according to chain length, branching and active group. Increasing chain length was associated with decreased passage. Branched PFOS was comparatively higher on the fetal side than linear PFOS, and the carboxylates seem to pass more easily than sulfonates for compounds at the same length. These findings document the need to take into account the partition between different blood compartments when assessing prenatal exposure to PFCs.
In Utero Arsenic Exposure and Epigenome-Wide Association in Placenta, Artery and HUVEC
Andres Cardenas, Oregon State University

Background: Prenatal exposure to arsenic has been associated with an increased risk of disease later in life. Studies have reported that arsenic exposure disrupts DNA methylation. However, epigenetic marks are tissue specific and the epigenome-wide association between arsenic exposure in utero and DNA methylation in placenta, artery and Human Umbilical Endothelial Cells (HUVEC) has not been previously evaluated. Furthermore, conducting epigenetic studies on different tissue types could yield important insight on the potential impact of environmental stressors on different biological functions.

Methods: Using a prospectively enrolled birth cohort recruited in Bangladesh, we aimed to evaluate the association between prenatal arsenic exposure DNA methylation changes in three tissues: placenta, artery and HUVEC. The primary drinking water source was identified by the participant and arsenic was measured using inductively coupled plasma-mass spectrometry (ICP-MS). Epigenome-wide methylation was assessed using the Illumina Infinium Methylation450K BeadChip array in 44 paired samples. Omnibus test for epigenome-wide associations were conducted using 1000 permutations for each tissue type. A gene-set analysis was also conducted using omnibus permutation tests over subsets of CpGs defined by their gene associations to identify potential gene targets related to arsenic exposure.

Results: Median arsenic concentration in water was 12 μg/L (range < 1-510 μg/L). No association was observed between log-transformed arsenic in drinking water and DNA methylation changes in HUVEC (omnibus P=0.18). Arsenic exposure from the mother's drinking water during pregnancy was associated with differential DNA methylation of placenta (omnibus P=0.02) and artery (omnibus P<0.001). The top three ranked genes that were differentially methylated for placenta were the NKX6-2, FLJ42875 and HIST1H3I genes. The top three ranked genes that were differentially methylated for artery were the MRI1, RAB6B and LIME1 genes.

Conclusion: The present work supports the hypothesis that arsenic exposure in utero can disrupt fetal programming in placental and umbilical cord artery tissue. Additional research is needed to confirm these findings and evaluate the impact of these methylation changes on health outcomes.

Source(s) of support:
Reference(s):
Air Pollutants Predict both DNA Methylation of Fetal Growth Genes and Birth Outcomes

Katherine E King, PhD, MA, US EPA

Background DNA methylation at regulatory sequences of imprinted genes is related to gestational growth, as well as later future cancer and obesity risk. Recent studies have linked air pollution with low birth weight and preterm birth as well as with DNA methylation in adulthood, but limited research examines air pollution and epigenetic regulation at birth.

Objective We investigated the association of PM2.5-related exposures during pregnancy on methylation of 9 fetal growth genes in umbilical cord blood.

Methods A birth cohort in Durham, NC (n>2200) had birth outcomes recorded and a subsample had 9 epigenetic markers pyrosequenced from their cord blood (n>800). Mothers’ addresses were geocoded and matched with the nearest Environmental Protection Agency Air Quality System monitoring station recording PM2.5 or components for each month and trimester beginning with estimated conception date, and over the entire gestation. Regression models were used to examine how pollution may predict methylation at 9 gene regions, as well as birth weight and gestational age, adjusted for birth season, maternal race/ethnicity, age, education, pre-pregnancy BMI, and cigarette smoking, and child gender and parity.

Results Gestational PM2.5 exposure significantly predicted methylation at 8/9 gene regions, as well as gestational age and preterm birth, but not birth weight. Fourteen PM2.5 components examined all predicted methylation of at least 3one gene regions, but not always in the same direction.

Conclusions Prenatal PM2.5 exposure can influence DNA methylation. Further elaboration of the mechanisms and consequences is needed, as well as disentanglement of which species are involved.

Source(s) of support:

Reference(s):
Sexually Dimorphic Influence of Phthalates and Phenols on the Regulation of Genes Implicated in Neurodevelopment and Metabolism in Human Placenta

Karin B. Michels, ScD, PhD, Harvard Medical School; Alexandra M. Binder, MS, Harvard School of Public Health, US; Jessica LaRocca, PhD, Harvard University Center for the Environment, US

Prenatal exposure to endocrine disrupting chemicals (EDCs) may disrupt normal hormone homeostasis during critical windows of structural and functional development, shaping adult disease susceptibilities. Phthalates and phenols are two classes of suspected EDCs that are of significant concern due to their ubiquitous human exposure and potential detrimental health effects. EDC exposure has been suspected to induce changes in placental physiology, potentially contributing to the intrauterine programming of these phenotypes. To investigate this etiology, we assessed genome-wide changes in methylation and gene expression in human placental tissue associated with first trimester urinary metabolites of 11 phthalates and 8 phenols. Accounting for the concurrent environmental exposure to these compounds, we modeled methylation and expression variation as a function of all metabolites. These associations were assessed separately in the placentas of males and females, due to potential effect modification by sex-specific patterns of methylation associated with cell growth and differentiation. We identified changes in methylation in proximity to genes implicated in neurodevelopment among placentas from both sexes. Sexually dimorphic variation in the methylome and transcriptome associated with EDC exposure was also enriched for the regulation of metabolic processes. This study represents the first investigation into the influence of phenols and phthalates on genome-wide regulation in human placental tissue. Notably, our study provides novel evidence for the molecular basis of the impact of prenatal phthalate and phenol exposure on neurodevelopment in a human population.

Source(s) of support:

Reference(s):
**From chromosome to exposome - the HEALS approach to health and environment-wide associations**

**Stephan Bose-O'Reilly, University Hospital Munich, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine; Denis Sarigiannis, Aristotle University of Thessaloniki, Greece**

**Background:** Genetic & environmental factors contribute & interact towards the pathogenesis of diseases. The importance of the chromosome is well known & to a lesser extent the exposome (1). The exposome is characterized by exposures beginning from conception & including all critical windows of development throughout people’s life span. To analyze the relevant factors, a range of innovative technologies, big data mining & analyzing & challenging modeling tools are required. HEALS (Health & Environment-wide Associations based on Large population Surveys) is an ongoing large scale research project to fill these gaps of knowledge.

**Materials & methods:** The improvement of an integrated methodology & the use of the equivalent analytical & computational tools for performing environment-wide association studies in support of EU-wide environment & health assessments is the objective of HEALS. Based on pre-existing population data this method will be further developed. A pilot environment & health examination survey covering eighteen EU Member States will be applied within the project.

**Results & discussion:** HEALS is organized in seven streams & twenty work packages. The key research areas are:

- Integrated use of existing environmental & biomonitoring data
- Improved assessment of the external exposome (environmental data fusion & Agent-Based Models, mobile phone apps, environmental sensor-webs, micro-sensors, satellite remote sensing)
- Linking external & internal exposome (integrated use of –omics & chemical biomarker data)
- Advanced tools for environmental & biological data analysis (PBBK modeling, plus gene regulation models)
- Novel bioinformatics strategies for biomarker prediction (Meta-modeling for biomarker fusion)
- Environment-wide association studies (linkage disequilibrium, use of advanced statistical tools)
- Enviromics (study of a wide array of environmental factors in relation to health & biology)

In existing population studies these tools will be applied to test the HEALS approach. Depending on the outcome of these population studies, a pilot exposure & health survey (EXHES) will be performed in 10 EU countries to test the applicability of the HEALS approach for EU-wide large population surveys. EXHES will combine a longitudinal & a nested case-control phase to permit for superior definition of environmental exposures & superior classification of disease & risk phenotypes. The technological & computational integration anticipated in HEALS could be confirmed through EXHES with regard to both technical practicability & cost-effectiveness. The final result should be improved scientific knowledge, including research protocols & guidelines for a future European Health & Exposure Survey.

**Conclusions:** HEALS delivers an holistic basis to detect essential indicators for identifying the proper covariates influencing important health endpoints. HEALS leads to “enviromics” sorting out the underlying associations between environment & health.

**Source(s) of support:** European Commission for co-funding the HEALS project under grant agreement Nr. 603946

**Reference(s):**
Association between maternal urinary arsenic and infant cord blood inflammatory marker levels in New Hampshire
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Accumulating evidence indicates that arsenic, a potent environmental toxicant, is related to increases in cardiovascular disease morbidity and mortality in exposed adult populations. Arsenic exposure in adults has also been associated with altered levels of plasma inflammatory markers that can indicate systemic inflammation and endothelial dysfunction. Pregnancy and fetal development are times of particular vulnerability to environmental insults, and effects of early life exposures influence not only child development and health, but can manifest later in life. As cardiovascular disease processes are thought to begin early in life, it is possible that in utero arsenic exposure may play a role in the development of later life cardiovascular dysfunction. As part of the New Hampshire Birth Cohort Study, we investigated whether in utero exposure to arsenic affects levels of early markers of cardiovascular dysfunction and inflammation in infant cord blood samples (n=156). We assessed levels of circulating markers sICAM-1, sVCAM-1, PAI-1, MMP-9, TNF-α, and IL-6 in cord blood samples by Luminex. In preliminary linear regression analyses adjusted for maternal age, BMI, smoking during pregnancy, parity, educational attainment, urinary creatinine, as well as infant sex and birth weight, we observed that maternal urinary arsenic during pregnancy was inversely related to infant cord blood levels of sICAM-1 (β: -0.38; 95% CI: -0.75, -0.003), sVCAM-1 (β: -17.4, 95% CI: -34.7, -0.10), and TNF-α (β: -0.08, 95% CI: -0.16, -0.01). To our knowledge, this is among the first studies to evaluate these markers in relation to arsenic exposure in newborns. Our work indicates that in utero arsenic exposure may alter levels of inflammatory cytokines at birth, which could potentially impact long-term health.

Source(s) of support:
Reference(s):
Soil Milieu as a Reservoir of Environmental Stressors that influence Clinical Health, Human Diseases, and Preeclampsia/Eclampsia

Howard Walter Mielke, Tulane University School of Medicine

Along with air and water, soil is a critical milieu of the environment and a primary interconnected link between the biosphere and human health. The impact of soil on health was made explicit through maps of inorganic and organic constituents across an entire city. The topic of children's exposure to lead illustrates the contribution of soil to health and disease. Blood is a commonly measured bioindicator for lead exposure in humans. Blood lead along with high density maps of soil and housing characteristics for Orleans and Thibodaux Parishes in Louisiana were compared to elucidate the role that soil lead and age of housing play on children's blood lead outcomes. Although age of housing had a strong association with blood lead of children, soil lead was twelve orders of magnitude stronger than age of housing at blood lead prognosis and ultimately health outcomes. A long list of diseases is associated with lead exposure including neurotoxicity (learning and behavioral diseases in children and violence in young adults), hypertension, kidney disease, and bone diseases. The clinical outcomes of the list of diseases recognized by clinicians correspond with community health outcomes associated with lead contaminated soil. Preeclampsia/eclampsia is a major clinical complication associated with lead. Cross-sectional analyses in New Orleans shows that a one standard deviation increase in soil lead increases the odds of eclampsia by a factor of 1.48 (95% confidence intervals 1.31 and 1.66). Mothers in areas with soil lead > 333 mg/kg were four times (95% confidence intervals 3.00 and 5.35) more likely to experience eclampsia than mothers residing in neighborhoods with soil lead < 50 mg/kg. Mothers residing in communities with large accumulations of lead in soil are at heightened risk of preeclampsia/eclampsia. Soil metal maps provide a view of the quality of community-scale soil milieu and assist with comprehending an alternative method for intervention. Maps are an invaluable diagnostic tool for evaluating the soil milieu-related stressors that effect clinical health outcomes.

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Reference(s):
Endocrine Disrupting Activity of Hydraulic Fracturing Chemicals and Health Outcomes Following Prenatal Exposure in Mice

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Hydraulic fracturing, a method developed over the last 60 years, has recently been combined with horizontal drilling to unlock previously inaccessible or unprofitable shale oil and natural gas. The hydraulic fracturing process involves the high-pressure injection of water, chemicals, and suspended solids to fracture shale or coal bed layers and release trapped natural gas or oil. The industry has reported use of over 750 chemicals, including many known or suspected endocrine disrupting chemicals (EDCs). Spills of wastewater and chemicals are common and have been shown to contaminate surface and ground water, and we have previously reported elevated estrogen and androgen receptor activities in surface and ground water near sites with natural gas drilling spills. We have also tested 24 chemicals used in hydraulic fracturing for EDC activity. We found antagonist activities of 21, 21, 10, 10, and 7 chemicals for the estrogen, androgen, progesterone, glucocorticoid, and thyroid receptors, respectively. Twenty-three of 24 chemicals exhibited disruption of one or more receptor systems.

Our current work extends this analysis to in vitro and in vivo studies of mixtures of chemicals used in hydraulic fracturing, as previous work has reported additivity of EDCs with the same mechanism of action. Different chemical mixtures were tested in estrogen, androgen, thyroid, progesterone and glucocorticoid receptor reporter gene assays in human breast cancer cells: 1) 24 fracturing chemicals at equimolar concentrations, 2) nine chemicals at equimolar concentrations that our team has analytically measured in hydraulic fracturing wastewater, and 3) five different receptor-specific mixtures of chemicals at equipotent concentrations. We found evidence of additive antagonist activity for several mixtures.

Next we tested a mixture of 23 chemicals in an in vivo mouse model. Pregnant mice were administered the mixture in drinking water at 4 different concentrations spanning 3 orders of magnitude from gestation day 11 to 18. At postnatal day 7, offspring were weighed and anogenital distance was measured. At postnatal day 21, necropsies were performed on offspring, with organ weights and tissue histology examined. Timing of puberty, and other hormone-sensitive endpoints will be assessed. Completion of these studies should substantially increase our knowledge of consequences of prenatal exposure to a complex mixture of hydraulic fracturing chemicals and of potential health risks associated with this process.

Source(s) of support:
Reference(s):
Biological effects of mixtures of endocrine disruptors: The “synergy” of new developments in toxicology, epidemiology and exposure science

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Epidemiology of mixtures is hampered by a lack of generally accepted methods for data analysis, while toxicological testing of mixtures is impeded by the extremely large number of possible combinations. However, not all possible mixtures occur in real world settings. There are thus two aspects to the mixtures problem: 1) What are the patterns of co-exposure that occur in populations and how do they depend on demographics? Exposure science and epidemiology have much to contribute to this part of the problem, including new non-targeted analytical chemistry methods. 2) What are the health effects of exposure to mixtures? Endocrine disrupting compounds (EDCs) may be more amenable to mixtures analysis than many systems because of a better understanding of mechanisms. Earlier work has shown that EDCs can have dramatic mixture effects yet ones that are often understood well enough for accurate modeling. Some groups of EDCs that act at the receptor level may be modeled using toxic equivalent factors (TEFs), a special case of concentration addition in which dose-response curves are “parallel” and have the same maximal effect. Generalized concentration addition extends this approach to compounds with different maximal effects, e.g., combinations of full agonists, partial agonists and competitive antagonists. Concentration addition (and its generalization) is often assumed for compounds with similar mechanisms, but how similar do they have to be? Recent work has shown that certain classes of compounds with similar but not identical mechanisms have approximately concentration additive effects, e.g., mixtures of compounds that either inhibit production of androgens or are competitive antagonists at the androgen receptor. Mixtures toxicologists often analyze mixtures data using response surface methods: testing individual compounds, constructing expected response surfaces from these marginal data assuming a mixtures model such as concentration addition, and then comparing the expected response with that observed using various experimental mixtures. Environmental epidemiology studies typically cannot control the composition of the mixture and do not have information on response to single chemical exposures. However, a variation of the response surface method can be still be used by examining the shape of the isoboles (contours) of the surface (For example, when TEFs apply, the isoboles are negatively sloped, parallel straight lines/hyperplanes). With sufficient data, response surfaces can be constructed using generalized additive models in which outcomes are regressed against a non-parametric smooth of the set of exposures while adjusting parametrically for other covariates. Examination of the pattern of isoboles brings toxicological insight to traditionally black-box epidemiologic methods.

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Dimensions of Injustice in the Developmental Origins of Disease

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Research into developmental origins of disease induced by chemical exposures and the best 20th century ideas of justice nicely mesh to reveal several ways in which people are treated unjustly from chemical exposures induced by other citizens. Exposures may constitute battery, harmful assaults, interferences with fair equality of opportunity, and potentially income and wealth inequality. Recognizing these relationships enhances our understanding of legal and moral wrongs revealed by the science.

i) Companies exposing citizens to untested substances during development or later in life commit the offense of battery, “a voluntary act one knows will cause contact that another would reasonably regard as offensive.” Battery protects bodily integrity and individual autonomy. If it is tortious to seriously insult or startle someone, it would seem an even greater transgression of social boundaries to inflict a silent, invisible bodily contact with a possible toxicant, leaving those ‘touched’ to await whatever may come. (1)

ii) When exposures that would constitute battery become embedded in a person’s biology (2) resulting in physical harm and any suffering that accompanies it, this constitutes a further injustice. (3)

iii) If the chemical becomes sufficiently embedded so that sustained harm interferes with a person’s normal biological functioning and reduces his or her normal opportunity range, it constitutes a violation of the widely shared principle of fair equality of opportunity. If embedded biological harm transfers across generations as some research shows, it could interfere with fair opportunity intergenerationally and transgenerationally. (1)

iv) Battery, harm and interferences with fair opportunity all impose negative externalities—social costs of activities that are not incorporated into the market prices of the activities, but imposed on others. Exposures themselves can impose costs or concerns, even in absence of harm, adversely affecting behavior. If harm and reduction in opportunities affect income and wealth, as they likely do, these can contribute to or exacerbate income and wealth inequalities. (1)

Chemical exposures caused by fellow citizens can be deeply unjust on several dimensions. Understanding these can enhance our understanding of the wrongs done and provide insights for developing strategies for legal interventions to reduce exposures.

Source(s) of support:

Reference(s):
Are Standard Testing Guidelines Adequate to Screen Chemicals for Prenatal Programming of Toxicological Response?

Susan Makris, US EPA; Babasaheb Sonawane, USEPA, US

Growing evidence suggests that exogenous substances may cause diseases via epigenetic mechanism-regulated gene expression changes. Epigenetic factors, including DNA methylation, histone modifications, and miRNA alterations, participate in these processes, thus controlling gene regulation. There is strong evidence that stimuli during critical periods of prenatal and immediate post-natal mammalian development can influence the developmental pathways, including permanent changes in metabolism and modulating chronic disease susceptibility. Standardized toxicology testing guidelines have been routinely used for screening environmental chemicals (pesticides, industrial chemicals, and pollutants) and pharmaceuticals. These guideline protocols were developed by and continue to be updated by national and international entities (e.g., USEPA, NTP, OECD, FDA, and ICH) and have been in use for many decades. They are considered the “gold standard” of toxicology study design and conduct for the purpose of hazard identification and dose response characterization, with application to risk assessment. Available protocols are varied and include acute, subchronic, chronic, carcinogenicity, prenatal developmental, reproduction and fertility (including continuous breeding), immunotoxicity, and neurotoxicity (including developmental neurotoxicity) studies. An examination of these protocols indicates that few of them are designed to detect the types of trans-generational outcomes that have been identified over the past decade as indicative of possible epigenetic mechanisms of action and prenatal programming of adverse health outcomes. Well-intentioned revisions and updates to standardized testing guidelines over this same time period have not enhanced the detection of trans-generational outcomes. Consequentially, prenatal programming of toxicological response, including epigenetic alterations as biomarkers of potential adverse consequences, is unlikely to be identified by typical toxicology screening programs. To date, reliable, validated protocols to screen for epigenetic changes, including trans-generational outcomes, for use in hazard characterization and dose response assessment, have not been developed.

(Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the Environmental Protection Agency.)

Source(s) of support:
Reference(s):
Perceptions of risk of in utero exposure to bisphenol-A

Using a combination of focus groups and written surveys, we will investigate the level of knowledge and perception of risk of in utero exposure to bisphenol-A among women of childbearing age in Meadville, Pennsylvania. We are interested in whether increased knowledge is correlated with the intent to implement behavioral changes (such as avoidance of handling thermal carbonless paper (i.e receipts), avoidance of canned foods and beverages, or a reduction in the use of polycarbonate food service items) when pregnant.

Source(s) of support:
Reference(s):
Perinatal exposure to environmentally relevant levels of bisphenol decreases reproductive success by affecting multiple targets

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In a series of experiments spanning over 15 years, we have investigated the effects of environmentally relevant doses of bisphenol A (BPA) on the decline in the reproductive capacity of perinatally-exposed female rodents. When testing reproductive success in females exposed perinatally to vehicle, 25, 250 or 25000ng BPA/kg body weight/day, or 10 ng/kg/day of the synthetic estrogen, diethylstilbestrol (DES-positive control) in a continuous 32-week forced breeding protocol, fertility and fecundity were significantly reduced over time in the 25 and 25000ng BPA and DES groups, but were not impaired in the 250 ng BPA group [1]. Of interest, exposure to 250ng BPA resulted in alterations in the anteroventral periventricular preoptic area (AVPV), a brain region essential for regular estrous cyclicity which is typically suppressed in a forced breeding protocol [2]. Therefore, we hypothesized that the diminished reproductive outcomes following perinatal exposure to BPA could be due to alterations in the hypothalamic-pituitary-gonadal axis. To address this, we assessed fertility in once-bred animals at 3, 6, and 9 months of age in the treatment groups described above. Measurement of anti-müllerian hormone (AMH) in relation to ovarian primordial/primary follicle count showed that AMH levels decreased with age but there was no effect of BPA exposure on this assessment of ovarian reserve. Despite a decrease in percent fertility and number of live pups delivered in relation to increased age of the dam, there was no difference in the length of gestation or the number of live pups delivered across treatments at each time point. However, there was an increase in the number of days to delivery from male pairing between dams exposed to either 250 or 25000ng BPA compared to controls at 9 months and in 250ng or DES-exposed dams at 3 months compared to their 9 month counterparts (p<0.05). To assess whether perinatal exposure to BPA alters the activation of hypothalamic gonadotropin-releasing hormone (GnRH) neurons essential for the generation of the LH surge, females exposed to vehicle, 25ng, 250ng BPA, or DES were ovariectomized at 3, 6, or 9months of age and treated with a regimen of gonadal steroids to induce an LH surge. The colocalization of Fos within GnRH neurons was used as an indicator of ‘activation’ and the percent of activated GnRH neurons was quantified at the time of LH surge induction. The percent of activated GnRH neurons was significantly reduced in BPA and DES-exposed females relative to controls at 3-6 months of age, suggesting altered development of neuronal circuitry essential for reproductive cyclicity. In summary, these experiments show that perinatal BPA exposure interferes with at least two mechanisms of ovulation, the one triggered by ovarian steroids and the one triggered by parturition. Additionally, increased time to delivery in 9 month old exposed females suggests that a 3rd mechanism, reflex ovulation, may also be affected.

Source(s) of support:
Reference(s):
Placental human chorionic gonadotropin is associated with sex-specific development and the response to the endocrine disruptor mono-n-butyl phthalate.

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Background. Circulating levels of the placental hormone—human chorionic gonadotropin (hCG)—are higher in pregnant women carrying a female fetus versus those carrying a male. Yet, the role of hCG in sex-specific development is unexplored even though it was established early on that hCG is essential to the differentiation of the fetal testes. A highly prevalent endocrine disrupting compound, mono-n-butyl phthalate (MnBP), increases expression of the hCG alpha subunit in female placentas and decreases expression in male placentas. In male infants, prenatal phthalate exposure is associated with shorter anogenital distance (AGD) at birth—a marker of hormonal action in utero and fetal sex differentiation. The primary aim was to evaluate associations of hCG with placental function and with AGD in male and female neonates. Birthweight and gestational age are considered here as markers of placental function. The secondary aim is to test the hypothesis that MnBP disrupts male sexual differentiation through its action on placental hCG expression.

Methods. Subjects were enrolled in The Infant Development and Environment Study (TIDES), a multicenter prospective pregnancy cohort examining prenatal phthalate exposure and AGD. Phthalates and hCG were measured in urine and serum samples, respectively, collected in the first trimester. Neonatal exams were performed by trained study staff at birth. Multivariate linear regression was used to estimate sex-specific associations of the placental hormones with AGD (males: AS: anus to scrotum, AP: anus to penis; females AF: anus to fourchette; AC: anus to clitoris), birthweight for gestational age z-score, and gestational age, and urinary phthalate concentrations. To combine data across centers, we generated z-scores of the analyte values. We are currently applying mediation models appropriate for testing causal hypotheses using observational data.

Results. Male and female fetuses were modeled together to study sexual dimorphism (N=362). The hCG z-score was associated with lower AGD-AS in males (-0.64 mm per 1 unit increase in the hCG z-score, standard error (SE) 0.31) but not females (interaction of hCG by fetal sex p=0.03). MnBP was associated with higher hCG expression in female fetuses and lower expression in males (interaction p-value=0.01). hCG was associated with birthweight in females (+0.14 units in birthweight z-score per 1 unit increase in hCG) but not in males (interaction p=0.04). AGD-AP and AGD-AC were not correlated with first trimester placental hormones.

Conclusion. First trimester hCG, a sexually dimorphic placental hormone, was associated with a marker of sex differentiation in males at birth (AGD) and with placental function (birth size) in females. hCG was also associated with maternal exposure to a common endocrine disruptor, MnBP. Our investigation offers insight into the role of the human placenta in mediating effects of endocrine disruptors on sex-specific fetal development.

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Reference(s):
Phthalate Metabolite Levels in Follicular Fluid among Fertile and Infertile Women
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Background:
Phthalates are endocrine disruptors widely used in personal care, consumer products and in the plastic industry. Animal studies suggest that exposure to phthalate metabolites during the vulnerable period of oogenesis might impair follicular formation and affect oocyte maturation. The human oocyte is bathed in follicular fluid (FF) within the ovarian follicle. The aims of this study were (1) to identify and measure phthalate metabolite levels in follicular fluid (FF) and (2) to compare metabolite levels among patients undergoing in vitro fertilization (IVF) for infertility treatment and fertile women undergoing IVF for pre-implantation diagnosis (PGD) of genetic diseases.

Study design:
Following IRB approval, FF samples aspirated during oocyte (egg) retrieval from 80 patients (52 infertile, and 28 fertile) were collected and frozen. After enzyme hydrolysis, samples were extracted using solid phase extraction and analyzed using high performance liquid chromatography-tandem mass spectrometry with isotope dilution calibration. The presence of eight phthalate metabolites was assessed: mono-3-carboxypropyl phthalate (MCPP), monoethyl phthalate (MEP), mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-carboxypentyl) phthalate (MECPP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), monobutyl phthalate (MBP) and mono-iso-buty 1 phthalate (MiBP). Limits of detection (LODs) were 0.1ng/ml for MEHP, 0.05ng/ml for MECPP, MEP and MBP, 0.02ng/ml for MCPP, MEHHP and MEOHP and 0.025ng/ml for MiBP.

Results:
Patients from the fertile and infertile groups were of similar age (33.3±5.4 vs. 32.3±5.1, p<0.387, respectively). Six phthalate metabolites were detected in human FF (MCPP, MEP, MECPP, MEHPP, MBP and MiBP). The most prevalent metabolite was MECPP which was found in 98% of samples whereas MEHPP and MCPP were only detected in 5% and 1% of samples, MEP and MBP were each measured in 45% of samples, and MBP was detectable in 61%. Median concentrations and ranges of MEP, MBP, MiBP and MECPP metabolites did not differ among fertile and infertile women (MEP: 0.04ng/ml vs. 0.04ng/ml; MBP: 2.58 vs. 4.37ng/ml; MiBP: 0.01ng/ml vs. 0.01ng/ml; and MECPP: 0.81 ng/ml vs. 0.74ng/ml).

Discussion:
We found low levels of some phthalate metabolites in FF. One potential explanation for the low levels and low prevalence of detection for some phthalate metabolites may be because women undergoing IVF fast for at least 6 hours prior to oocyte (egg) retrieval, thus those food-borne phthalates with very short half-lives may have been mostly excreted prior to FF collection. FF levels of phthalate metabolites were similar among fertile and infertile patients. The association between low levels of phthalate metabolites in FF and fertility remains to be determined.

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Reference(s):
Maternal occupational exposure to Endocrine Disrupting Chemicals across Europe and Birth Outcomes

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Background: Many women of reproductive age are exposed to endocrine disruptors (EDCs) in the workplace. Occupational exposure to EDCs may adversely affect the development of the fetus.

Aims: This study assesses whether maternal occupational exposure to EDCs is associated with birth weight and length of gestation in a population-based birth cohort design.

Methods: We used data from more than 100,000 mother-child pairs enrolled in 12 European birth cohorts. We used the Job Exposure Matrix developed by Brouwers et al [1] to estimate occupational exposure to EDCs during pregnancy. This JEM classifies EDCs into 10 groups [polycyclic aromatic hydrocarbons (PAHs), polychlorinated organic compounds (PCBs), pesticides, phthalates, organic solvents, bisphenol A (BPA), alkylphenolic compounds (APCs), brominated flame-retardants (BFRs), metals, miscellaneous], and a “sumscore” group indicating exposure to any EDC group, and assigns three levels of exposure probability for each group: possibly, probably, and unlikely. We evaluated the association between maternal occupational exposure to EDCs and birth outcomes by comparing women classified as possibly and probably exposed to each of the EDCs groups with women classified as unlikely to be exposed to any EDC group. Outcomes assessed included birth weight, gestational age, small for gestational age (SGA), term low birth weight (term LBW), and preterm birth. We performed meta-analyses of cohort-specific estimates and explored heterogeneity.

Results: Eleven percent of women was classified as possibly or probably exposed to any of the EDCs groups in the workplace during pregnancy; 89% of women were classified as unlikely to be exposed to any EDC group and were used as comparison group. Women exposed to PAHs, pesticides, phthalates, organic solvents, APCs, metals, or any EDC group in the workplace were at higher risk for term LBW compared to women non-exposed to any EDC group (sumscore) [ORs ranging from 1.25 (95%CI: 1.02, 1.33) for the sumscore group to 2.39 (95%CI: 1.16, 4.91) for phthalates]. Exposure to organic solvents was also associated with an increased risk of SGA (OR: 1.11, 95%CI: 1.01, 1.21). Mothers occupationally exposed to BPA or BFRs during pregnancy were at risk for longer length of gestation (β 3.89, 95% CI: 0.70, 7.08; β 2.89 95% CI: 0.20, 5.59 respectively). These associations did not change after excluding the two largest cohorts from the analysis (79% of the population). There was little evidence for heterogeneity between cohorts.

Conclusion: This large European study suggests that occupational exposure during pregnancy to EDCs, particularly PAHs, pesticides, phthalates, organic solvents, APCs, and metals, is associated with impaired fetal growth at birth. Further studies are needed to elucidate the role of individual exposure to each of these compounds separately on birth outcomes.

Source(s) of support:

Reference(s):

Exposure to Bisphenol A and Phthalates during Pregnancy and Fetal Growth
Maribel Casas, PhD, Centre for Research in Environmental Epidemiology (CREAL)

Background: Prenatal exposure to bisphenol A (BPA) and phthalates may affect fetal growth and these effects may be sex-specific; however, previous findings are inconsistent and based on few studies.

Aims: We assessed whether prenatal exposure to BPA and phthalates affected fetal growth and birth outcomes in a Spanish birth cohort of 488 mother-child pairs.

Methods: We measured BPA and eight phthalates [five high molecular weight: four di-2-ethylhexyl phthalate metabolites (DEHPm) and, mono-benzyl phthalate (MBzP), and three low molecular weight phthalate metabolites (LMWPm)] in two spot-urines collected in the 1st and 3rd pregnancy trimesters. We estimated growth curves for femur length (FL), head circumference (HC), abdominal circumference (AC), biparietal diameter (BPD), and estimated fetal weight (EFW) during pregnancy (weeks 12-20 and 20-34), and for birth weight, birth length, head circumference at birth, and placental weight.

Results: Exposure to BPA and DEHPm during pregnancy was not associated with any of the outcomes studied. Prenatal MBzP exposure was positively associated with FL at 20-34 weeks resulting in an increase of 3.70% of the average FL (95% CI = 0.75 to 6.63) per doubling of MBzP concentration. In boys, MBzP was associated with an increase in birth weight of 48 g (95% CI = 6 to 90). The LMWPm mono-n-butyl phthalate (MnBP) decreased HC at 12-20 weeks (-4.88% of HC average [95% CI = -8.36 to -1.36]) but not in pregnancy. Confounding factors, extreme creatinine values, and other pollutants did not influence these associations.

Conclusion: This study, one of the first to combine repeat exposure biomarker measurements and multiple growth measures during pregnancy, finds little evidence for an effect of BPA or phthalate exposure on fetal growth. Phthalate metabolites MBzP and MnBP may affect some fetal growth parameters and these findings require replication.

Source(s) of support:

Reference(s):
Cord blood cadmium and fetal growth indices in a Bangladesh birth cohort

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Introduction: In humans, absorbed cadmium (Cd) is retained for decades in the kidney and liver, but during pregnancy it is distributed to and can permeate the placenta. As many of the mechanisms for metabolism and transport of cadmium intersect with those necessary for fetal development and nutrient delivery, it is plausible that exposure to Cd during pregnancy may impact fetal growth. In a cohort of Bangladeshi mother-infant pairs environmentally exposed to Cd, we investigated the association of cord blood Cd (CB-Cd) with birth measures.

Methods: A prospective birth cohort was recruited in Bangladesh from 2008-2011 (N=1,613). This study used data from 946 maternal-infant pairs. Pregnant women, all non-smokers, were drawn from two geographic areas in Bangladesh, enrolled during their first trimester and, through 4 study visits, followed until one month postpartum. Cord blood was collected at delivery and analyzed for Cd and other metals via ICP-MS. Birth weight, head circumference, and birth length were recorded at the time of delivery. We modeled the relationship between CB-Cd and each birth measure, adjusted for maternal covariates and co-exposure to other metals, using multivariable linear regression. To identify effect modification by gestational age, generalized additive models (GAMs) were used to describe the association of CB-Cd with birth weight across the range of gestational ages in our cohort.

Results: The median CB-Cd was 0.26 μg/L, and mean (SD) birth weight was 2,820 (386) g. In multivariable linear regression models, a 1-μg/L increase in CB-Cd was associated with a 31-g decline (95% CI: -53, -9; p=0.007) in birth weight adjusted for BMI, income, clinic, season of birth, CB-As, and CB-Mn; a 0.11-cm decline (95% CI: -0.18, -0.04; p=0.003) in head circumference after adjustment for BMI, income, clinic, CB-As, and CB-Mn; and a 0.39-cm decline (95% CI: -0.52, -0.25; p<0.001) in birth length after adjustment for income, clinic, and CB-Mn. Our GAM model results identified gestational age as an effect modifier of the association between CB-Cd and birth weight, with statistically significant negative associations of CB-Cd with birth weight appearing at gestational ages ≤ 36 weeks and no association at higher gestational ages. The significant effect sizes ranged from -420 g per 1-μg/L CB-Cd (95% CI: -638, -202) at 29 weeks’ gestation to -73 g per 1-μg/L CB-Cd (95% CI: -131, -15) at 36 weeks’ gestation.

Conclusion: Gestational age was found to be an effect modifier of the association between CB-Cd and birth weight, with an inverse relationship between size of the effect and gestational age up until 36 weeks, after which we saw no association between CB-Cd and birth weight.
Associations of cord blood cadmium with placental gene expression and fetal growth indices in a Bangladesh birth cohort

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Introduction: Leptin and 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) are important regulators of fetal growth. In vitro studies suggest that cadmium may inhibit the production of the gene transcripts that code for these proteins in placenta cells, but no epidemiologic studies have so far investigated this.

Methods: We used quantitative PCR (qPCR) to amplify and quantify the expression of candidate gene transcripts (lep and hsd11b2) in fetal placental tissue from the placentas of 80 women in a Bangladesh birth cohort. We first modeled the association of cord blood cadmium levels with normalized gene expression levels using ANOVA and multivariable linear regression models. We then investigated the association of gene transcripts with birth measures (birth weight, head circumference, birth length) in the cohort.

Results: After adjustment for maternal BMI, gestational age, and cord blood arsenic, we found no statistically significant overall association between cord blood Cd and expression of the target gene transcripts, although the associations for lep and hsd11b2 were in the expected directions. However, a 2-fold increase in leptin expression was associated with a 38-g decline in birth weight (95% CI: -73.4) while the same fold-change in leptin receptor expression was associated with a 161-g increase (95% CI: 34, 288). Expression of 11β-hydroxysteroid dehydrogenase type 2 was marginally associated (p=0.08) with a decline in birth weight.

Conclusion: Leptin gene expression was associated with a significant decrease in birth weight. We found no association of cord blood cadmium levels with either placental leptin or 11β-HSD2 mRNA expression.

Source(s) of support:
Reference(s):
The influence of arsenic exposure on infant birth size by maternal weight status among a sample of women in the Northeastern United States.

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In-utero exposure to arsenic (As) has been associated with decreased fetal growth in studies primarily conducted in As-endemic regions where malnutrition rates are also high. Limited data exist regarding fetal growth at lower-level As exposure. Moreover, few studies have assessed As exposure on birth size outcomes in the US where more than two-thirds of women are overweight or obese. In our previous work, we found that increased maternal As exposure related to an increased expression of the arsenite tranporter AQP9 in placental tissue, which, in turn, related to decreased expression of the phospholipase ENPP2 and decreased birth weight. ENPP2 is derived from adipose tissue and may regulate adipose tissue growth. Therefore, in the current study, we investigated the associations of maternal urinary As concentrations with gestational age (weeks), birth weight (g), birth length (cm), head circumference (cm) and ponderal index (PI, kg/m^3) among women enrolled in the prospective New Hampshire Birth Cohort Study by maternal weight status (N=706). The study enrolled pregnant women who used a private, unregulated water system at home and analyzed maternal urinary samples collected at approximately 24-28 weeks gestation. Samples were analyzed for As species (inorganic arsenic [iAs], monomethylarsonic acid [MMA] and dimethylarsinic acid [DMA]) using high-performance liquid chromatography. In a series of regression models adjusted for maternal age, BMI, education, infant sex and gestational age, MMA, DMA and total As concentrations were positively associated with birth length among overweight/obese women: β, 1 unit increase in outcome per ln-transformed measure (95% confidence interval): MMA 0.2 (0, 0.4), DMA 0.4 (0.01, 0.7) and total As 0.4 (0.1, 0.7) and inversely associated with PI among overweight/obese women: MMA -0.5 (-0.8, -0.2), DMA -0.8 (-1.2, -0.4) and total As -0.8 (-1.2, -0.4); As concentrations were not associated with birth length or PI among healthy weight women. There were no statistically significant associations with maternal As concentrations and gestational age, birth weight or head circumference. Results were similar when limited to women (N=594) who did not consume seafood in the two days prior to urine collection. These initial findings suggest that low-dose in-utero As exposure during pregnancy may impact fetal growth in our population, particularly among overweight or obese women.

Source(s) of support:
Reference(s):
Does variation in fetal growth rate affect maternal concentrations of perfluoroalkyl acids during pregnancy?

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Background: Epidemiological studies have consistently observed modest inverse association between maternal concentrations of perfluoroalkyl acids (PFAAs) and birth weight. Although minimally addressed, it has been suggested that these associations could be confounded by shared determinants of PFAA concentrations and birth weight including maternal blood volume expansion, variation in glomular filtration rate and fetal uptake.

Aim: To examine whether variation in fetal growth rate affects maternal concentrations of perfluorooctane sulfonate (PFOS) perfluorooctanoic acid (PFOA) in pregnancy.

Methods: In 1988-89 a total of 965 pregnant women were recruited in week 30 of gestation for the birth cohort “DaFO88” in Aarhus, Denmark. As our target population we selected women of normal pre-pregnancy body mass index with singleton term pregnancies who provided blood samples in weeks 30 and week 37 of gestation (n=420). Using a nested case control design we then selected 35 mothers whose offspring had the highest and 35 mother whose offspring had the lowest birth weight z-scores for gestational age and sex. Changes in PFAA concentrations between week 30 and 37 between the two groups were then compared.

Results: The mean birth weight (range) in the high and low birth weight groups was 2.8kg (2.0-3.2) and 4.3kg (3.6, 5.5), respectively. This corresponded to a mean difference of around 3.4 z-scores in birth weight between the two groups. The mean PFOA concentrations in week 30 were 4.1 and 4.2 ng/ml in the high and low birth weight groups respectively. By week 37 maternal PFOA concentrations had decreased by approximately 0.5-0.7ng/mL in both groups and the mean decrease did not differ significantly between the two groups (p=0.35). However when stratified by parity there was on average a 0.6ng/mL (95% confidence interval 0.1, 1.0) larger decrease in PFOA concentrations between weeks 30 and 37 among parous women in the high compared to low birth weight group. Changes in concentrations among nulliparous women were, however, stable and not significantly different between the high and low birth weight groups. When examining associations between maternal PFOA concentrations in week 30 of gestation and birth weight in our target population (n=420) no association was observed among nulliparous women (n=244, p for trend =0.25) while a modest inverse association was observed for parous women (n=176, p for trend =0.01). Similar pattern was observed for maternal PFOS concentrations.

Conclusion: Overall changes in maternal PFOA and PFOS concentration between week 30 and 37 of gestation did not differ among women giving birth to relatively high versus low birth weight infants. However, maternal PFOA and PFOS concentrations appeared to be less stable between week 30 and 37 among parous women and this instability might explain a modest inverse association observed between maternal PFOA concentrations and birth weight among parous women only in our cohort.

Source(s) of support:

Reference(s):
Manipulation of pre- and postnatal androgen environments and male anogenital distance in rats

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Anogenital distance (AGD) (the distance from the anus to the genitals) has been used as an external indicator of prenatal androgen production/action in toxicological and epidemiological studies. In laboratory animals and humans, a shortened (feminized) AGD in males is associated with the incidence and severity of several reproductive tract abnormalities and impaired reproductive function. Although AGD has been proposed as a stable landmark that can retrospectively indicate fetal androgen exposure, there is no conclusive data on the effects of postnatal androgen exposure/privation on AGD. In the present study, we have investigated the effects of the manipulation of pre- and postnatal androgen environments on male rat AGD. Wistar rat dams were treated from gestation day 13 to 20 with canola oil (vehicle), the androgen receptor antagonist flutamide (20 mg/kg/day), the plasticizer di(2-ethylhexyl) phthalate - DEHP – (750 mg/kg/day), or testosterone (1.0 mg/kg/day). All substances were given by oral route with exception of testosterone, which was administered by subcutaneous injections. On postnatal day four, male pups were individually marked and AGD was measured by digital caliper, adjusted for cubic root of body weight. After weaning, male pups within each litter were randomly assigned to one of four postnatal groups using a split-litter design. Each of the four groups was given one of the prenatal treatments – vehicle, flutamide, DEHP, or testosterone – using the same doses and routes. Thus, sixteen treatment groups were established based on the combination of pre- and postnatal exposures. The postnatal treatment was continued for 30 days from postnatal day 23. At the end of the treatment (postnatal day 53), AGD was measured again and corrected by body weight. A total of 10-12 dams/group will be used, but here we report results from the first set of experiments with 3-7 dams/group. AGD on postnatal day 4, reflecting the effects of in utero treatments, was reduced by 38% and 13% in flutamide and DEHP groups, respectively, when compared to control, but no changes were observed in testosterone-treated animals. We saw no change in AGD on day 53 in rats treated postnatally with either flutamide or DEHP, indicating absence of any postnatal effects of anti-androgens on AGD, regardless of the prenatal treatment. Similarly, postnatal treatment with testosterone did not alter AGD on day 53 in any experimental group, including animals that had shortened AGD following prenatal treatment with flutamide. On the other hand, other androgen-dependent parameters, like the age of preputial separation, were responsive to postnatal treatment to anti-androgens and testosterone. Overall, these preliminary data lend support to the hypothesis that AGD is a stable marker programmed in utero by androgens and that postnatal androgen manipulation does not alter this developmental landmark.

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Reference(s):
Spermatogenic capacity in fertile men with high exposure to polychlorinated biphenyls

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Background: Endocrine disrupting industrial chemicals, such as polychlorinated biphenyls (PCBs), are suspected to adversely affect male reproductive functions.

Objectives: The Faroe Islands community exhibits an unusually wide range of exposures to dietary contaminants, and in this setting we examined the possible association between PCB exposure and reproductive function parameters in fertile Faroese males.

Methods: Participants in this cross-sectional study included 266 proven fertile men residing at the Faroe Islands. PCB and hormone profiles were measured in serum samples at clinical examinations that included sperm quality parameters.

Results: Elevated PCB exposure was associated with increased serum concentrations of FSH (medians, 3.9 and 3.0 IU/L in the highest and lowest quartiles of PCB, p=0.05) and SHBG (medians, 43 and 38 nmol/L in the highest and lowest PCB quartiles, p=0.01) and a significant positive association was seen between serum-PCB and the testosterone/estradiol ratio (p=0.04). We found no association between the serum PCB concentration and the semen quality variables, although there was a tendency toward a higher percentage of morphologically normal spermatozoa in men with high PCB exposures.

Conclusion: In this population of highly exposed fertile men, a high serum-PCB concentration seemed to be adversely associated with the spermatogenic capacity of the testicles and the hepatic SHBG production. The adverse effect on the spermatogenesis appeared to be compensated by an increased stimulation by the gonadotropin FSH.

Source(s) of support:

Reference(s):
Urinary paraben exposure, reproducibility, and reproductive hormones in premenopausal women

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Exposure to parabens is widespread through personal care products, medications and food; where they are added as antimicrobial preservatives. Limited evidence suggests that parabens may act as estrogenic endocrine disruptors. Further, parabens are nonpersistent and we sought to evaluate their reproducibility among a cohort of healthy, premenopausal women. Six parabens were measured, methyl (MeP), ethyl (EtP), propyl (PrP), butyl (BuP), heptyl (HeP), and benzyl (BzP) paraben from stored urine specimens (n=509) at key time points of hormonal variation (during menses, mid-cycle/ovulation, mid-luteal phase) across two menstrual cycles in 143 women for an average of 3.6 measurements per woman. Estrogen, follicle stimulating hormone (FSH), luteinizing hormone (LH), and progesterone were measured in blood across both cycles. Mixed models were used to evaluate reproducibility of parabens across two menstrual cycles using intraclass correlation coefficients (ICCs). Linear mixed models with inverse probability of exposure weights were used to evaluate the relationship between log-transformed chemicals and hormones. Geometric mean (95% CI) levels were: BuP 0.26 (0.20, 0.34), BzP 0.01 (0.009, 0.01), EtP 0.85 (0.69, 1.06), MeP 49.47 (43.16, 56.70), PrP 12.51 (10.59, 14.77) ng/ml. ICCs for log-transformed parabens were highest for MeP [0.62 (95% CI 0.54, 0.69)] and lowest for HeP [0.11 (0.05, 0.23)], while most analytes had moderate reproducibility with ICCs between 0.4-0.5. MeP and PrP values were statistically significantly higher among black women and older women while HeP was higher among younger women. There was some evidence that parabens varied across the course of the menstrual cycle. Other parabens were not associated with race, age, or body mass index. Parabens were not associated with reproductive hormones among this population of healthy young women.

Source(s) of support: NICHD Intramural Research Funding

Reference(s):
Assessing the prevalence of phthalate metabolites in a population of pregnant women

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Endocrine disrupting compounds (EDCs) are substances that disrupt normal functioning of the endocrine system. Phthalates are known endocrine disruptors, which are used commercially as plasticizers or solubilizers, and are commonly found in PVC plastics, food packaging, and personal care products. Phthalates are metabolized rapidly, but are so ubiquitous in our environment that they have been referred to as pseudo-persistent chemicals. In the U.S., 99-100% of pregnant women have detectable levels of phthalates (1), which raises concern over their effects during fetal development. Phthalates are anti-androgenic and exposure in utero leads to abnormal sexual development in male rodents (2). Recent studies have supported the hypothesis that prenatal phthalate exposure at environmental levels can adversely affect male reproductive development in humans as well (3). Here, we sampled urine from a population of 135 women pregnant with male fetuses and examined eight phthalate monoester metabolites: Mono-butyl phthalate (MBP), mono-benzyl phthalate (MBzP), mono-ethyl-hexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MiBP), and mono-methyl phthalate (MMP). Phthalate metabolites were detected in every maternal urine sample, and concentrations detected in this study were similar to those reported elsewhere. On average, concentrations of MEP were the highest (median = 46.92 ng/ml), and concentrations of MMP were the lowest (median = 2.44 ng/ml). African American women made up 48.2% of our patient population, while 47.7% were Caucasian. The mean age of participants was 27.4 years old, the mean body mass index (BMI) was 29.5, and 85.8% of participants were non-smokers. We observed a significant positive correlation (p < .01) between maternal BMI for all phthalate metabolites except MEHP. In addition, race/ethnicity was significantly correlated (p < .01) with all analytes except MEHHP, with higher concentrations in African American compared to Caucasian women. Our results indicate that infants of African American mothers or mothers with above average BMI may be at higher risk of prenatal phthalate exposure. We are in the process of determining whether higher concentrations of these analytes are correlated with measures of reproductive development.

Source(s) of support:
Reference(s):
High odds ratios for hyperemesis gravidarum associated with exposure to carbon monoxide sources and multi-sensory sensitivity during pregnancy

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Hyperemesis gravidarum [HG] is a potentially fatal disorder of nausea and vomiting that afflicts approximately 1-3% of all pregnancies for more than 3 months and usually persists until the day of termination or birth. Hormonal causes are suspected, but sufferers also report multi-sensory sensitivity to lights, sounds, odors, tastes, and/or touch which is a hallmark of carbon monoxide [CO] poisoning. Given this overlap, we developed a survey to test the hypothesis that exposure to CO sources such as gas appliances during pregnancy may be a significant risk factor for HG. Whether CO poisoning is the cause will require prospective studies.

We attended an HG rally organized by HELPER.org at National Harbor, MD on May 12, 2013, and with the executive director’s permission, randomly recruited 39 mothers to complete an anonymous questionnaire: 15 with no HG pregnancies and 24 with one or more; all but one of them non-smokers. We asked about 5 sensory sensitivities and 11 sources of CO exposure during their last pregnancy. Consistent with the hypothesis, the number of sources of CO exposure in pregnancy correlated positively with the prevalence of HG and multi-sensory sensitivity syndrome (MUSES), defined by the authors as chronic hypervigilance affecting 4 or 5 senses.

None of the mothers with HG-free pregnancies developed MUSES and the average number of CO sources to which they were exposed while pregnant was just 1.1 [range 0-5]. Over half [53%] lived in all-electric homes that did not store vehicles in attached garages. In contrast, 11 mothers with HG alone averaged 1.9 sources of CO exposure during pregnancy [range 0-4], and 13 with both HG and MUSES averaged 3.4 [range 0-10]. Only 17% lived in all-electric homes. The odds ratios for CO exposures and MUSES syndrome being associated with HG were 5.7 (p=.02) and 36.4 (p=.002), respectively.

We have since developed a longer anonymous survey asking mothers about 75 possible toxic exposures: 33 in the home, 20 outdoors and 22 in the workplace. This is posted at www.SurveyMonkey.com/s/HGresearch. It also asks mothers if they experienced any of 38 other possibly CO-related disorders before, during or after pregnancy, such as chronic fatigue syndrome and fibromyalgia, and whether any of these same disorders have been diagnosed or are suspected in their children. An additional hypothesis in this larger survey is that children exposed to CO sources in utero and/or in childhood have higher odds of MUSES and other CO-related disorders than children conceived and raised in homes without CO sources. Preliminary results based on responses received through September 2014 will be presented at the Endocrine Society’s PPTOX-IV conference.

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Reference(s):
Search for the signaling pathways involved in the hepatic tumor increase in the F2 male C3H mice born to gestationally arsenite-exposed F0 females

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Gestational exposure can affect not only F1 generation but also F2 generation through exposure of F1 germ cells. Male of C3H mice are prone to stochastically develop spontaneous hepatic tumors in adulthood. Previous studies by others and us showed that gestational arsenite exposure of female C3H mice (F0) increases late-onset hepatic tumor incidence in the F1 males. Recently we have further showed that gestational arsenite exposure of F0 females increases hepatic tumors even in the F2 males (arsenite-F2 males). Reciprocal crossing experiment among the control and arsenite-F1 males and females showed that the tumor-increasing phenotype by gestational arsenite exposure is transmitted to the F2 males via the F1 males irrespective of exposure of F1 females. In the present study, aiming at characterizing the hepatic tumors in arsenite-F2 males, we investigated gene expression changes focusing on several signaling pathways that have been reported to be involved in hepatic cancers and cancers in other organs by previous studies. The results of the assay detected activation of a variety of genes involved in several signaling pathways, including NF-κB and β-catenin signaling pathway, in the tumors compared to the normal tissues in both the control and arsenite-F2 males. Among the genes participating in these signaling pathways, we found genes whose expression are more greatly affected in the tumors of the arsenite-F2 males compared to that of the control males. These results suggest that gestational arsenite-exposure further augments activation of the signaling pathways that are involved in the development of spontaneous hepatic tumors in the male C3H mice. Further study is required to identify the key reaction that leads to activation of the oncogenic signaling pathways in the adult liver of gestationally arsenite-exposed F2 male. It is also an open question how gestational exposure of F1 fetus or germ cell induces the key reaction in the F2 liver.

Source(s) of support:
Reference(s):
Centrosome amplification in prostate cells induced by bisphenol A and its analogues
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The adverse health effects caused by endocrine disrupting chemicals (EDCs) are extensive. Bisphenol A (BPA), a prototype EDC, is a mimic of estrogen used in the manufacture of polycarbonate plastics and epoxy resins contained in a variety of consumer products, as well as in thermal paper used for printing receipts. However, leakage of BPA from these products results in its ubiquitous presence at significant levels in the environment. Its estrogenic effects suggest it can reprogram the developing human and animal tissues, particularly those sensitive to estrogens such as the prostate. As a result, alternatives to BPA are being developed and are increasingly replacing BPA. Alarmingly, structural analogues of BPA have already been detected in foods, in thermal receipt papers and in humans.

Chromosome instability (CIN) is one of the most important phenotypes in tumor progression, introducing multiple mutations required for acquisition of further malignant characteristics. Abnormal amplification of centrosomes, the organelles which form the spindle poles, is frequently observed in human cancer and has been shown to contribute to CIN by increasing frequency of mitotic defects. We had found that low dose BPA (100 pM) increased centrosome amplification, promoted microtubule (MT) nucleation and regrowth at centrosomes and enhanced anchorage-independent growth, all of which characterize cancer initiation and progression.

We hypothesize that chronic exposure to low-dose environmentally relevant levels of BPA and some of its analogues, can augment the risk to prostate carcinogenesis. We have thus examined, in cell-based models (RWPE-1, LNCaP, C4-2), the adverse effects of BPA/analogues on the centrosome cycle and MT dynamics, as a mechanism contributing to prostate carcinogenesis. We find that from the 6 BPA-analogues examined, Bisphenol S (4,4'-sulfonyldiphenol, BPS), and 2,2'-Bis(4-hydroxy-3-methylphenyl)propane (DMBPA/BPRO) induced amplification of centrosome numbers. Using antagonists, we identified ERα as an upstream receptor responsible for BPA-induced centrosome dysregulation in prostate cancer cells. Nucleophosmin (NPM) is a key molecule whose dissociation from non-duplicated centrosomes is the first step for centrosome duplication. We found that NPM dissociated from non-duplicated centrosomes at an earlier timepoint in G1-phase in the presence of BPA. We have now identified four cell cycle regulators, involved in NPM-centrosome interaction, whose expression is changed by BPA. Three of these are kinases involved in cancer progression. Our results thus indicate that BPA, BPS and DMBPA, through ER-α, induce centrosome amplification.

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**Abstract type:** Basic Research  
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**Effects of Developmental Exposure to Nonylphenol and alpha-Zearalenol on Adult Energy and Glucose Homeostasis**  
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Environmental chemicals with estrogenic activity can disrupt developmental programming in early life that lead adverse effects in the adult. These estrogenic endocrine disrupting compounds (EDC) have most recently been linked to the development of obesity and type-2 diabetes in adults. Zearalenone, and its metabolite alpha-zearalenol (Z), is an EDC with known estrogenic capabilities. Nonylphenol (N) is an EDC with a similar profile. The effects of maternal exposure to either one of these two compounds on adult energy homeostasis is mostly unknown. Pregnant C57 mice received either vehicle, 17alpha-ethynylestradiol (0.25 microg/kg/day), Z (0.5 and 50 microg/kg/day), or N (5 and 500 microg/kg/day) from gestation day 7 to postnatal day 7. At postnatal day 21 pups were sorted by sex and given either normal diet (ND) or high fat diet (HFD). Weekly food intake and body weights were tracked. At postnatal day 112 pups were subjected to body composition tests, metabolic tracking, glucose homeostasis tests, blood chemistry tests, and dissected to determine uterine weight. Z effected glucose tolerance and insulin sensitivity in a sex-specific manner. Female mice were more glucose tolerant and insulin sensitive. Male mice were less glucose tolerant and more insulin resistant. There was no consistent pattern of findings across parameters of obesity for any treatment. Developmental exposure to Z affects the glucose homeostasis of both male and female adult mice. Z and N have various effects on parameters of obesity dependent on the diet and sex of the mouse when they are exposed during development.

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High sensitivity detection of exogenous and endogenous analytes by electron capture atmospheric pressure chemical ionization mass spectrometry
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Concentrations of molecules within human biospecimens including blood can range over 11 orders of magnitude. The challenge in detection of trace compounds is exacerbated by the need to preserve precious samples, and the inherent complexity of any biological matrix. Therefore, to detect trace levels of compounds of interest from a biological sample, sensitive and specific methodology is required. To meet this stringent methodological requirement, we examined the performance of liquid chromatography-electron capture atmospheric pressure chemical ionization mass spectrometry (LC-ECAPCI-MS) for detection of endogenous carboxylic acids, non-steroidal anti-inflammatory drugs (NSAIDs), and the endocrine disrupting compound bisphenolA. Samples were spiked with appropriate isotopically labeled internal standards, and then derivatized using pentafluorobenzyl bromide. LC was performed using a chiral normal phase separation on a ChiralPak ADH column. MS/MS was performed on a Thermo TSQ Quantum using an atmospheric pressure chemical ionization source. Across compounds, the method proved robust and highly sensitive, allowing detection limits orders of magnitude below reported literature values. Furthermore, the method provided chiral separation for the endogenous proto-oncometabolite (R)-2-hydroxyglutarate from (S)-2-hydroxyglutarate, as well as for the chiral NSAID metabolite racemic hydroxy-ibuprofen. Finally, the method is amenable to high resolution MS on an Orbitrap mass spectrometer, potentially making high sensitivity untargeted metabolomics feasible using this method.

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Reference(s):
Low prenatal vitamin D exposure associated with increased risk of prediabetes in Faroese adolescents
Christine Dalgård, PhD, MSc, University of Southern Denmark; Maria S Petersen, The Faroese Hospital System, Faroe Islands; Pál Weihe, The Faroese Hospital System, Faroe Islands; Philippe Grandjean, University of Southern Denmark, Denmark

Observational studies suggest that a low vitamin D status, indicated by the serum 25-hydroxy vitamin D (25OHD) concentration, may predispose to abnormal glucose homeostasis in adults. As less attention has been paid to the role of developmental vitamin D exposure and future risk of disturbed glucose metabolism, we measured blood glycosylated hemoglobin (HbA1c) concentrations and used HbA1c>5.7% as marker of prediabetes in adolescent members of a Faroese birth cohort, where the umbilical cord serum 25OHD concentration was measured as marker of prenatal vitamin D exposure.

At follow-up, 405 adolescents (mean age 13.3 years; range: 12.1 – 15.0 y) had available measures of prenatal 25OHD exposure, glycosylated hemoglobin HbA1c, and information on covariates for the present study. The median serum 25OHD concentration was 24.6 (25%-75% percentiles; [15.0 – 36.0]) nmol/L and 82 (18 %) were severely deficient, i.e. the 25OHD concentration was lower than12 nmol/L. A total of 130 (32%) subjects were vitamin D deficient, i.e., 25OHD<25 nmol/L, and 172 (37%) were insufficient, i.e. 25OHD between 25 and 50 nmol/L. Approximately 5% of the adolescents had prediabetes by HbA1c.

Although not statistically significant, HbA1c was increased in subjects with deficient (β-coef (95% CI): 0.09 (-0.01 - 0.18), p=0.07) or insufficient (β-coef (95% CI): 0.07 (-0.02 - 0.16), p=0.13) vitamin D status after adjustment for sex, age, BMI, and birth month. However, further adjustment for non-fasting glucose strengthened somewhat the regression coefficient, and the p values became significant.

Furthermore, vitamin D deficiency showed an increase in prediabetes risk as compared with subjects with better vitamin D status, (odds ratio [OR] 1.5 [95% CI 0.62-→ 3.63]; p =0.375) after adjustment for sex, age, BMI, and birth month. Again, results were not statistically significant.

In conclusion, low prenatal vitamin D status tended to associate with increased HbA1c and thus an increased risk of prediabetes. If replicated in larger studies, vitamin D supplementation during pregnancy may be an important add-on preventive strategy to decrease future risk of diabetes.

Source(s) of support:
Reference(s):
Impact of gestational bisphenol A on oxidative stress and free fatty acids - a multispecies study

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Bisphenol A (BPA) is a high production volume chemical and an endocrine disruptor. Developmental exposures to BPA have been linked to adult metabolic pathologies, including type 2 diabetes, but the pathways through which these disruptions occur remains unknown. Free fatty acid imbalance and oxidative stress are common traits of disorders manifesting insulin resistance and are thus potential targets for insult from BPA. Recently, we found that women exposed to higher unconjugated BPA (uBPA) (27.8 ± 8.4 ng/ml, n=12, mean±SEM) during early to mid-pregnancy (8-14 weeks of pregnancy) and their matching term cord samples had a 4 fold increase in 3-nitrotyrosine levels, a marker of nitrosative stress relative to those with low uBPA levels (0.08 ± 0.01 ng/ml, n=12, mean ± SEM) [1]. For this study, BPA measures were performed using the Round Robin validated method [2]. Interestingly, high BPA exposed mothers also had increased palmitic acid, that positively correlated with levels of 3-nitrotyrosine. To determine if the positive association found in human pregnancies between BPA and oxidative stress was indeed a response to high BPA exposure, a multispecies study was undertaken. Blood and adipose tissue samples from adult sheep, rats and mice prenatally treated with relevant human exposure levels of BPA (sheep: 0.5 and 5mg/kg BW, sc injections; rats: 50 µg/kg and 50 mg/kg BW, via vanilla wafer cookie; and mice: 50 mg/kg diet) and blood samples from female fetuses of sheep (day 65 and 90 of gestation) were obtained to assess the impact of BPA on oxidative stress and free fatty acid homeostasis. Internal doses of BPA achieved with the treatment doses used in this study were found to be within human exposure levels in previous studies. Products of tyrosine oxidation (chlorotyrosine, dityrosine, and nitrotyrosine), markers of oxidative stress and free fatty acids were measured using isotopic dilution liquid chromatography electrospray ionization tandem mass spectrometry and gas chromatography, respectively. Statistical analysis revealed that plasma samples from sheep fetuses at both ages, as well as plasma and adipose tissue of adult sheep and rats treated prenatally with BPA had significantly increased levels of plasma 3-nitrotyrosine. The strongest effect of BPA treatment on circulating free fatty acids was observed in adult mice in the absence of increased oxidative stress, manifested as a reduction in myristic acid. This is the first multispecies study that addresses the direct impact of prenatal BPA treatment on oxidative stress and free fatty acid dynamics. These animal studies in concert with the earlier human findings provide evidence supportive of the induction of nitrosative stress by prenatal BPA exposure and raises the exciting possibility of use of maternal 3-nitrotyrosine as a biomarker for offspring health.

Source(s) of support: NIH Grant NIEHS R01 ES016541; NIH Grant NIEHS P01 ES022844
Reference(s):
(1) Veiga-Lopez et al., ICE/ENDO Meetings 2014, LB-OR01-5.
(2) Vandenberg et al., Environ Health 2014; 13:25.
Developmental Exposure to PBDE and Metabolism Reprograming via mTOR Pathway

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Polybrominated diphenyl ethers (PBDEs) is a group of flame-retardants with endocrine disruptive properties. Accumulating experimental and epidemiological evidence links developmental exposures to PBDEs with the current epidemic of metabolic disorders. We hypothesize, that effects of PBDE toxicity may be mediated by mTOR – a metabolic master-switch which at starvation suppresses biosynthetic programs and increases the recycling of proteins and organelles to provide an internal resource of metabolites and upon stimulation by nutrients and growth factors causes activation of biosynthesis and suppression of autophagy. To test this hypothesis we use publicly accessible data on transcriptome changes in response to PBDE exposure in mammalian models. We predicted that given our hypothesis is true, then big blocks of functionally related molecules, targets of the mTOR pathway, would be coregulated. Namely, we predicted that ribosomal, mitochondrial genes and genes – targets of PPARγ will be regulated in one direction, while phagosomal genes and genes – targets of PPARα will be regulated in the opposite direction in exposed animals. The results of gene-set enrichment analysis correspond to our prediction for all 5 genomic datasets used in this study. Regulation of functional groups of genes after perinatal exposure to PBDE was very similar across tissues and time points indicative of long-term and global reprogramming of metabolic profile of the organism. The response of mTOR pathway to PBDE exposure is likely mediated through autocrine, paracrine and endocrine IGF signaling. Our hypothetical mechanism of metabolic reprogramming by PBDE explains some controversy concerning the ability of PBDE to induce PPAR. Structure-activity analysis predicted that PBDEs do not have potential for PPAR interaction. However it was shown in several studies that PBDEs induce PPARγ, adipocyte differentiation, and lipid accumulation. According to our model induction of PPARγ is not a direct effect of exposure, but rather a downstream consequence of mTORC1 activation. mTOR-centered molecular pathway is a major pathway of regulation of growth and metabolism, linked to aging and to the development of cancer, obesity, and type 2 diabetes. The potency of PBDE to reprogram this pathway raises concern for public health and calls for an additional research of mTOR pathway sensitivity to environmental stressors.

Source(s) of support:
Reference(s):
Early Life Exposure to Metals and Precursors of Diabetes: A Prospective Birth Cohort Study
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Background: The epidemics of diabetes may be due, in part, to chemical exposures in-utero and during early childhood. These early developmental periods are most vulnerable to environmental exposures, and are critical stages for metabolic conditioning and subsequent risk of diabetes. Mercury (Hg), lead (Pb), and selenium (Se) have drawn attention because of their widespread distribution worldwide, transplacental and breast milk passage, fetotoxicity, and multi-organ effects. Hg levels were associated with incident diabetes in a large prospective study of young adults. Pb is an established risk factor for hypertension, that is part of the metabolic syndrome definition. Se is an essential nutrient with a narrow safety margin and it has been related to increased diabetes risk in observational studies and interventional trials. To date, the effects of these metals on metabolic disorders have been studied almost exclusively in adults. There is a scarcity of adequately powered birth cohort studies that prospectively ascertain exposures to Hg, Pb, and Se, and assess metabolic consequences, across developmental stages.

Objective: To present our preliminary work on (1) exposure to metals in utero and early childhood; (2) association of in-utero metal exposure with preterm birth; and (3) association of preterm birth with elevated plasma insulin levels (a surrogate marker of insulin resistance) at birth and early childhood.

Results: We measured levels of Cd, Hg, Pb, and Se in 50 paired maternal and cord blood samples from the Boston Birth Cohort (BBC), a large-scale U.S. urban predominantly minority cohort. Maternal exposure to these metals was 100% detectable, and there was a high degree of maternal-fetal transfer of Hg, Pb, and Se. In particular, we found that higher levels of Hg in maternal and cord blood were associated with increased risk of preterm births in a dose-response fashion. Furthermore, we investigated the relationship between preterm birth and plasma insulin level among 1358 children in the BBC. We found that the more severe the prematurity, the higher levels of plasma insulin at birth, which persisted into early childhood (up to 6.5 years).

Conclusion: Maternal exposure to Hg, Pb, and Se was widespread in the BBC, and maternal-fetal transfer was a major source of early life exposure to Hg, Pb, and Se. Fetal Hg exposure was associated with increased risk of preterm birth. Our findings underscore the importance of recognizing preterm birth as a risk factor for future development of insulin resistance and type 2 diabetes. It also raises the possibility that preterm birth may be a mediator of prenatal exposure to environmental toxicants and later metabolic outcomes. More work remain to be done in order to better understand metal exposure-diabetes relationships over a life course; and identify sensitive and reliable biomarkers that can reflect early biological effects and inform long-term metabolic risk.

Source(s) of support: This study is supported in part by the grants from the National Institute of Health (R21 ES011666; R01 HD32505; R01 ES11682; R03 ES022790).

Reference(s):
(1) Chen et al, J Expo Sci Environ Epidemiol, 2014
(2) Wang et al, JAMA, 2014 and JAMA Editorial in the same issue
Methylmercury burden of disease estimate among riverside populations in the Amazon: health program development with the Minamata convention

Ana Boischio, PAHO

Mercury, in it is diversity of forms and compounds is a global neurotoxic pollutant currently addressed in the Minamata convention on mercury, a global binding environmental agreement, where health aspects are directly addressed. Health program development to address populations at increased risk of exposures is included in the convention. Exposures to methyl mercury (MeHg) during prenatal life, at relatively low levels have been recently proven to be harmful to neurodevelopment. Methods to estimate MeHg induced mild intelligence disability (formerly named mild mental retardation) can be used to identify critically exposed populations for short, medium term and long term risk mitigation health programs.

In the Amazon, different sources of mercury, including deforestation, soil erosion, and artisanal small scale gold mining activities, has contributed to the uneven pollution of aquatic food chains, which are used by riverside populations. These are often heavy fish eaters, given the richness of fish availability and diversity, and limited access to other protein sources. Along the Madeira River, mothers and infants have been investigated, during the 1990s and 2010s, with maternal hair mercury concentration means from 12 and 17 ppm and standard deviations from 6 and 18 ppm, respectively; infant hair mercury concentration means from 4 to 10 ppm and standard deviations from 3 to 7 ppm, respectively.

The WHO environmental burden of disease series has been used to estimate the incidence rate of mild intelligence disability and the Disability-Adjusted Life Years (DALYs). Using different disability weights and other parameters and assumptions, preliminary results among mothers range from 20 to 150 DALYs per 1,000 newborns, and among infants from 6 to 70 DALYs per 1,000 newborns. These figures are discussed in terms of methodological assumptions, applications and results utilization. These results are consistent with the conclusions made from a systematic review of MeHg biomarkers, where the combination of artisanal and small scale gold mining activities with fish consumption among riverside population has been considered of high risk at the global level.

Under the Minamata convention, local and national estimated DALYs can be used for policy orientation on health services. Identification of critically exposed populations should be target for short term risk mitigation with locally tailored fish advisories. The healthy balance of benefits and risks of fish consumption, in the specific conditions of exposed populations, should be included in health promotion programs. The WHO tools – with guidelines, protocols and methodologies to address health aspects of mercury exposures are available to develop health programs for monitoring and risk communication for women at reproductive age, in the context of the Minamata convention implementation.

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**Prenatal exposure to organic solvents and neurocognitive performance in 6-year-old children**

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Oxygenated solvents, including glycol ethers, are present in a wide range of occupational and domestic products, including paints, cosmetics, and cleaning products. Some of them are suspected reproductive or developmental toxicants in humans. Using maternal urinary metabolites as biomarkers of exposure for glycol ethers within a longitudinal birth cohort, this study aims to determine the impact of prenatal exposure on neurocognitive performance in 6-year-old children.

Participants come from the PELAGIE mother-child cohort in Brittany, France. Women were recruited during pregnancy and returned a questionnaire and urine sample in which 5 alkoxyacetic acids were measured. A random subcohort of children (n=287) was evaluated with neuropsychological tests at 6 years of age using the Wechsler Intelligence Scale for Children (WISC IV) and the NEPSY. Statistical analysis was conducted using both linear and negative binomial regressions with a priori adjustment, including scores of maternal intelligence and familial stimulations.

Increasing prenatal urinary concentration of PhAA (phenoxyacetic acid, 95% detected, with precursors mainly contained in cosmetics) was associated with decreasing score of the WISC Verbal Comprehension Index [β_1st tertile = ref, β_2nd tertile = -3.2 (CI95%: -7.9, 1.5), β_3rd tertile = -6.2 (-10.8, -1.6), p trend = 0.01]. Simultaneously, increasing urinary concentrations of MAA (methoxyacetic acid, 50% detected, with precursors mainly contained in cleaning agents) was associated with increasing score of the WISC Verbal Comprehension Index [β_nondetects = ref, β_detects≤median = 1.9 (-4.1, 8.0), β_detects>median= 5.1 (1.0, 9.2), p trend = 0.01]. Other glycol ether metabolites or NEPSY scores did not show any significant association.

This study is the first to assess neurocognitive performance in children prenatally exposed to glycol ethers, using urinary biomarkers of exposure. The findings related to the urine MAA metabolite is unexpected and might reflect uncontrolled confounding in the associations tested.

**Source(s) of support:** The French National Research Agency (ANR)

**Reference(s):**
Developmental Fluoride Neurotoxicity in Chinese Children
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Background: Fluoride may cause neurotoxicity in animal models and acute fluoride poisoning causes neurotoxicity in adults, but very little is known of its effects on the neurodevelopment of children.

Method: We first performed a systematic review and meta-analysis of published studies to investigate the effects of increased fluoride exposure and delayed neurobehavioral development. We searched the MEDLINE, EMBASE, Water Resources Abstracts, and TOXNET databases through 2011 for eligible studies. We also searched the China National Knowledge Infrastructure database because many studies on fluoride neurotoxicity have been published in Chinese journals only. We identified 27 eligible epidemiological studies with high and reference exposures, and endpoints of IQ scores. Using random-effects models, we estimated the standardized mean difference between exposed and reference groups across all studies. Based on these findings (Choi et al, 2012), we carried out a field study of 51 first-grade children in southern Sichuan using more advanced methods for exposure assessment, including fluoride in morning urine after usage of fluoride-free drinking water, fluoride in normal water source, and dental fluorosis status. As outcome tests, we included the WRAML, WISC-R digit span and block design, finger tapping, and grooved pegboard. Associations between exposure indicators and outcomes were assessed while taking into account age, sex, and other covariates.

Results: The meta-analysis using a random-effects model showed a standardized weighted mean difference in IQ score between exposed and reference populations – 0.45 (95% confidence interval: -0.56, -0.35), corresponding to an average difference of 7 IQ points. Thus, children in high-fluoride areas had significantly lower IQ scores than those who lived in low-fluoride areas. Subgroup and sensitivity analyses also indicated inverse association, although the substantial heterogeneity did not appear to decrease. The field study supported these findings, with the dental fluorosis score as the exposure indicator with the strongest association with the outcome deficits. WISC-R digit span appeared to be the most sensitive outcome test.

Conclusion: The results support the possibility of an adverse effect of high fluoride exposure on children’s neurodevelopment. The field study supports the notion that fluoride in drinking water may produce developmental neurotoxicity, and that the dose-dependence needs to be characterized in further detail.

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Reference(s):
Background: The relationship between the benefits and risks associated with fish and seafood consumption is a classic example of negative confounding: methylmercury, a worldwide contaminant of fish and seafood, can cause adverse effects on the developing nervous system; however, long-chain n-3 polyunsaturated fatty acids in seafood provide beneficial effects on brain development. Thus the presence of negative confounding will likely result in the underestimation of both mercury toxicity and nutrient benefits unless mutual adjustment is included in the analysis.

Methods: We examined these associations in 176 Faroese children, in whom prenatal methylmercury exposure was assessed from mercury concentrations in cord blood and maternal hair. The relative concentrations of fatty acids were determined in cord serum phospholipids. Neuropsychological performance in verbal, motor, attention, spatial, and memory functions was assessed at 7 years of age. Multiple regression and structural equation models (SEMs) were carried out to determine the confounder-adjusted associations with methylmercury exposure. Supplementary SEM analyses on verbal and motor functions included a larger previous cohort with similar characteristics, but the fatty acid measurements were missing. A total of 1016 children with available data were included in the joint-cohort analyses.

Results: A short delay recall (in percent change) in the California Verbal Learning Test (CVLT) was associated with a doubling of cord blood methylmercury (-18.9, 95% confidence interval [CI] = -36.3, -1.51). The association became stronger after the inclusion of fatty acid concentrations in the analysis (-22.0, 95% confidence interval [CI] = -39.4, -4.62). In structural equation models, poorer memory function (corresponding to a lower score in the learning trials and short delay recall in CVLT) was associated with a doubling of prenatal exposure to methylmercury after the inclusion of fatty acid concentrations in the analysis (-1.94, 95% CI = -3.39, -0.49). Results of the supplementary SEM analyses for both cohorts showed that methylmercury exposure was associated with deficits in verbal but not motor performance.

Conclusions: Associations between prenatal exposure to methylmercury and neurobehavioral deficits in memory function at school age were strengthened after fatty acid adjustment, thus suggesting that n-3 fatty acids need to be included in the analysis of similar studies to avoid the underestimation of the associations with methylmercury exposure.

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Reference(s):
Effect of phthalate exposure on pregnancy duration, birth outcomes and child neurodevelopment

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Background: Widespread phthalate exposure has prompted investigations concerning their potential adverse health effects.

Aim: The objective of this study was to evaluate the impact of phthalate exposure on pregnancy duration, anthropometric measures at birth and child psychomotor development based on the data from the prospective Polish Mother and Child Cohort Study (REPRO_PL).

Methods: Phthalate exposure was determined by measuring 11 phthalate metabolites (MEP, MiBP, MnBP, 30H-MnBP, MBzP, MEHP, 50H-MEHP, 5oxo-MEHP, OH-MiNP, oxo-MiNP, and MnOP) in the urine collected from mothers during the third trimester of pregnancy (prenatal exposure) and from their children at 24th month of age (postnatal exposure). The analysis was performed by HPLC-MS/MS method. The following measures at birth were considered: gestational age, birth weight, birth length, head and chest circumference. Child psychomotor development was assessed at the 2nd year of age by Bayley Scales of Infant and Toddler Development.

Results: Significant inverse association was observed between exposure to MEP and pregnancy duration after adjustment for a variety of confounders (β=-0.2; 95% CI -0.3 to -0.03). Child motor development was inversely associated with natural log concentrations (µg/g creatinine) of 30H-MnBP (β=-2.3; 95%CI -4.0 to -0.6), 50H-MEHP (β=-1.2; 95%CI -2.2 to -0.3), 5oxo-MEHP (β=-1.8; 95%CI -3.3 to -0.2) and DEHP metabolites (β=-2.2; 95%CI -3.6 to -0.8) and sum of high molecular weight phthalates (β=-2.5; 95%CI -4.1 to -0.9) in the urine collected from mothers during pregnancy. Postnatal child exposure to phthalates was not associated with any of the measured scores of child psychomotor development.

Conclusions: The study findings add further support to the possibility that prenatal phthalate exposure may be associated with a shortened pregnancy duration and decreased child neurodevelopment and underscore the importance of policies and public health interventions to reduce such exposure.

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Reference(s):
Prenatal Exposure to Polyfluoroalkyl Chemicals and Childhood Cognition

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Background: Among pregnant women, exposures to polyfluoroalkyl chemicals (PFCs), synthetic compounds used in non-stick cookware, food packaging, and other industrial and consumer products, are highly prevalent. Toxicological evidence suggests that PFCs may act as developmental neurotoxicants, but epidemiological evidence on neurodevelopmental effects of exposure to PFCs is limited.

Aims: Examine associations of prenatal PFC exposure with performance on assessments of cognition in childhood.

Methods: We studied 787 mother-child pairs in Project Viva, a longitudinal birth cohort with mothers enrolled at clinics in urban and suburban Eastern Massachusetts during 1999-2002. We measured 4 common PFCs in archived early pregnancy plasma (median=9.6 weeks gestation; range 5.6–20.9): perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA). At median age 7.7 years, we assessed children’s verbal and non-verbal intelligence (Kaufman Brief Intelligence Test (KBIT-2)), visual motor abilities (Wide Range Assessment of Visual Motor Abilities), and visual memory (Wide Range Assessment of Memory and Learning). We estimated associations of prenatal PFC plasma concentrations with children’s cognitive assessment scores using linear regression models adjusted for gestational age and estimated glomerular filtration rate at time of blood collection, as well as characteristics of the mother (race/ethnicity, age, education, parity, IQ (KBIT-2), pre-pregnancy body mass index, smoking status), child (sex, age at cognitive assessment), and family (household income, home environment).

Results: Included children had a mean verbal IQ of 112.5 and non-verbal IQ of 106.5 and 48% were female. 30% of mothers were non-White. Mothers’ median (25th–75th percentile) PFC plasma concentrations were: 5.5 (3.9–7.6) ng/mL (PFOA), 24.7 (17.9–32.9) ng/mL (PFOS), 2.3 (1.6–3.6) ng/mL (PFHxS), and 0.6 (0.5–0.9) ng/mL (PFNA). Compared to children born to participants in the first quartile (Q1) of PFOA plasma concentrations, those born to participants in the top three quartiles scored lower on assessments of verbal IQ (Q2: -5.4 points, 95% confidence interval (CI): -7.9, -2.8; Q3: -4.8, 95% CI: -7.5, -2.2; Q4: -3.9, 95% CI: -6.7, -1.2) and visual motor abilities (Q2: -3.5, 95% CI: -6.9, -0.1; Q3: -3.1, 95% CI: -6.5, 0.4; Q4: -2.7, 95% CI: -6.4, 0.9). There was also evidence of lower visual motor abilities in upper quartiles of PFOS and PFHxS concentrations, as well as lower non-verbal IQ in upper quartiles of PFHxS concentrations. There were no consistent patterns of association between prenatal PFNA concentrations and children’s cognitive outcomes.

Conclusions: In a cohort with plasma PFC concentrations similar to those observed in 1999-2000 National Health and Nutrition Examination Survey, higher prenatal exposure to several PFCs was inversely associated with verbal and non-verbal IQ and visual motor abilities in childhood.

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Prenatal methylmercury exposure and genetic predisposition to cognitive deficit at age 8 years: Study II
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Background: Genetic polymorphisms are thought to interact with the impact of prenatal methylmercury exposure on cognitive functions at school age. Based on previous results from a UK birth cohort, the results have now been extended to all eligible cohort members.

Methods: Additional cohort members (n = 1,031) from the Avon Longitudinal Study of Parents And Children (Bristol, UK) were added to a former subsample (n = 1,311) to include all eligible members. Total mercury concentrations were measured in freeze-dried umbilical cord tissue as a measure of prenatal methylmercury exposure. A total of 2,162 children had available data on 261 single-nucleotide polymorphisms (SNPs) within relevant genes, as well as the Wechsler Intelligence Scale for Children Intelligence Quotient (IQ) scores at age 8 years. Multivariate regression models were used to assess the associations between methylmercury exposure and IQ and to determine possible gene-environment interactions.

Results: Mercury concentrations indicated low background exposures (mean = 25 ng/g, standard deviation = 13), corresponding to a hair-mercury concentration of about 0.5 µg/g. Log-10-transformed mercury was positively associated with IQ, which attenuated after adjustment for nutritional and socio-demographic cofactors. Among 44 SNPs showing nominally significant main effects, interactions were detected for rs662 (Paraoxonase 1), rs1042838 (Progesterone Receptor), rs3811647 (Transferrin) and rs10636 (Metallothionein 2A) (p < 0.05), and for rs5746136 (Superoxide Dismutase 2), rs1883025 (ATP-binding Cassette, Sub-family A) and rs933271 (Catechol-O-methyltransferase) (p < 0.10).

Conclusions: In this population with a low level of methylmercury exposure, interactions from heterogeneities in several relevant genes were confirmed. The genetic polymorphisms that showed predispositions to methylmercury neurotoxicity occur in a substantial proportion of the population. These results show that the risk of methylmercury neurotoxicity may be unevenly distributed in the population.

Source(s) of support:
Reference(s):
Maternal intakes of seafood types and child neurodevelopment: A longitudinal study based on a population with high consumption levels

Jordi Julvez, PhD, CREAL

Seafood consumption during pregnancy is thought to be beneficial for child neurodevelopment, but is also a source of neurotoxic contaminants. Guidelines suggest pregnant women balance these risks and benefits by limiting overall consumption or avoiding large fatty fish subtypes, but recommendations have not been assessed using empirical intake data. The authors examined associations between maternal seafood consumption and two time points of child neurodevelopment, at age of 14 months and 4-5 years among 1,892 and 1,589 mother-child pairs, respectively, in a prospective Spanish cohort. Bayley (14 months) and McCarthy scales (4-5 years) were used for cognitive and motor assessments. A rating scale was used for assessing autistic spectrum symptoms (CAST). Multivariate linear regression was used to assess associations between neurodevelopment scores and seafood intakes, adjusting for covariates and further analyses adjusting for cord mercury or long chain polyunsaturated fatty acid (LCPUFA) concentrations. Overall, intakes exceeding recommended limits of 340 g/week were associated with increases in scores, particularly at child age of 4 years. Large fatty fish, consuming 238 g/week (last Quantile) was associated with adjusted increases of +2.29 points of McCarthy general scale (95% confidence interval [CI] 0.42, 4.16) and decreases of -0.57 points of CAST (-1.01, -0.13). While most species, including small fatty fish and lean fish were positively associated with test scores, coefficients diminished about 15-30% after adjusting for mercury or LCPUFA. Results do not support avoiding large fatty fish, but suggest benefits. Such associations embrace a wide range of cognitive functions and protective associations with autistic spectrum symptoms.

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Reference(s):
Long-term Behavioral Dysfunction Caused by Early Developmental Exposure to Low Dose Tobacco Smoke Extract or Nicotine in Rats
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Tobacco smoke during pregnancy has been associated with higher rates of attention deficit/hyperactivity disorder (ADHD). Gestational nicotine exposure in rat models has been shown to cause long-term neurochemical alterations and behavioral dysfunction. The risk of lower level tobacco smoke exposure with second-hand smoke (also known as environmental tobacco smoke) has not been as well studied. We are testing the effects of nicotine and tobacco exposure during gestational development in Sprague-Dawley rats. Female rats are exposed to nicotine or complete tobacco smoke extract (TSE) for a four-week period (sc) via osmotic minipump (Alzet, Model 2ML4) starting three days prior to mating. The pumps deliver 0, 0.2 or 2 mg/kg/day of nicotine based on pre-mating weight. The fourth group is administered TSE at a dose that has 0.2 mg/kg/day of nicotine together with the rest of compounds in TSE. Male and female offspring are assessed on a behavioral battery with tests for locomotor hyperactivity, emotional dysfunction and cognitive impairment. We found earlier that gestational exposure to the TSE that delivers 0.2 mg/kg nicotine causes locomotor hyperactivity in the figure-8 apparatus that is significantly (p<0.01) greater than groups treated with vehicle control solution or 0.2 mg/kg/day of nicotine alone, which was not by itself seen to produce locomotor hyperactivity. The degree of hyperactivity produced by gestational exposure to TSE delivering 0.2 mg/kg/day was nearly significantly (p=0.07) greater than the activity in rats exposed to ten times the nicotine (2 mg/kg/day) alone. We have more recently found with the novel object recognition test that TSE exposure during development caused significant impairments relative to controls in recognition of the novel vs. familiar object (p<0.05). The other constituents in tobacco appeared to potentiate the effect of nicotine such that gestational exposure to nicotine together with the other constituents in tobacco smoke produced locomotor hyperactivity in juvenile rats and impaired object recognition in young adults. The neurochemical and epigenetic bases for this long-term behavioral dysfunction are being investigated.

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Reference(s):
Environmental arsenic exposure is associated with reduced protective effect of folic acid in neural tube defect prevention

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Background: Arsenic induces neural tube defects in several animal models, but its potential to cause neural tube defects in humans is unknown. Our objective was to investigate the associations between maternal arsenic exposure during early pregnancy, periconceptual folic acid supplementation, and risk of neural tube defect among a highly exposed population in rural Bangladesh.

Methods: We performed a case-control study based on a case ascertainment system that recruited physician-confirmed cases from community health clinics served by Dhaka Community Hospital in Bangladesh, as well as local health facilities that treat children with neural tube defects. Controls were selected from pregnancy registries in the same areas. Maternal arsenic exposure was estimated from samples of mothers' nails and from drinking water samples taken from wells that mothers used during the first trimester of pregnancy.

Findings: Fifty-seven cases of neural tube defects were identified along with 55 controls. A significant interaction was observed between drinking water arsenic and periconceptual folic acid use. As drinking water arsenic concentrations increased from 1 to 25 µg/L, the estimated effect of folic acid use declined (OR 0.32 to 1.01), and was not protective at higher concentrations of arsenic.

Interpretation: Our study found a significant interaction between drinking water arsenic concentration during the first trimester of pregnancy and reported intake of periconceptual folic acid supplements. Results suggest that environmental arsenic exposure during early pregnancy reduces the effectiveness of folic acid supplementation in preventing neural tube defects.

Source(s) of support: Funding for this study was provided by the Child Neurology Foundation and the Harvard School of Public Health NIEHS Center (ES000002). Dr. Mazumdar was supported by a Mentored Career Development Award from the NIEHS, National Institutes of Health (K23 ES017437). Additional support was provided by NIEHS grant P42 ES16454.

Reference(s):
**Poster #: TUES-19**

**Abstract type:** Population Research  
**Category:** Nervous System  
**Keywords:** Epidemiology, Exposure Assessment, Prenatal

Air pollution, emotional dysregulation and risk of social impairment in adolescence  
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We evaluated the impact of prenatal exposure to widespread urban air pollutants on deficient emotional self-regulation (DESR) and social responsiveness in a prospective cohort of children born to nonsmoking African American and Dominican women in New York City. Air pollutant exposure was estimated categorically by level of polycyclic aromatic hydrocarbon (PAH)-DNA adducts in maternal blood collected at delivery (detected vs not detected), providing a biologic dosimeter of maternal exposure to PAH, detoxification and DNA repair over a 2-3 month period. DESR was defined as moderate elevations (greater than 1 sd above the mean) on three specific scales of the Child Behavior Checklist (anxiety/depression, aggression, and attention symptoms), by maternal report. The Social Responsiveness Scale (SRS) is a continuous, quantitative measure of social ability giving scores that range from significant impairment in communication and social behavior (autism spectrum disorders) to above average ability, also determined by maternal report. We first used repeated measures Generalized Linear Models (GLM) to assess the impact of PAH exposure (measured by adducts) on DESR phenotype in the same 226 children at 7, 9 and 11 years of age, adjusted for child sex, race/ethnicity, and full scale IQ (WISC); and maternal education, prenatal depression/anxiety, and ADHD-type symptoms. The between-groups test showed that children whose mothers had detectable PAH-DNA adducts at delivery had significantly higher overall mean DESR scores as compared to children whose mothers did not have detectable adducts (x=163.8, CI:161.4,166.2 vs x=159.0, CI:158.1,161.7; F=6.41, p=0.012), and the effect was consistent over time (no exposure-by-time interaction). Next, we assessed the impact of PAH-DNA adduct damage on SRS, both directly and indirectly via exposure effects on DESR phenotype. Multiple linear regression revealed that direct effects of PAH exposure on SRS were entirely mediated by the DESR phenotype (p-values for DESR at all time-points <0.001, rendering PAH effects ns by mediation analysis), suggesting that PAH-associated central nervous system dysregulation, observed throughout middle childhood, is a predictor of emerging social problems with possible real-world consequences for high-risk adolescent behaviors and autism-like symptoms in this minority urban cohort.

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**Reference(s):**  
(2) Sheng L et al., Toxicol Sci 2010; 118:625-634.  
Poster #: TUES-20

Abstract type: Population Research
Category: Nervous System
Keywords: Birth Cohort, Mechanisms & Pathways, Postnatal

Postnatal exposure to PBDEs and visual processing in school-aged children in Nunavik
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Introduction: Polybrominated diphenyl ethers (PBDEs) have been detected worldwide in humans with levels substantially higher in North America, including in Inuit people living in Canada’s Arctic Quebec (Nunavik). By contrast to several other contaminants, our knowledge of the toxicity of PBDEs on brain function development in humans is very poor. In line with previous works showing that environmental contaminants may alter the visual system, we examined whether visual processing is impaired as a function of PBDE exposure in the Nunavik Child Cohort.

Method: Visual evoked potentials (VEPs) to motion-onset, achromatic and chromatic visual stimuli were recorded over the occipital central site (Oz) in 148 Inuit children (mean age ± standard deviation = 11.3 ± 0.6). Blood concentrations of PBDE congeners 47, 99, 100 and 153 were measured at the time of VEP testing. Co-exposure to methylmercury, lead, PCB-153 and n-3 fatty acids, measured at the time of testing and at birth in cord blood, as well as other potential confounding variables were taking into account by multivariate regression analyses to assess the relationships between each PBDE congener, and their sum (ΣPBDEs), with VEP amplitudes and latencies.

Results: The amplitude of the chromatic VEP (N1 response) was negatively and significantly associated with all PBDE congeners except PBDE 153 before and after adjustment for confounders (βs range = -0.21 to -0.24, ps = .007 to .029). PBDE 47 exposure was associated with a decrease of amplitude of the achromatic VEPs (rs range = -0.17 to -0.19, ps < 0.05), in particular at low contrast levels (4 and 12%) but, after adjustment for confounders, only the association with the VEP response at 4% of contrast remained significant (β = -0.17, p = 0.03). No significant association between PBDEs and motion VEPs was found, either for amplitude or latency.

Conclusion: Our study shows clearly an adverse impact of postnatal exposure to PBDEs on color visual processing in school-age children. This result was not attributable to co-exposure to the other contaminants including PCBs, which shares physical and chemical properties with PBDEs. Considering that PBDEs are persistent and bioaccumulative, the alterations of visual processing reported here may result from cumulative exposure during prenatal period and after birth. Further prospective cohort studies are needed to address this issue.

* Our colleague and close collaborator Dr. Éric Dewailly passed away while the analyses of this study were being conducted. He was an authority on environmental and human health in the circumpolar world, an exceptional mentor, and a brilliant mind. This study is dedicated to him.

Source(s) of support: Supported by grants from the National Institute of Environmental Health and Sciences/US National Institutes of Health (R01 ES07902, to J.J.), Indian and Northern Affairs Canada Northern Contaminants Program (to G.M.), the State of Michigan (Joseph Young Sr Grant, to S.J.), the Nunavik Regional Board of Health and Social Services, and the Canadian Institutes of Health Research (to D.SA.). The authors declare no conflicts of interest.

Reference(s):
POPs measured in maternal serum and IQ of male offspring at conscription at 18-24 years of age
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Background: Organochlorine pollutants are frequently found in elevated concentrations in seafood, and food intake has been revealed as a major contemporary exposure pathway for perfluorinated compounds. Early exposures to both of these groups of persistent organic pollutants (POPs) have been linked with adverse neurodevelopment, but very few studies have follow up beyond early childhood.

Previously we investigated the association between levels of POPs, including perfluorinated compounds, polychlorinated biphenyls, ppDDE and hexachlorobenzen, in maternal serum and proxies of neurobehavioural outcomes during 20 years of follow up; we found no association with offspring ADHD, depression and average 9th grade examination marks at the end of compulsory school at age 15 (Strøm et al. 2014 Env Int). To follow up on these findings we obtained IQ measurements from the Conscript Registry for the male subset of the offspring cohort. With the exception of individuals with disqualifying diseases (such as epilepsy and diabetes) all Danish men are required to appear before the draft board at age 18 years, where a medical assessment and IQ testing by the ‘Børge Priens Prøve’ is conducted.

Aim: The aim of this study was to examine the association between POPs measured in maternal serum and IQ of male offspring at conscription at age 18-24.

Methods: Between 1988-89 a total of 965 pregnant women were recruited during a routine antenatal visit in week 30 of gestation for the birth cohort “DaFO88” in Aarhus, Denmark. Participants answered questionnaires and a blood sample was taken, processed, and serum was frozen and stored at -20°C.

Approximately 20 years later we were able to identify 915 mother-child pairs out of the original cohort, and for 872 of these serum samples were available for analysis of POPs. Out of these, we obtained IQ assessments for 401 males. The ‘Børge Priens Prøve’ is a 45 min group test with four sub-tests (letter matrices, verbal analogies, number series and geometric figures) and a total score ranging from 0 to 78. The total score correlates 0.82 with the Full Scale IQ of Wechsler’s Adult Intelligence Scale, indicating that it is a high-quality measure of general IQ.

Twelve perfluorinated compounds, 6 polychlorinated biphenyl congeners, ppDDE, and hexachlorobenzen were quantified in maternal serum.

Results: Compared to levels ~10 years later in the Danish National Birth Cohort concentrations of PFCs in our cohort were similar while the organochlorine pollutants were around 3 fold higher. The median (5-95th percentile) for age at conscription and IQ were 19 (18-21) years and 46 (31-58), respectively. There was no association between maternal levels of POPs and offspring IQ.

Conclusion: Our analyses based on biomarkers from a cohort of ~400 pregnant women combined with follow up data from a high quality registry showed little evidence of an association between organochlorine and perfluorinated compounds and IQ in young adult male offspring.

Source(s) of support: The study is part of the research programme of Centre for Fetal Programming, which is supported by the Danish Council for Strategic Research (09-067124).

Reference(s):
Common plastifiers and the developing brain: links to thyroid disruption, nutrition, attention deficit/hyperactivity and autism

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Children in developed countries are exposed to a complex chemical environment. More than 100,000 man-made chemicals are currently present in consumer products; nearly 3,000 of these substances are produced in quantities exceeding 500,000 kg/year, but for almost half of these high-volume chemicals there are no basic in vitro, animal or human toxicity data, and for 80% of them we have no information about developmental or pediatric toxicity. About five percent of the more than 4.4 million babies born each year in North America will be affected by neurodevelopmental disabilities during their childhood, with known etiology for less than 25% of those disabilities. The market for chemicals such as flame retardants (FRs) continues to increase as does their accumulation within the general population, but for the majority of chemicals found in umbilical cord blood there is no solid scientific data with respect to their safety. Many FRs have structural similarities with natural hormones and other physiologically active molecules. This presentation will summarize human and experimental evidence that common FRs, such as PBDE, affects the developing brain. The focus will be on the consequences of subtle thyroid disruption in utero on the development of attention deficit and autistic phenotypes in human. Particular individual susceptibilities including genetic, epigenetic, and nutritional status (iodine, selenium, folate, and choline intake), as well as social aspects (e.g. increased parental / teacher’ awareness and diagnosis) will be discussed.

Source(s) of support: Canadian Institutes of Health Research (CIHR)
Reference(s):
Neuronal differentiation and epigenetic modulation of the androgen receptor in vitro
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Increasing evidence shows that environmental influences during key developmental periods can affect epigenetic patterns in the brain. Epigenetic modification can cause phenotypic variation, which can play a role in behavioral changes, childhood disorders as well as adult diseases, such as Alzheimer’s disease. DNA methylation is a major epigenetic regulator, especially of genes containing CpG-rich sequences surrounding their transcriptional start site, such as the androgen receptor. The androgen receptor (AR) plays a crucial role in early life leading to permanent effects on brain morphology and reproductive behavior. Here, we studied changes in DNA methylation of the murine AR promoter in murine neural progenitor cells (mNPCs) and mouse embryonic ES-D3 stem cells. mNPCs were isolated from embryonic mouse brains at embryonic day 14 (1). Global methylation percentage was determined in undifferentiated cells and at day 7 of differentiation using MethylFlash quantification kit. The methylation pattern of the AR was determined using a bisulfite conversion followed by cloning and DNA sequencing. Gene expression was determined by qPCR using SYBR green. The results show that during the 7-day differentiation, global methylation slightly increased in mNPCs. In undifferentiated mNPCs, the 17 CpGs in the AR promoter region showed around 10-20% methylation. After 7 day differentiation, this increased to 21-49% methylation, depending on the CpG. Gene expression of DNA methyltransferase DNMT1 was unaltered, while expression of DNMT3a and DMNT3b increased after 7 days of differentiation. Interestingly, gene expression of AR and estrogen receptors (ER) α and β also increased. Similar results for gene expression were found in the well-established embryonic stem differentiation assay using murine ES-D3 cells (2). In order to assess the neuronal functionality of the developing neuronal cells, electrical activity was determined using multielectrode arrays (MEA). Previously, we demonstrated that electrical activity in mNPCs was low, but detectable after 7 days of differentiation and was increased at day 14 and 21 of differentiation (1). Murine ES-D3 cells also showed electrical activity at day 7 of neuronal differentiation. Together, these data promote further characterization and development of predictive in vitro developmental neurotoxicity (DNT) models. Studies to determine DNT effects should include epigenetic modifications of key proteins involved in neurodevelopment such as AR and ERs, that are prerequisite for correct neuroendocrine development and reproductive behavior later in life.

Source(s) of support:
Reference(s):
Using Early Infant Neurobehavioral Assessment to Assess Impact of Gestational Exposure to Environmental Toxicants

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Neurobehavioral assessment tools have traditionally been used to measure the effects of gestational exposure to drugs of abuse. A small number of studies have used this technique to assess the earliest impact of gestational exposures to environmental toxicants. Within the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort study, we have measured gestational exposure to an array of toxicants using maternal biomarkers measured at 16 and 26 weeks gestation and in infant cord blood. By including 389 women with singleton live births, from urban, suburban, and rural settings, the HOME Study provides information pertinent to the general US population with respect to levels of exposure. Neurobehavioral assessments, using the NICU Network Neurobehavioral Scale (NNNS), were completed on 355 infants at about 5 weeks of age during a home visit. The NNNS provides an assessment of neurological status, behavior, and stress response and is validated for infants 32 to 46 weeks gestation.

We have examined associations between gestational exposures to individual environmental toxicants and early infant neurobehavior with appropriate covariate adjustment. Observed effects are unique to each toxicant. We found no significant associations between gestational exposure to bisphenol-A or PBDEs and infant neurobehavior. Gestational exposure to nicotine, measured by serum cotinine, was significantly associated with neurobehavioral outcomes that differed by race. With higher cotinine concentrations, white infants exhibited increased arousal (p=.03) and excitability (p=.03), and decreased self-regulation (p=.01); black infants exhibited lower arousal (p=.001), excitability (p=.02), and required special handling (p=.003), and demonstrated greater self-regulation (p=.02) and hypotonicity (p=.02). Higher concentrations of di-2-ethylhexyl phthalate were associated with nonoptimal reflexes in males only (p=.02). In contrast, higher di-butyl phthalate concentrations were associated with improved neurobehavior evidenced by lower arousal (p=.04), increased self-regulation (p=.05), and decreased special handling (p=.02) in all infants. A 10-fold increase in PFOA concentrations was associated with an increased likelihood of hypotonicity (aOR=3.8, CI 1.1-12.8). In analyses of organophosphate pesticides, we reported associations that suggest no harm but potential benefit to neurobehavioral outcomes. Total mercury was associated with better attention (p=.046), less special handling required (p=.04), and increased asymmetric reflexes (p=.03). Similar results to those found for total mercury were found for fish intake. These findings must be viewed in the context of potential overpowering influences of socioeconomic status and maternal diet. We will provide background on neurobehavioral assessment of young infants, measurement interpretation, study design considerations, and a summary of findings from the HOME Study.

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Reference(s):
Prenatal exposure to the organophosphate chlorpyrifos delays motor development in the BTBR inbred strain, a mouse model of autism
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Chlorpyrifos (CPF) is a widely diffused organophosphate insecticide. Recent epidemiological studies indicate that prenatal environmental exposure to CPF in children can alter the morphology of some brain areas involved in cognitive and behavioural processes.

In the present study we analyzed the effects of developmental exposure to a sub toxic dose of CPF in the idiopathic mouse model of autism, the BTBR T+tf/J (BTBR) mouse strain, which displays several behavioral traits relevant to autism. To this aim, pregnant BTBR mice were administered from gestational day 14-17 with either vehicle or CPF at a dose of 6 mg/kg/bw by oral gavages. Offspring of both sexes underwent early assessment of spontaneous motor behaviour and analysis of vocalization patterns. CPF-BTBR pups appear delayed in development of motor competences, since they show more pivoting (an immature, transient motor response based on the use of forelimbs only) than controls and later appearance of adult-like locomotion; no significant differences were evident in vocalization repertoire and rates. As a whole these findings indicate neonatal motor endpoints as sensitive early markers for prenatal organophosphate exposure in rodents. Several clinical studies suggest that anomalies in motor milestones in new borns and infants may be indicative of later neurological and neuropsychiatric conditions. Thus neonatal motor behaviors can be used to assess the interaction among vulnerable gene backgrounds and environmental neurotoxicants in the etiology of neurodevelopmental disorders.

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Reference(s):
Poster #: TUES-26

Abstract type: Population Research  
Category: Nervous System  
Keywords: Birth Cohort, Exposure Assessment, Prenatal

Risk of Subsequent Maltreatment in Infants with Neonatal Abstinence Syndrome
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Purpose
1) To determine risk for subsequent maltreatment after hospital discharge for patient’s diagnosed with neonatal abstinence syndrome (NAS). 2) To determine if this risk diminishes over time. 3) To determine risk of medical neglect in the form of missed appointments and immunization delay for routine well child care.

Methods
We conducted a retrospective chart review of a cohort of infants who were (1) born at Boston Medical Center between January 2010 and October 2011, (2) who were diagnosed with NAS, and who (3) received their primary care at Boston Medical Center Primary Pediatrics Clinic, as evidenced by at least one primary care visit over the age of one month.

By state law, prenatal exposure to narcotics must be reported to the Department of Children and Families. In our hospital 85% of these infants are discharged in mother’s custody. We reviewed the charts of those infants who were in mother’s custody and received primary care beyond age one month. Chart notations indicating DCF involvement beyond the report filed at birth and immunization data were recorded until the most recent BMC visit of each infant.

Results
There were a total of 136 infants diagnosed with NAS during the study period. 55% of mothers in ORT were prescribed methadone as compared to 45% buprenorphine. A majority (62.5%) of mothers were also prescribed adjunctive psychotropic medications. A minority of mothers, 16.2%, in structured maintenance therapy programs, also used illicit drugs (heroin, cocaine, methamphetamines, PCP, or marijuana) during their pregnancy. 86% of infants required treatment with neonatal morphine.

We had a minimum of two years of follow-up data for the 34 (25%) patients followed at BMC Primary Care Clinic. 18 (51.6%) were subsequently removed from parents’ custody, with mean age occurring at 377 days post birth and ranging from 64 to 841 days. An additional 22.6% had a subsequent report filed with CPS and 16.1% had a third report filed.

These families fell behind in primary care; . 37.9% of these infants were more than a month overdue for their 3rd PCV Immunization, and 51.9% of these infants were more than a month overdue for their MMR at 12 months of age. Only 22% of active patients met all of the following criteria: 1) up to date on well infant care, 2) no subsequent report filed with CPS 3) in the custody of parent.

Conclusions
This retrospective chart review followed a small cohort of infants with prenatal narcotic exposure. The data suggest that they are at high risk for subsequent maltreatment. Our data identifies the need primary prevention programs tailored to the needs of these highly vulnerable infants and their families.

Source(s) of support: 
Reference(s):
Poster #: TUES-27

Abstract type: Population Research  
Category: Obesity  
Keywords: Birth Cohort, Epidemiology, Prenatal

Prenatal exposure to polyfluoroalkyl chemicals (PFCs) and childhood obesity in Project Viva
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Background: Growing evidence supports the prenatal period as a sensitive time window for exposure to chemical obesogens. Polyfluoroalkyl chemicals (PFCs), used in stain and water resistant products, bind to peroxisome proliferator-activated receptors, which play a key role in adipogenesis.

Objective: To examine the association between prenatal exposure to PFCs and childhood obesity.

Methods: We measured PFCs in plasma collected from women recruited 1999-2002 at their first prenatal visit (median = 9.7 weeks gestation) in Project Viva, a Boston-area pre-birth cohort. We fit multivariable regression models to estimate associations of PFCs with body mass index (BMI) and dual x-ray absorptiometry (DXA) total fat mass index and trunk fat mass index in 871 children aged 6-10 years (median age = 7.7 years), and adjusted for maternal age, education, race/ethnicity, smoking status, parity, gestational age and creatinine at the time of blood collection, and child’s age and sex.

Results: Median (25, 75th percentile) concentrations of perfluorooctane sulfonate [PFOS, 24.7 ng/mL (18.2, 33.6)], perfluorooctanoate [PFOA, 5.6 (3.9, 7.6)], perfluorohexane sulfonate [PFHxS, 2.3 (1.6, 3.7)], and perfluorononanoate [PFNA, 0.6 (0.5, 0.9)] were similar to NHANES 1999-2000. Among girls, PFCs were associated with higher BMI z-scores among girls [β for highest vs. lowest quartile of PFOS (95% CI) = 0.29 (-0.01, 0.59), PFOA = 0.46 (0.16, 0.75), PFHxS = 0.28 (-0.01, 0.56), and PFNA = 0.37 (0.04, 0.70)]. Greater odds for obesity (BMI ≥95 vs. <85th percentile) were observed [adjusted OR for the highest vs. lowest quartile of PFOS (95% CI) = 1.8 (0.7, 4.3), PFOA = 3.1 (1.3, 7.6), PFHxS = 3.9 (1.5, 10.3), and PFNA = 2.7 (0.9, 7.7)]. PFCs were also associated with DXA total fat mass [β for highest vs. lowest quartile of PFOS (95% CI) = 0.70 (0.05, 1.34), PFOA = 1.06 (0.44, 1.67), PFHxS = 0.73 (0.13, 1.33), and PFNA = 1.05 (0.34, 1.77)]. PFCs were also positively related to DXA trunk fat [β for highest vs. lowest quartile of PFOS (95% CI) = 0.30 (0.05, 0.59), PFOA = 0.41 (0.13, 0.69), PFHxS = 0.28 (0.01, 0.56), and PFNA = 0.42 (0.10, 0.74)]. PFCs were not associated with anthropometry or DXA measurements among boys.

Conclusions: Prenatal PFCs were associated with higher childhood BMI, odds of obesity, total fat mass index, and trunk fat mass index among girls in Project Viva. Our findings support PFCs as obesogens of public health concern, given their ubiquity and persistence in the environment.

Source(s) of support: NIEHS Grant R01 ES021447 awarded toward SKS
Reference(s):
Neonatal gene expression: Marks of prenatal exposure to PFOA, PFOS, PCB153, and DDE

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The prevalence of obesity and/or diabetes has reached alarming proportions globally. More than 20% of the world population is overweight, while nearly 300 million are obese. It has been suggested that sensitivity to develop obesity and/or T2DM is programmed during development and that early life exposure to environmental contaminants may be implicated.

In the European FP7 project OBELIX (OBesogenic Endocrine disrupting chemicals: Linking prenatal eXposure to the development of obesity later in life) the hypothesis was examined that prenatal exposure to endocrine disrupting chemicals (EDCs) plays a role in the development of obesity later in life. The OBELIX project focused on assessing prenatal exposure to chemicals from six major classes of EDCs found in food, including dioxins and dioxin-like polychlorinated biphenyls (PCBs), non-dioxin-like PCBs, brominated flame retardants (BFRs), organochlorine pesticides, phthalates and perfluorinated alkyl acids (PFAAs). One of the objectives of the project was to relate early life exposure to the above mentioned EDCs with neonatal effect biomarkers and health outcome data which are related to risk of obesity later in life.

In a birth cohort - initiated as part of the Flemish Human biomonitoring program (FLEHS II) - we examined associations between biomarkers of prenatal exposure to EDCs measured in cord blood samples and changes in gene expression assessed by whole genome transcriptomics in cord blood cells. The panel of EDCs that was studied included dichlorodiphenyldichloroethylene (DDE), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and polychlorinated biphenyl-153 (PCB153). Based on upstream transcription factor analysis, we suggest new hypotheses to clarify the molecular basis that may link prenatal EDC exposure to adult disease. Gene expression marks related to PFOA exposure indicated that the progesterone receptor may be incriminated. Inhibition of ESR2 (estrogen receptor 2) was associated with exposure to PCB153. The most significant transcription factor associated to DDE was NR3C1 which is also known as the glucocorticoid receptor (GR). In addition to metabolic diseases, this receptor is also involved in asthma. It has been reported that the prevalence of asthma increases with increasing DDE levels. As NR3C1 is involved in multiple adverse outcomes associated with DDE – metabolic disease and asthma – and as it is influenced by DDE in our dataset, we hypothesize that adverse regulation of the glucocorticoid receptor during development is a candidate pathway that links prenatal exposure to adult onset of disease.

Source(s) of support: The studies of the Flemish Center of Expertise on Environment and Health were commissioned, financed and steered by the Ministry of the Flemish Community; The research received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) under grant agreement OBELIX 227391.

Reference(s):
In Utero Exposure to Phthalates and Childhood Growth and Blood Pressure

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Background: Rapidly accumulating evidence from in vitro and in vivo studies suggests that developmental exposure to phthalates may increase the risks of obesity and cardiovascular disease in later life. Evidence in humans, however, is so far limited to few cross-sectional studies.

Aims: We evaluated the associations between prenatal phthalate exposure and childhood growth and blood pressure in the Spanish INMA-Sabadell Birth Cohort Study.

Methods: We assessed exposure using the average of two phthalate metabolite spot-urine concentrations collected from the mothers in the first and third pregnancy trimesters (n=391). Phthalate metabolite concentrations were creatinine-adjusted and log2-transformed. Study outcomes were child weight-for-age-and-sex Z-score difference between birth and 6 months of age, repeated body mass index (BMI)-for-age-and-sex Z-scores at 1, 4 and 7 years and repeated waist-to-height ratio and systolic and diastolic blood pressure-for-age-and-height Z-scores at 4 and 7 years. Linear regression analysed continuous outcomes and generalized estimating equations analysed repeated outcomes.

Results: The sum of 5 high molecular weight phthalate metabolites (ΣHMWPm; including MBzP and four DEHP metabolites) was associated with decreased weight Z-score difference between birth and 6 months (adjusted β per doubling of exposure=−0.41; 95%CI: -0.75,-0.06) and BMI Z-score at later ages in boys (adjusted β=−0.28; 95% CI: -0.60, 0.03) and with increased weight Z-score difference (adjusted β=0.24; 95% CI: -0.16, 0.65) and BMI Z-score in girls (adjusted β=0.30; 95% CI: -0.04, 0.64) (P for sex interaction=0.01 and 0.05, respectively). The sum of 3 low molecular weight phthalates (ΣLMWPm; including MEP, MiBP and MnBP) was not associated with any of the growth outcomes evaluated. ΣHMWPm and ΣLMWPm were associated with decreased systolic blood pressure Z-scores in girls but not in boys.

Conclusions: These findings suggest that prenatal phthalate exposure may be associated with postnatal growth and blood pressure and that the associations may differ according to child sex. Inconsistencies with previous cross-sectional findings highlight the necessity for evaluating the health adverse effects of phthalates in prospective studies.

Source(s) of support:
Reference(s):
The correlation structure of the Pregnancy Exposome: multiple environmental exposures in the INMA-Sabadell Birth Cohort

Maribel Casas, PhD, CREAL; Oliver Robinson, MSc, PhD, CREAL, Spain; Xavier Basañga, CREAL, Spain; Carles Hernandez, CREAL, Spain; Martine Vrijheid, CREAL, Spain

Background and aims: Common childhood diseases can be highly complex pathologies, yet most previous environmental epidemiological studies only consider single exposure-health effect relationships. A more global “exposomic” view of how exposures co-exist and interact may improve our aetiological knowledge and the pregnancy period is a key starting point in developing a life course exposome. The INMA (INFancia y Medio Ambiente) Sabadell birth cohort, in Catalonia, Spain has measured exposure to many environmental factors during pregnancy. We aimed to collate these disparate measurements to describe the correlation structure of the pregnancy exposome, as a first step in developing statistical tools appropriate to exposome data.

Methods: Estimates on 103 exposures covering the pregnancy period were obtained. Biomonitoring data included organochlorines, perfluorinated compounds and heavy metals in blood, polybrominated diphenyl ethers (PBDEs) in breast milk, and metals, phthalates, parabens, halogenated phenols, bisphenol A and cotinine in urine. GIS data included air and water pollutants, the built environment, green spaces, noise and temperature. Questionnaire data included gas cooking, pesticide and cleaning product use and environmental tobacco smoke exposure. All continuous variables were log-transformed and pair-wise Pearson’s correlations were calculated to produce a correlation heat map.

Results: Available exposure estimates ranged from 30 women for the parabens and up to 728 women for temperature (mean number of women per exposure: 416). There were strong levels of correlation within exposure groups (eg. For air pollutants, mean: 0.54, range: 0.24 to 1.00 and for PBDEs, mean: 0.37, range 0.02 to 0.87) but generally weak levels between groups (eg between air pollutants and PBDEs, mean: 0.03, range -0.18 to 0.16). The full correlation heat map will be presented.

Conclusions: The correlation structure of the pregnancy exposome will aid in interpretation of epidemiological studies in general and inform simulation studies to plan appropriate analyses for the next generation of exposome studies.
Contribution of breast milk, formula and rice cereal intake to arsenic exposure in U.S. infants

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Background
Arsenic is a known carcinogen that can also adversely affect the cardiac, respiratory, neurological and immune systems. Young children are estimated to have higher dietary arsenic exposure than adults, however little is known about the relative contribution of various dietary sources to exposure during the first year of life.

Aims
To estimate exposure to arsenic via breast milk, formula and rice cereal during the first year of life for a population of U.S. infants.

Methods
The New Hampshire Birth Cohort Study is an ongoing prospective cohort study of over 1,250 maternal-child dyads. Pregnant women who reported living in a household served by private water system were enrolled at approximately 24-28 weeks gestation. Home tap water samples were tested for arsenic, and infant diet was assessed via telephone interviews at 4, 8 and 12 months of age. We estimated body-weight-adjusted arsenic exposure via breast milk, formula, and rice cereal based on reported diets and tap water arsenic concentrations from our cohort along with the available literature.

Results
During the first year of life, formula-fed infants had estimated arsenic exposures approximately 5 times higher than breastfed infants, largely due to exposure from the formula powder. As the proportion of infants consuming formula increased from 31% to 66% between 4 and 12 months of age, overall estimated arsenic exposure increased slightly from a median of 0.07 to 0.10 µg kg⁻¹ d⁻¹. At 6-12 months of age, three servings (51 g) of rice cereal per day contributed to a higher estimated median daily exposure (1.11 µg kg⁻¹ d⁻¹) than infants fed with formula mixed with water containing arsenic at 10 µg/L (0.92 µg kg⁻¹ d⁻¹).

Conclusions
While overall arsenic exposure via breast milk and formula is relatively low, our data suggest that exposure increases as the prevalence of formula-feeding increases during the first year of life. Moreover, estimated arsenic exposure increased substantially with the introduction of rice cereal.

Source(s) of support: NIH Grants P01 ES022832, P20 ES018175, and P42 ES007373; EPA Grants RD-83459901 and RD-83544201.

Reference(s):
Determinants of Hair Metal Concentrations in Children Aged 6 – 12
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Low level metals exposure may be neurotoxic to children. The best biomarker matrix for measurement of metals exposure depends on a number of factors, including metal toxicokinetics and ease of collection. With the exception of mercury, hair has typically been rejected as a biomarker for metals because of contamination concerns, but new cleaning and processing procedures have made it a viable matrix.

Scalp hair is an easy, non-invasive medium to work with because it does not require specialized resources to collect, handle, or store. Hair grows approximately 1 cm a month and incorporates substances that are circulating in the body over periods of months. Given the emerging use of hair as a biomarker for metals exposure, identifying determinants of hair metal concentrations in children can enhance understanding and interpretation of results from this child-friendly matrix.

We collected occipital scalp hair samples from 231 children aged 6–12 years participating in a study of chemical exposure and neurodevelopment in an industrial region of the Mid-Ohio Valley in 2009–2010. We had abundant questionnaire data on demographics and residential and medical histories. Hair was cleaned, processed, and analyzed for As, Cd, Mn, and Pb by magnetic sector inductively coupled plasma mass spectrometry. We analyzed the 2.5 cm of hair closest to the scalp, which represents exposure from approximately the 2 months prior to collection. Known environmental exposures in the region include perfluorooctanoate from contaminated drinking water and metals in air pollution emitted from an industrial complex, including a metallurgical manufacturing facility. From 2007 – 2008, air monitors detected levels of arsenic, cadmium, and manganese exceeding ATSDR and EPA health-based comparison values.

We used a multi-step process to identify determinants of hair metals concentration. Models were built separately for each metal. Variables with p<0.25 in bivariate analyses were entered into full models. The SAS GLMSELECT procedure with stepwise selection, partition of testing and validating datasets, and cross-wise validation was used to identify models with the best fit according to lower AIC and higher R2.

Mean hair metal concentrations were low (As=0.05 ug/g; Cd=0.03 ug/g; Mn=0.26 ug/g; Pb=0.42 ug/g). The best models explained a fair amount of the variance (As R2=0.34; Cd R2=0.32; Mn R2=0.24; Pb R2=0.17). Sets of determinants differed for each metal, although child sex was a strong determinant for all but Pb. Boys predicted an approximately 100% increase in concentration compared to girls. While birth weight was a moderate predictor for both Cd and Pb, body mass index was relevant only to Cd. Lower rated health status predicted higher As levels.

The limited predictive ability of individual level residential, demographic, and health information may indicate that differences in observed hair metal concentrations are related to actual differences in exposure.

Source(s) of support: K01 ES019156; R21 ES019643; C8 class action settlement agreement [Jack W. Leach, et al. v. E.I. du Pont de Nemours & Company (no. 01-C-608 W.Va., Wood County Circuit Court, West Virginia, USA) between DuPont and plaintiffs with funds administered by Garden City Group
Reference(s):
Cotinine validation of self-reported smoking during pregnancy in the Swedish Medical Birth Register
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INTRODUCTION: Many epidemiological studies use self-reported data on smoking behavior during pregnancy from the Medical Birth Register of Sweden (MBR). However, underreporting of such behavior may occur, leading to biases. It is thus of importance for future research to validate the smoking data in the MBR. The main objective was to investigate the agreement between self-reported smoking data from the MBR and cotinine levels in maternal serum among women from the general population in the region of Skåne, Sweden. We also estimated the transfer of cotinine between mother and fetus.

METHODS: From a cohort used previously to investigate the relationship between intrauterine environmental exposures and offspring neuropsychiatric outcomes, there were 204 control children retrieved from the MBR with data on maternal smoking in early pregnancy registered. Data on maternal and umbilical cord cotinine at delivery were available for these children from a regional biobank.

RESULTS: There was a high agreement between cotinine levels and MBR smoking data (κ = 0.82) and a high correlation between cotinine levels in maternal and umbilical cord serum (rs = 0.90, p<0.001).

CONCLUSION: In these data from the MBR we found that the agreement between mothers’ self-reported smoking habits during pregnancy and their levels of serum cotinine was high, as was the transfer of cotinine from mother to fetus. This indicates that birth register data on pregnancy smoking in Sweden could be considered a valid measure.
Abstract type: Translational Research  
Category: Other: Exposure Assessment  
Keywords: Exposure Assessment, Mechanisms & Pathways, Prenatal

Fetal accumulation and metabolism of PBDE flame retardants during second trimester of pregnancy  
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Background. Prenatal exposure to polybrominated diphenyl ethers (PBDEs) may disrupt fetal development. However, little is known about human exposure and metabolism of these chemicals during mid-gestation.  

Objective. To characterize partitioning of PBDEs and their hydroxylated metabolites (OH-PBDEs) across the maternal-fetal unit in second trimester pregnant women and evaluate the role of cytochrome p450 (CYP) gene expression in the developing fetus on PBDE metabolism.  

Methods. We collected maternal serum, fetal liver, and fetal cord serum samples from 36 patients having a voluntary pregnancy termination in San Francisco, California. PBDEs and their OH-PBDEs were measured by GC/HRMS and GC/LRMS, respectively. Expression of 8 CYP genes was quantified through qT-PCR in fetal liver mRNA.  

Results. PBDEs were detected in all samples. Maternal serum was more highly correlated with concentrations in fetal liver (Spearman rho: 0.5 – 0.8; p < 0.05) than cord serum (Spearman rho: 0.3 – 0.6; p < 0.05). A greater percentage of PBDEs were measured in fetal liver than in cord blood or maternal blood and this difference became more pronounced in higher brominated PBDEs (e.g. PBDE-153). OH-PBDEs showed a different pattern of partitioning and accumulation with higher concentrations in maternal serum and cord blood than fetal liver. Expression of all 8 CYPs were detected in fetal liver mRNA. Higher mRNA CYP expression was positively associated with OH-BDE-99 concentrations in fetal liver (p < 0.05) in multivariate models.  

Conclusions. This is the first human study to examine concentrations of PBDEs and OH-PBDEs in paired human samples of maternal serum, fetal liver, and cord blood serum during mid-gestation. Our data suggests that PBDEs cross the placenta and accumulate in the fetal liver, and cord blood concentrations may not be an accurate representation of fetal exposures. There was considerable expression of CYPs in fetal liver mRNA suggesting that the developing fetus may have the capacity to metabolize environmental chemicals in utero.

Source(s) of support: National Institute of Environmental Health Sciences (NIEHS) R00ES019881 and ViCTER supplement to 5R01ES010026.

Reference(s):
Time trends in serum concentrations of perfluorinated compounds (PFC) in the Faroese population

Perfluorinated chemicals (PFC) are a class of manmade fluorinated organic compounds first produced on a large scale in the early 1950s. Since, the PFCs have been widely detected in humans and wildlife. Retrospective time trend studies are a valuable tool for assessing the development of an environmental pollution situation. Results from studies exploring the historical trends of PFCs in human samples have been inconsistent as some observed clear trends while others have not.

Objectives: To determine serum concentrations of selected PFCs in a group of randomly selected Faroese and to assess the time trend 10 years later in the same individuals.

Design: Population-based study

Participants: 209 randomly selected Faroese men (N=107) and females (N=102) aged 18 – 70 at the time of recruitment.

Results: In 2003, the mean serum PFOS and PFOA levels were 35.30 ng/mL (95% CI: 13.81-70.92) and 3.63 ng/mL (95% CI: 1.50-6.82) compared to significantly lower levels (P<0.0001) measured in the same individuals in 2012 (PFOS: 20.01 ng/mL (95% CI: 5.74-48.02) and PFOA: 2.51 ng/mL (95% CI: 0.96-4.60). However, the concentrations of PFNA and PFDA were significantly higher in 2012 (2.48 (95% CI: 0.80-5.86) and 0.77 (95% CI: 0.27-1.72)) than in 2003 (1.37 (95% CI: 0.46-3.05) and 0.56 (95% CI: 0.21-1.22)) and further the brPFOS concentration was unchanged (p=0.7). Men had significantly higher concentrations than female and a positive correlation with age was observed in the whole group.

Conclusions: A clear decline in the PFOS and PFOA concentrations was observed in the same Faroese individuals from 2003 to 2012. Conversely the PFNA and PFDA concentration were increased, while the brPFOS concentration was unchanged during his period.
An attempt of development of PCBs exposure assessment using food frequency questionnaire in birth cohorts in Japan

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Health effects by fetal and children's environmental exposures to chemicals have been concerned. Persistent organic pollutants (POPs) such as PCBs are the major chemicals of such environmental chemicals. However, it is extremely expensive and time consuming to analyze and calculate each of those chemicals. The authors have reported that PCB contamination level correlates with many other POPs level in human blood, and it is possible to assume fetal exposure level of PCBs from the maternal blood PCB level. On the other hand, the source of exposure to PCBs has been reported as food. If highly contaminated group to PCBs can be identified from the Food Frequency Questionnaire (FFQ) without blood samples, it became possible to save the cost and time to detect high risk group. In this presentation, the correlation between FFQ and blood PCB contamination level in Japan Environment and Children's Study will be reported. Blood PCB level in 197 fathers who were recruited in Chiba Regional Center, one of the 15 Regional Centers of Japan Environment and Children's Study (JECS) were analyzed and calculated by Packed Column Gas Chromatography Electron Capture Detector (GC/ECD). The relationships between Body Mass Index (BMI), ages and PCB level were compared with Wilcoxon's Test. The answers of FFQ were analyzed and the relationship between food items, frequencies and blood PCB level was discussed with Partial Least Squares (PLS) analysis. The current FFQ data contains tentative data. From the blood PCB analysis, it became clear that blood PCB level increased with age, but the variation also became larger with age. No correlation was found between PCB level and BMI. From the results of FFQ and age data, it became clear that age, quantity of fish intake, frequency of fish intake had stronger correlation with blood PCB level. There was no correlation between dairy products and PCB level since there is a big variation of dairy products intake in Japanese people. PCB level expected values which are gained from the answers to FFQ and the actual blood PCB level correlated ($r^2 = 0.50$) by PLS analysis. It was found that it was possible to estimate blood PCB level from FFQ and age data. The data of mothers who participated in JECS Project has not been open yet, so the data couldn't be analyzed, however, same kind of result can be expected. In children's cohort study, it is important to detect high risk group and to evaluate health effect on the parents and their children. From the current study, it became clear that it was possible to detect high exposure group by FFQ and age data. If FFQ in each culture is developed and used in children's cohort study, it will be easier to compare the results of chemical exposure levels worldwide. (This study was conducted as an additional research of JECS. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the above government.)

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Reference(s):
DNA methylation in umbilical cord blood as surrogate makers for prenatal exposure of HCB and PCB138

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Background: Faroe islanders consume considerable amount of marine food which has been contaminated with mercury (Hg) and polychlorinated biphenyls (PCB). Prenatal exposure to such environmental toxicants has been associated with neurobehavioral deficits in childhood. DNA methylation in cord blood could serve as potential surrogate biomarkers for mixed exposure.

Objective: We aimed to dissect exposure (Hg or PCBs)-associated DNA methylation marks in cord blood.

Method: DNAs were isolated from 72 cord blood samples. DNA methylome was profiled using the Illumina Infinium Methylation 450K BeadChip array. We applied recently published normalization methods and models for data analysis. We determined the relationship between each CpG loci and exposures to Hg (maternal hair Hg, cord blood Hg), hexachlorobenzene (HCB), PCBs (28, 52, 105, 118, 138, 153, 156, 80), and DDT/DDT (opDDE, ppDDE, opDDT and ppDDT). We also utilized cell mixture deconvolution method for 6 different reference cell types to determine whether the exposure could change proportion of white blood cells in the cord blood.

Result: Out of 15 different exposure indicators measured, we identified over 1000 CpG methylation sites showed significant linear response relationship with increased exposure of HCB and PCB-138, but not with Hg, in a mixed gender analysis. In region level analyses, we selected 5 genes (KCNAB3, NSDHL, PGK, SLC12A9 and TTC22) that have four or more significant CpG sites within a CpG island and are associated with high HCB exposure for pyrosequencing analyses. The CpG island near the promoter region of KCNAB3 was relatively hypermethylated in high HCB group. Similar results were observed in high PCB-138 group. Interestingly, when stratified by gender, more significant CpG loci were associated with HCB, ppDDE, PCB-118, PCB-105 and PCB-138 in the male group. The majority of these significant sites related to HCB exposure are located at chromosome X. Cell type deconvolution analyses suggested that Hg or PCBs exposure did not significantly alter the proportion of blood cell population after multiple adjustment.

Conclusion: Our data support that prenatal exposure to HCB and PCB-138 may alter DNA methylome in cord blood. Genes are regulated by HCB might be used as surrogate biomarkers for exposure in future.

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Reference(s):
Disruption of the placental imprintome is associated with birth weight
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The importance of imprinted genes on appropriate embryonic and placental development has been long established. Syndromic disorders due to mutations or deletions in imprinted genes present with clinical features that include metabolic, mental, and behavioral defects. In fact, abnormal birth weight, an indicator of a metabolic defect commonly observed in imprinting disorders, can manifest as both overgrowth (e.g. Beckwith–Wiedemann syndrome) and undergrowth (e.g. Silver–Russell syndrome). These defects likely arise due to abnormalities during fetal development, as imprinted genes are typically most active during this period.

While the clinical manifestations associated with such disorders have informed our understanding of the relevance of imprinted genes on the development of the fetoplacental unit, such severe disruption of gene activity occurs relatively rarely. Few studies have examined the impact of more subtle variations in the expression of imprinted genes on growth and development, likely of greater relevance from a public health perspective. Additionally, while 200 genes are believed to be imprinted in humans, most studies have restricted their focus on assessing a few loci at a time. A comprehensive assessment of the role of the imprintome on gestational quality as indicated by birth weight has yet to be conducted.

We generated an expression profile of imprinted genes in the placenta and investigated the association between the expression of these genes and birth weight. Placental samples (n=693) were obtained from newborn infants enrolled in the Rhode Island Child Health Study, and RNA was analyzed using a custom-designed code-set of 150 known and putative imprinted genes (Nanostring technologies, Seattle, WA). In a linear regression analysis, nine genes (BLCAP, CD44, CDKN1C, DLK1, H19, IGF2, MEG3, MEST, PLAGL1) were positively associated with birth weight as a continuous outcome, adjusting for batch, gestational age, infant gender, infant race, maternal BMI, maternal age, parity, maternal insurance and gestational weight gain. Additionally, a one-fold change in the expression of MEST, a paternally expressed gene involved in embryonic development, was associated with both SGA status (OR=0.36, [0.2,0.65]) and LGA status (OR=4.28, [2.34,7.83]) in reference to average for gestational age (AGA) upon categorizing birth weight in a polytomous regression analysis, adjusting for the same factors.

In this study, we have identified a panel of genes whose subtle variation in gene expression is associated with infant birth weight. The identified targets include both known as well as not previously established genes relevant to fetal growth.

Source(s) of support:
Reference(s):
Proximity to major roadways and DNA methylation of repetitive elements in human placenta

Samantha L Kingsley, MPH, Brown University

Background: Exposure to traffic-related pollution has been associated with decreased fetal growth. However, the mechanisms of this association remain unknown. We hypothesize that exposure to traffic pollution impacts fetal growth through alterations in epigenetic mechanisms in the placenta.

Objectives: To examine the association between residential distance to nearest major roadway, as a marker of traffic-related pollution, and birth weight, infant growth status, and levels of placental LINE-1 and AluYb8 methylation among 476 mother-infant pairs from the Rhode Island Child Health Study (RICHS).

Methods: We obtained residential addresses, placenta samples, and demographic data from 476 women following delivery at Women and Infants Hospital in Providence, RI. Women with babies that were small (SGA) or large for gestational age (LGA) were oversampled. We geocoded addresses and calculated distances to the nearest major roadway, defined by census feature class codes A1 (primary highway with limited access), A2 (primary road without limited access), and A3 (secondary and connecting roads). We used generalized linear models to evaluate the association between living close to a major roadway, defined as living ≤150 m from an A1 or A2 roadway or ≤50 m from an A3 roadway and birth weight, infant growth status, and LINE-1 and AluYb8 methylation levels, adjusting for maternal age, BMI before pregnancy, maternal education level, tobacco use during pregnancy, prenatal vitamin use, annual household income, health insurance, maternal ethnicity, neighborhood SES z-sum (the sum of the z-scores for median household income, percent of households with interests, dividends, or rent income, percent of residents with high school diploma, percent with college degree, percent with professional occupation, and median value of owner-occupied housing units), parity, and infant gender.

Results: About 21% of mothers lived close to a major roadway, about 77% were White, non-Hispanic, and the mean age was 30. Among the newborns, about 16% were SGA and about 27% were LGA. Living close to a major roadway was associated with a 184.7 g (95% CI: -320.9, -48.6) lower birth weight and 1.9 (95% CI: 0.9, 3.9) times the odds of being SGA. Those living close to major roadways had mean placental LINE-1 methylation levels 0.78 percentage points (95% CI: -1.51, -0.06) lower compared to those living farther from a major roadway. We found no statistically significant associations between residential proximity to major roadways and mean placental AluYb8 methylation levels.

Conclusions: We found a significant association between maternal residential proximity to major roadways and birth weight and observed evidence of placental epigenetic activity through the association between residential proximity to major roadways and LINE-1 methylation. Epigenetic changes in the placenta may underlie the observed associations between traffic-related pollution and fetal growth.

Source(s) of support:

Reference(s):
Fetal mammary gland development in a dish: observing the effects of BPA ex vivo

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Fetal exposure to the xenoestrogen Bisphenol-A (BPA) results in morphological alterations of the mammary gland (MG) (1) which can lead to neoplasia later in adulthood (2;3). At embryonic day (E) 18, the mammary epithelium of BPA-exposed animals is overall more developed than controls. Lumen formation is delayed in BPA exposed animals. In the stroma, collagen deposition and expression of extracellular proteins related to the biomechanical properties of the ECM, versican and tenasin C, are altered in BPA exposed MGs compared to controls (1;4).

Although estrogen receptors are present in the stroma of the fetal MG (4), it is yet unknown which BPA effects are direct and which ones are mediated indirectly via the hypothalamic-pituitary-ovarian axis (HPOA). The complexity of the animal precludes answering this question using in vivo models.

Here we apply an ex vivo culture method (5) to address the question of whether BPA exerts a direct effect on mouse fetal MG development. This method allows for the direct observation of development as it occurs. Because the unit of exposure is the explant, multiple fetuses per litter can be used. In vivo experiments require, instead, that the unit of exposure be the entire litter. Therefore, this model reduces the number of animals needed.

Mammary buds of CD1 mice were dissected at E14 and cultured for 5 days (5). Typically, 3-4 mammary buds developed in each explant. On day 5 of culture, the explants were fixed, stained with Carmine Alum and mounted. Morphometric analysis was performed on the whole-mounted explants. Parameters studied included ductal area, area subtended by the ductal tree and number of ductal tips. Overall, the development of the cultured MG (E14 + 5 days ex vivo) was comparable to E18-19 stage in vivo. The cultured MGs were smaller in terms of area of growth of the ductal tree (ductal area = 0.067 +/- 0.007 mm2; area subtended = 0.121 +/- 0.014 mm2) than E18 (ductal area = 0.098 +/- 0.004 mm2; area subtended = 0.197 +/- 0.012 mm2) and E19 (ductal area = 0.186 +/- 0.011 mm2; area subtended = 0.52 +/- 0.062 mm2) MGs. The cultured MGs had a higher number of ductal tips (7.52 +/- 0.85) than E18 (4.0 +/- 0.23) and less than E19 (12.0 +/- 2.30) MGs. Lumen formation, a feature observed in vivo at E18, was also observed in the cultured MGs using confocal microscopy.

Finally, this ex vivo method is now being adapted to hormone-free conditions. This method will allow us, for the first time, to tease out the direct effects of BPA in the MG anlagen from those occurring through alterations in the HPOA. Moreover, this method will facilitate testing the effect of additional endocrine disruptors.

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Reference(s):
(2) Murray TJ, Maf
Exploring metabolic effects of prenatal POP exposure using metabolomics
Deepti Sood, Imperial College London

Introduction: Persistent organic pollutants (POPs) are developmental toxicants with complex and poorly understood mechanisms of action in humans. In the present study we used a liquid chromatography mass spectrometry (LC-MS) metabolomics approach to explore the associations between cord serum and maternal serum metabolite concentrations and prenatal (first trimester) environmental POPs exposure within the mother-child cohort ‘Rhea’ study based in Crete, Greece. The aim of this study was to uncover new potential metabolic biomarkers of prenatal/in utero exposure to environmental toxicants and thus understand better the influence of these chemicals on metabolic pathways.

Method: Polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB) and dichlorodiphenyldichloroethylene (DDE) levels were determined in first trimester maternal serum using GC-MS/MS. Using fully-quantitative (LC-MS/MS) and semi-quantitative (FIA-MS/MS) assay (Biocrates P180) 145 metabolites were quantified including amino acids, biogenic amines, acylcarnitines, phosphatidylcholines (PCs) and sphingomyelins (SM) in 86 cord serum and 67 first trimester healthy maternal serum samples. To explore effects on specific enzymatic reactions, intra-metabolite ratios were also explored. Associations between first trimester maternal POPs concentrations and metabolite concentrations were determined using adjusted linear regression models that were validated using 1000 bootstrap models.

Results: Prenatal POPs were positively correlated in cord serum with two diacyl glycerophospholipids and the tyrosine to phenylalanine ratio (Tyr/Phe) whereas negative correlations were identified to the amino acids citrulline and lysine and to one lysophosphatidylcholine. In maternal serum negative correlations were identified to citrulline, kynurenine, the kynurenine to tryptophan ratio (Kyr/Trp) and one acyl-alkyl glycerophospholipid whereas positive correlations were observed with one diacyl-phosphatidylcholine. Citrulline was found to be negatively correlated in both prenatal and cord serum in relation to PCBs and HCB.

Discussion: The current study shows the potential of LC-MS based metabolomics approach coupled with multivariate statistical analysis in the investigation of the molecular signature of prenatal environmental POPs exposure. The results showed that prenatal POPs were associated with metabolites: diacyl/acyl-alkyl glycerophospholipids (unsaturated long chain fatty acids), citrulline: nitric oxide- urea cycle pathway and kynurenine tryptophan metabolism. Larger prospective studies are required for validation of these potential signature markers.

Source(s) of support:
Reference(s):
Trichlorocarbanilide Exposure during Early Life Induces the Overgrowth of Clostridium difficile in Rat Offspring Cecum Contents

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BACKGROUND: Clostridium difficile is a Gram-positive, endospore-forming obligate anaerobe acquired either through environmental exposure or fecal-oral transmission and is an important nosocomial pathogen associated with substantial morbidity and mortality. C. difficile infection (CDI) is one of the most common sources of antibiotic-associated diarrhea (AAD). Most cases of CDI result from exposure to antibiotics along with toxin-producing strains of C. difficile. Widely used as an antimicrobial in personal care products, triclocarban (3,4,4′trichlorocarbanilide; TCC) is effective against Gram-positive bacteria, but to date has not been tested against endospore-forming bacteria. The effect of exposure to antimicrobials found in personal care products to the overgrowth of C. difficile is elusive. Previously, we have shown that TCC exposure from 0.2-0.5% w/w during lactation substantially reduced offspring survival in rats. In the current study we investigated whether early life TCC exposure resulted in a gastrointestinal change that would favor the overgrowth of C. difficile.

METHODS: Pregnant SD rats were randomized and provided either control chow or chow supplemented with 0.1% w/w TCC (a dose non-lethal to offspring) from gestational day 5 (GDS) to postnatal day 20 (PND 20). On PND 20, offspring cecum contents were removed and pooled (3 pools per treatment group) and C. difficile (ATCC, BAA-1803) at a final concentration of 1 x 10^6 CFU/ml was inoculated into cecum content pools and incubated anaerobically at 37ºC for 24 or 48 hours. Half the cecum slurries were plated on C. difficile selective agar and total CFU/ml was enumerated after 24 hrs incubation. The remainder was heat shocked at 56ºC for 10 minutes followed by incubating as stated above to enumerate C. difficile-like endospores. A parallel experiment was conducted in which Gram-positive Staphylococcus aureus (ATCC, 25923) was used instead of C. difficile as a positive control.

RESULTS: Vegetative C. difficile–like CFU/ml counts were significantly increased in cecum content pools collected from TCC exposed compared to unexposed offspring at 24 and 48 hours after initial inoculation respectively. In comparison, no S. aureus CFU/ml were observed in either control or TCC exposed cecum pools, indicating: 1) the efficacy of normal microbiota in the control cecum against the overgrowth of C. difficile and S. aureus and/or 2) the efficacy of suppression of Gram positive, non-spore forming bacteria by TCC but with increased risk of opportunistic endospore forming C. difficile overgrowth.

CONCLUSIONS: Our results suggest that the integrity of microbiota in the gastrointestinal tract provides protection against C. difficile growth, and that disturbances in the composition of the gut microbiota by TCC may increase the susceptibility of the individual to CDI.

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Reference(s):
Systematic Analysis of the Strength of the Association between Developmental Exposures to Environmental Chemicals and Later Life Disease/Dysfunctions

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The scientific field of Developmental Origins of Health and Disease (DOHaD) originated over 20 years ago. It posits that programming of tissue development can be modified by environment (poor nutrition, stress, environmental chemicals) which leads to increased susceptibility to disease/dysfunction across the lifespan. We set out to determine the strength of the data supporting the DOHaD hypothesis by developing a systematic analysis of the scientific literature focusing on the role of environmental chemical exposures. We identified peer-reviewed original research in humans that examined prenatal or early childhood exposure (up to 8 years of age) to any environmental chemical other than tobacco smoke, alcohol, drugs, and pharmaceuticals except DES. Studies needed to assess at least one health outcome occurring later in life (either after one month of age or one month after the exposure of interest). We searched Medline (via PubMed) and ISI Web of Science on May 29, 2013. We identified 343 publications by examination of key descriptive information from each publication. All data were imported into a Microsoft database and we utilized the data pivot module of HAWC (Health Outcomes Workspace Collaborative) to display descriptive information on studies with associated forest plots of reported effect estimates. Examination of disease focus showed the largest number of publications were related to neurological/cognitive outcomes (n=169), followed by cancer (45), respiratory (33), immune disorders (23), metabolic outcomes including obesity (23) and cardiovascular dysfunctions (15) with less than 10 publications each focusing on skin, thyroid, visual problems and liver. Overall 60 different chemicals and mixtures were examined across publications, with the most studied chemicals being POPS (176), air pollutants (129) and metals (103) in contrast to fewer articles focusing on phthalates (9) and bisphenol A (6). A preliminary examination of all the reported outcomes in the data set showed that 283 publications reported a significant positive or negative association between a developmental exposure and some disease/dysfunction outcomes, while there were 60 non-significant associations, indicating a more detailed analysis would be worthwhile. We plan to conduct a detailed analysis of the state of the data supporting the DOHaD hypothesis as well as to outline data needs and gaps for each of the outcomes with a sufficient number of publications (>10 publications). This presentation will report our initial findings with a focus on the obesity data in detail with regard to study quality/potential for bias, exposures and observed trends in reported health effects.
Interindividual Variability of Dose-Response in Human Developmental Studies: A Systematic Search and Lessons Learned

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The variation in dose response between early lifestages and adulthood can result from a number of factors related to differences in exposure, toxicokinetics, or toxicodynamics. The National Research Council’s (NRC) 2009 report “Science and Decisions” recommended that the U.S. Environmental Protection Agency (EPA) develop a phased-in approach to implementing a unified dose response assessment methodology for cancer and noncancer endpoints, incorporating a systematic evaluation of background exposures and disease processes, possible vulnerable populations, and modes of action that may affect human dose-response relationships. In this and other recent reports, the NRC has also made recommendations to the EPA to develop a systematic review process that allows for transparent, reproducible and comprehensive literature searches when conducting chemical risk assessments. Therefore, a systematic search was conducted to identify published literature related to human variation in dose response, with a focus on prenatal or postnatal exposures which may result adverse outcomes observed either during development or later in life. PubMed, a free database of biomedical literature managed by the U.S. National Institutes of Health, was used as the search engine. Within PubMed, keywords were selected from the Medical Subject Headings (MeSH®) thesaurus, a hierarchical system of indexing information. Keywords were identified for: human variation; toxicokinetics and toxicodynamics; study design; developmental endpoints and prenatal programming. The identification of relevant keywords and application of age filters to include in the search was an iterative process, with some minor changes having large impacts on the results, and refinements of search terms resulting in more accurate results. The concluding search identified relevant citations that may be useful for quantitatively evaluating variability in dose response at EPA.

Source(s) of support:
Reference(s):
Developmental programming as a propagator of intergenerational health disparities
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Introduction. Racial and/or ethnic minorities carry the highest burden of many adverse health outcomes and these disparities persist across generations. Developmental programming processes transmit adverse maternal exposures as elevated disease risk in the offspring, often involving heightened response to adverse exposures (“second hits”) encountered in childhood or adulthood. We hypothesize that developmental programming exacerbates the effects of racial patterning of adverse environmental conditions, thereby contributing to persistent health disparities. Methods. We conducted a multidisciplinary literature review and synthesis to evaluate evidence for each component in the hypothesized intergenerational processes: (1) the “second hit” phenomenon reported in animal and human studies from three domains (air, stress, nutrition environments); original studies that included a gestational air, stress, or nutrition exposure and a childhood or adulthood second hit exposure were retained; and (2) persistent racial patterning of environmental exposures from the racial residential segregation, environmental justice, and built environment literature. Results. Animal evidence suggests that exposure to air pollutants by neonates during gestation is associated with a hypersensitive or exaggerated reaction to subsequent air pollution exposure during child- or adulthood, which results in worse and persistent effects. Animal research also indicates offspring exposed to maternal stress produce an exaggerated response to subsequent stressors, including anxiety and hyper-responsiveness of the hypothalamic-pituitary adrenal axis. Similarly, animal studies demonstrate that weight gain, metabolic dysfunction, and atherosclerotic risk exhibit synergistic response to Western-style diets among offspring exposed to poor maternal nutrition during gestation. Cross-domain second hits, e.g., gestational air pollution followed by childhood stressor, also result in exaggerated, negative responses. Adverse environmental conditions (pollution, social, and built environment) linked to racial differences in these critical maternal exposures exhibit racial patterning that persists intergenerationally. Conclusion. Suboptimal gestational environments induce altered or exaggerated offspring response to subsequent environmental and social exposures. Maternal exposure to adverse environments may prime the offspring for detrimental health effects to environmental stressors; furthermore, such offspring tend to experience the same negative exposures by ongoing residence in a suboptimal environment. Empirical assessment of these hypothesized process are needed. Future research on health disparities must be intergenerational and explicitly consider synergistic relationships among maternal conditions and offspring exposures when assessing causes for persistent health disparities.

Source(s) of support:
Reference(s):
Perinatal PFAAs exposure cause various health outcomes on offspring including effects on reproductive and thyroid hormone; the Hokkaido study

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The latest researches done in the Hokkaido study on Environment and Children’s Health in Japan show the clear evidences that relatively low level exposure to environmental chemicals could lead various adverse health outcomes to children. The Hokkaido study is an ongoing birth cohort that began in 2002, consists of the Sapporo cohort (n=514), and the Hokkaido large-scale cohort (n=20,929). The primary goals of the study are to examine the potential negative effects of perinatal multiple environmental chemical exposures on birth outcomes. Perfluoroalkyl acids (PFAAs) have extensive industrial applications, and in this abstract, their associations to fetus health outcomes, including growth retardation, disturbances of the thyroid and reproductive hormone homeostasis, and immune systems were examined.

PFOS and PFOA concentrations in maternal blood in this study were lower compared to that of in other countries, however, several negative associations between PFOS/PFOA and offspring's health outcomes were found. PFOS level was inversely associated with inhibin B and progesterone, whereas positively associated with estradiol in cord blood of male offspring. In female, inverse associations with PFOS and progesterone and prolactin were observed. PFOS level was inversely associated with birth weight, and offspring's IGFB2 methylation in cord blood, which elicit the possibility of PFOS' modification of DNA methylation in utero induce growth retardation of offspring. PFOA concentration was inversely associated with cord blood IgE level of children at birth. Meanwhile, significant negative association between concentration of PFOS and triglyceride and several fatty acids in maternal blood was observed. Elevated concentration of PFOS was found to exhibit higher maternal TSH but lower offspring's TSH without affecting fT4 level. PFOS may disrupt thyroid hormone homeostasis differently from normal negative feedback mechanism. We have also found that recently emerged longer carbon chain PFAAs, such as PFNA and PFDA, was increased in maternal blood over the time period, after PFOS was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants. Prenatal exposure to PFTrDA decreases birth weight and lower the risk of developing eczema at 24 months. These effects of PFAAs exposure on fetus have sex differences.

The findings from the Hokkaido study suggest the possibility that even relatively low levels of PFAAs exposure could disrupt maternal thyroid hormone and lipid metabolism, as well as infants’ growth, reproductive and thyroid hormone homeostasis, and immune function through placental transfer of PFAAs. For further studies, it is important to find the lowest active dose on adverse health outcomes. In addition, the environment-gene interaction should be noted, for example, biological activity of PFAAs is mainly attributed to the transactivation of PPAR. Insight on epigenetics influence should be also focused.

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Reference(s):
Endocrine disrupting chemical exposure during pregnancy and risk of preeclampsia
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Background
The incidence of preeclampsia in the United States has risen over the past three decades to 3.8% of pregnancies in 2010. In developed countries maternal mortality resulting from this condition has decreased, though preeclampsia still represents a major cause of maternal mortality and morbidity worldwide. Fetuses are at risk for still birth, premature delivery, intrauterine growth restriction, delivery complications, and early life adverse outcomes. Maternal later life outcomes include chronic hypertension, diabetes, coronary artery disease, and cognitive issues. While it is known that the placenta plays a central role in development of preeclampsia, investigation into contribution of environmental toxicants into altering placental development and ultimately the risk of preeclampsia, has been sparse.

Objectives
In the present study we examined the relationship between longitudinally measured BPA and phthalate exposure during gestation and preeclampsia.

Methods
A nested case-control study of preterm birth was performed in 2011 from women enrolled in a prospective birth cohort study at Brigham and Women’s Hospital in Boston during 2006-2008. Urine samples were analyzed for BPA and nine phthalate metabolites concentrations at a minimum of three time points during pregnancy on 50 cases of preeclampsia and 432 randomly assigned controls. Preeclampsia was diagnosed with criteria from the American College of Obstetricians and Gynecologists and validated by a panel of board certified physicians. Adjusted logistic regression models were weighted to reflect results generalizable to the base population.

Results
Geometric means of visit 1 (median gestational age 9.7 weeks, range 4.6 – 16.1 weeks) BPA, MECPP, and MEP were significantly higher among PE cases compared to controls. In adjusted logistic regression analysis early exposure to BPA [1.37; 95% CI 1.02, 1.85], MEOHP [1.18; 95% CI 0.99, 1.40], MECPP [1.34; 95% CI 1.13, 1.61], MEP [1.34; 95% CI 1.15, 1.56] were all associated with a significantly increased odds of preeclampsia. When analyzing the average exposure across pregnancy MECPP [1.45; 95% CI 1.14, 1.84] and MEP [1.20; 95% CI 1.00, 1.45] were significantly associated with increased odds of preeclampsia.

Conclusions
BPA and several phthalate metabolites were significantly associated with increased risk of preeclampsia. Interestingly, levels earlier in pregnancy to these endocrine disrupting chemicals had more consistent and significant adverse relationships with risk of preeclampsia. If validated, these results indicate an environmental contribution of endocrine disrupting chemicals to preeclampsia and pose a modifiable means to reduce the mortality and morbidity associated with this condition.

Source(s) of support:
Reference(s):
The effect of prenatal exposure to Perfluorinated compounds on adverse birth weight by GSTT1, GSTM1, and CYP1A1 genetic polymorphism

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Background

Studies examining prenatal exposure of PFCs in relation to birth weight have shown conflicting results. In this study, we investigated whether the association between prenatal exposure to PFCs and birth weight differs by GSTT1, GSTM1, and CYP1A1 polymorphism.

Methods

We collected 151 pregnant women and newborn through a retrospective cohort study of Ewha Birth & Growth between 2006 and 2010 in Ewha Womans University. Information on birth weight was obtained from medical records. We analyzed cord serum samples for PFCs by high-performance liquid chromatograph coupled with a Triple Quad LC-MS/MS system. The genotyping of CYP1A1 Ile462Val and GSTT1, GSTM1 were examined using PCR-RFLP and PCR methods. We assessed the association between the PFCs levels and birth weight according to genotype by multiple linear regression analysis.

Results

PFDA, PFDoDA, and PFOS levels showed a significantly negative association with birth weight. For mothers with GSTT1 and GSTM1 null type, PFDA levels were significantly associated with lower birth weight (adjusted $\beta=-381.07$, $P=0.03$ for GSTT1 null, $\beta=-470.15$, $P=0.01$ for GSTM1 null). The birth weight of infants whose mothers had the CYP1A1 Val variants significantly decreased in PFOS levels.

Conclusions

This study suggests that GSTT1, GSTM1, and CYP1A1 polymorphism may important mechanism in the inverse association between prenatal exposure to PFCs and birth weight.

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Reference(s):
Concentrations of the essential element manganese (Mn) in ground water vary considerably, and reported associations between elevated Mn concentrations and impaired child development have raised concern. We have evaluated the effects of drinking water Mn exposure during pregnancy on child growth and development. The studied mother-child cohort originates from a supplementation trial (MINIMat) conducted during pregnancy. Trial recruitment occurred from Feb 2002 to Oct 2003 in Matlab, rural Bangladesh, where ground water often contaminated with elevated concentrations of arsenic (>50 µg/L) and manganese (>400 µg/L) is the main source of drinking water. We selected women with singleton birth over a period of one calendar year, whose newborns had measured birth anthropometry (n= 1,177). The children were followed-up for developmental assessment at 9-10 years of age (n= 1,163). Concentrations of Mn in the drinking water, used by the mothers during pregnancy, were analyzed using ICP-MS. Anthropometry (weight and length) was measured within 72 hours after delivery. The children’s full scale intelligence quotient (FSIQ), verbal comprehension index (VCI), and perceptual reasoning index (PRI) were assessed at 10 years of age using the adapted Wechsler Intelligence Scale for Children- 4th version (WISC-IV). Overall mean and median mother’s drinking water Mn concentrations were 693 µg/L and 236 µg/L, respectively (range=3.0-6,550µg/L). The mean (SD) birth weight and length were 2,683(402)g and 47.8(2.2)cm, respectively. At 10 years of age, the children’s average FSIQ, VCI, and PRI scores were 67(11), 69(11), and 67(11), respectively. In multivariable-adjusted linear regression analyses, water Mn concentrations (natural log transformed) were inversely associated with birth length (B= -0.10; 95% CI: -0.19, -0.01), but not birth weight (-5.4; 95% CI: -23,12). In preliminary analyses, prenatal exposure of water Mn concentrations was not significantly associated with child intelligence scores at 10 years of age.

In conclusion, our results suggest that elevated early life Mn exposure through drinking water may have an adverse effect on birth length, but no long term effects on child development.

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Reference(s):
Story of Health multi-media eBook – Using storytelling to translate science for health promotion and disease prevention

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Narrative approaches and storytelling are emerging as powerful health promotion tools that can help increase understanding of determinants of health and translate complex science. A Story of Health multi-media eBook capitalizes on this approach by using fictional stories to help convey how multiple environmental factors affect health across the lifespan. By grounding the real science of health in stories of fictional people, their families, and communities, readers are able to explore risk factors for common illnesses that are a serious problem for the health of our nation – asthma, developmental disabilities, cancer, infertility, diabetes, and cognitive decline. These conditions and diseases impose a huge health, social and economic burden, and it is critical that people understand how to prevent them. The stories explore how what we are exposed to in our environments, influence health across the lifespan—from the beginning of fetal development to elder years—and how they can promote health and resilience, or disease and disability. Important determinants of health come from the natural, built, chemical, food, economic, and social environments. Individual stories reveal how these environments are further expressed through such things as education, family structures, housing, nutrition, access to health care, social supports or stressors, and more. And, how they may interact to create the conditions for health and wellness, or vulnerability to disease. The stories are enriched by colorful illustrations and graphics, videos from health and policy experts, key concepts, and links to numerous online resources, to keep readers engaged and help them navigate the complex world of health, and learn about personal and policy prevention strategies. This fully referenced eBook describes the complex interactions that occur among many variables and across individual, community, and societal levels. Through the stories we see how these aspects of our lives are not independent of one and other, but interact in an ecological framework. We understand how individual biology is progressively nested within the person, family, community, ecosystem and society. Interactions within and across these levels are the rule, and we see their influences in health at all levels, through the lives of our fictional characters. The stories are accessible to an educated lay audience, with more technical sections for scientists and medical professionals, who can access free continuing education credits through the eBook. A Story of Health is a collaboration among the Agency for Toxic Substances and Disease Registry (ATSDR), the Collaborative on Health and the Environment (CHE), the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA), the Science and Environmental Health Network (SEHN), and the University of California Pediatric Environmental Health Specialty Unit (PEHSU).

Source(s) of support:
Reference(s):
Biomonitoring Trends in Women of Child-Bearing Age and Potential Prenatal Programming Effects, from EPA’s America’s Children and the Environment


Prenatal exposure to environmental contaminants may lead to adverse birth outcomes and the development of conditions in childhood that are associated with increased morbidity and mortality in adulthood. Biomonitoring in women of child-bearing age can provide insight into prenatal exposures to environmental contaminants and help inform research on environmental origins of adverse outcome pathways and prenatal programming effects. To assess trends in prenatal biomonitoring data and the potential impact on adult health outcomes, we utilized U.S. Environmental Protection Agency’s (EPA’s) America’s Children and the Environment (ACE) report (1). The ACE report tracks trends in children’s environmental health, including nationally representative biomonitoring data for women of child-bearing age. Here, we present graphical indicators of biomonitoring measurements in women of child-bearing age (16 to 49 years) for several contaminants, including phthalates and perfluorochemicals. Changes in biomonitoring data over time are presented where such data are available. Proposed linkages between prenatal exposures and adult health outcomes addressed in the report, such as the potential association between prenatal exposure to phthalates and reduced fertility in adulthood, are highlighted. Data gaps and limitations in epidemiological and toxicological literature with regards to prenatal biomonitoring data and associated diseases are addressed when appropriate.

Source(s) of support:

Reference(s):
Prenatal traffic-related air pollution influences miRNA expression in sorted cord blood

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A limited body of evidence suggests that air pollution is associated with altered miRNA expression levels in the peripheral blood of adults. We aimed to investigate whether prenatal air pollution exposure might also influence miRNA expression levels in newborn blood, specifically in sorted monocytes and lymphocytes. As part of an ongoing birth cohort study, a 50 cc cord blood sample was collected at delivery and transported to the molecular biology lab for processing. Monocytes and lymphocytes were isolated using the Stem Cell magnetic bead positive isolation kits, after which miRNA was extracted and expression quantified using the Nanostring assay. A total of 23 paired samples (monocytes and lymphocytes), including 4 duplicates, were assayed. Nanostring miRNA values were normalized separately for each cell type using the NSolver software. Traffic-related air pollution (TRP) estimates, specifically total oxides of nitrogen (NOx) from freeway and non-freeway sources, were assigned to each subject using the CALINE-4 line dispersion model using residential address at the time of birth. Linear regression models were used to analyze the association between TRP and miRNA expression. In order to be included in the analysis, 50% of subjects had to have a value for the miRNA that was above background levels (> 2SD from the average of the negative control values). Thirty-six out of 800 miRNA met these criteria for lymphocytes and 38 for monocytes. Twenty-eight (77%) of these were common to both cell types indicating a fair amount of overlap. Nine miRNAs were significantly associated with non-freeway NOx in lymphocytes whereas no statistically significant associations were observed for monocytes. For all but one of these associations, high non-freeway NOx was associated with a 43-58% decrease in miRNA expression. In sum, we provide preliminary evidence that prenatal exposure to high levels of non-freeway NOx is associated with decreases in miRNA expression levels in the cord blood of the neonate that are cell specific. The health implications for these changes in expression are currently unknown.

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Reference(s):
Urinary phthalate metabolites and bisphenol-A in association with circulating biomarkers of placental function across pregnancy

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Maternal exposure to phthalates and bisphenol-A (BPA) during pregnancy has been linked to a number of adverse health outcomes including preterm birth, slowed fetal growth, and altered neurodevelopment in infants and children. These adverse effects are strongly tied to the successful development of the placenta, and though effects of phthalates and BPA on placental implantation and function have been hypothesized no supporting evidence exists in human studies. Angiogenic factors, such as placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), play roles in vascularization of the placenta. Decreased PIGF and increased sFlt-1 are indicative of impaired placental development and function. In this study we explored the relationship between these markers and urinary phthalate metabolites and BPA.

Subjects were part of a nested case-control study of preterm birth (N=130 cases, N=352 controls). The parent study consisted of mothers who were recruited early in gestation as part of a longitudinal cohort at Brigham and Women's Hospital in Boston. Mothers provided demographic information as well as urine and plasma samples at four study visits (median 10, 18, 26, and 35 weeks gestation). Urine samples were analyzed for 9 phthalate metabolites and BPA, as well as specific gravity. Plasma samples were analyzed for angiogenic markers. Linear mixed effects (LME) models were used to examine the relationship between each exposure measurement and PIGF, sFlt-1, or a ratio of the two (sFlt-1/PIGF), which may be a stronger predictor than either marker alone. Regression models were weighted so that results were generalizable to the base cohort population.

In weighted LME models adjusted for gestational age at sample collection and urinary specific gravity only, BPA was associated with a significant increase in sFlt-1 (% change with interquartile range [IQR] increase in BPA=7.08, 95% confidence interval [CI]=2.04, 12.4). No associations were observed between sFlt-1 and phthalate metabolites. PIGF was inversely associated with the sum of the di-2-ethylhexyl phthalate metabolites (ΣDEHP; % change with IQR increase=6.58, 95% CI=12.1, -0.69). Associations with the ratio of the two measures were stronger both for BPA (% change with IQR increase=12.3, 95% CI=2.62, 22.8) and ΣDEHP (% change with IQR increase=10.4, 95% CI=1.56, 22.0). In models additionally adjusted for maternal age, health insurance provider, and body mass index, associations were similar in direction but slightly attenuated. However, the associations between sFlt-1 and BPA, and between the sFlt-1/PIGF and ΣDEHP and BPA, remained statistically significant.

These associations suggest that phthalate and BPA exposures may disrupt placental development and/or function during gestation, findings which may be useful for future studies investigating mechanisms by which phthalate and/or BPA exposure may lead to adverse pregnancy outcomes and development of the child later in life.

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Reference(s):
A developmental origin of adult reproductive dysfunction in the zebrafish associated with an embryonic exposure to the herbicide atrazine.

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It is now well accepted that there are windows of enhanced susceptibility to environmental chemical exposures during critical periods of development and that developmental chemical exposure can influence the onset of adult disease, disorders, and dysfunction. It is acknowledged that the adverse health outcomes of these developmental chemical exposures can illicit different effects later in life in adults in comparison to exposures only during adulthood. Ongoing studies in our laboratory are defining the genetic and epigenetic mechanisms of toxicity of an embryonic exposure to the herbicide atrazine and assessing the later in life adverse health outcomes from this developmental chemical exposure using the zebrafish model system.

Atrazine, an herbicide commonly applied to agricultural areas throughout the Midwestern United States and a common contaminant of potable water supplies, is implicated as an endocrine disruptor and potential carcinogen. The specific adverse health effects associated with atrazine exposure and the underlying genetic and epigenetic mechanisms of toxicity are not well defined. In an effort to delineate the mechanisms of atrazine toxicity, zebrafish embryos were exposed to environmentally relevant concentrations of atrazine shortly after fertilization through the end of embryogenesis (72 hours post fertilization). Transcriptomic profiles immediately following the embryonic atrazine exposure identified expression alterations in genes associated with neuroendocrine and reproductive system development and function, cell cycle regulation, and carcinogenesis. From these exposures a subset of individuals was permitted to mature under normal conditions to evaluate later life effects of the embryonic exposure. Adverse health outcomes observed were associated with genetic pathways identified immediately after the embryonic exposure including altered reproductive function. Additional transcriptomic analysis was completed on adult female and male zebrafish brains and gonads to further define and link genetic mechanisms of the developmental origin of atrazine-induced adult disease and dysfunction on the neuroendocrine and reproductive systems. Transcriptomic results showed that an embryonic atrazine exposure elicits multiple genetic alterations that persist into adulthood and show sex differences in gene expression and biological pathway alterations. Overall this study is providing further evidence in support of the ability of atrazine to be an endocrine disrupting chemical causing reproductive dysfunction and genetic alterations that persist into adulthood.

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Reference(s):
Using structural equation models to examine the association between prenatal arsenic exposure, maternal health, and birth weight
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Previous epidemiological studies have reported inconsistent findings on the relationship between arsenic exposure from drinking water and birth weight. We enrolled a prospective birth cohort in Bangladesh from 2008-2011 (N=1,036). Arsenic was measured in personal drinking water using inductively coupled plasma mass spectrometry at enrollment (<16 weeks gestational age [WGA]). Questionnaires collected health data at enrollment, at 28 WGA, and within one month of delivery. A structural equation model was used to estimate the direct and indirect effects of arsenic on birthweight. In our model, birth gestational age and maternal weight gain were considered as potential mediators, while adjusting for the direct effects of maternal education, tobacco smoke exposure, infant sex, maternal BMI at enrollment, and maternal age. Natural log-transformed arsenic had a total negative indirect effect that was mediated through birth gestational age and weight gain during pregnancy (β=-19.96 grams, 95% CI: -25.50, -14.17 grams). The majority of this effect was mediated through birth gestational age (β=-15.6, 95% CI: -21.33, -9.81), and a small portion was mediated through maternal weight gain (β=-4.4, 95% CI: -6.88, -1.90). The direct effect of log-transformed arsenic on birth weight was not significant after accounting for the mediated indirect effects. These results show that prenatal arsenic exposure is strongly associated with decreased birthweight and that this relationship is completely mediated through birth gestational age and maternal weight gain.

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Reference(s):
Diet-induced obesity increases the spermatozoal toxicity of acrylamide in the absence of oxidative stress

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There is an intimate interplay between nutritional stress and environmental chemicals in human health, the importance of which is becoming increasingly clear. There are indications that obesity may increase the susceptibility to the toxicity of environmental chemicals. Recent studies suggest that dietary-induced obesity may exacerbate reproductive toxicity of the heat induced food contaminant acrylamide. In search for underlying mechanisms of such interactions, we examined the male reproductive toxicity of acrylamide in normal and obese mice.

Administration of acrylamide to experimental animals induces a range of male mediated reproductive effects including chromosomal aberrations in male germ cells, and increased pre- and post-implantation losses. Possible mechanisms through which obesity can increase the reproductive toxicity of acrylamide, include changes in hormonal status and metabolism, and increased oxidative stress. Increased levels of oxidative stress and lipid peroxidation have been observed in obese men as well as in animal models of obesity. Sperm cells are particularly sensitive to DNA and/or chromatin oxidation and overt oxidative stress is considered to be a major cause of reduced sperm chromatin integrity in humans. We therefore examined the potential role of oxidative stress in the combined effects of diet and acrylamide for male germ cell toxicity.

In the present study, we examined whether there is an increase in oxidative stress in a dietary-induced obesity mouse model that could sensitise the sperm for further attack. Acrylamide is metabolised to the reactive epoxide glycidamide, which reacts with cellular DNA and protein and is considered the primary mediator of the reproductive effects in males. Mice kept on a normal or a high fat diet were exposed to a single dose of glycidamide seven days prior to sacrifice, which is the most sensitive period for acrylamide induced spermatozoal toxicity and paternally mediated embryo losses. A modified Comet assay was used for sensitive detection of oxidative DNA lesions and protein carbonyls were measured by Elisa. The sperm chromatin structure assay (SCSA) was used as a measure of sperm quality. In addition, glycidamide-haemoglobin adducts were measured analytically.

We found no indications of increased oxidative stress under the experimental conditions in the current study as both the level of oxidative DNA lesions in blood and tissue, and the protein carbonyl levels in the epididymal fluid, were not elevated in the obese animals. Furthermore, obesity did not seem to influence the level of glycidamide-induced DNA damage as measured by the Comet assay. However, obesity markedly increased the spermatozoal toxicity of glycidamide and the haemoglobin-glycidamide adduct levels were higher in the obese animals than in control animals. In conclusion, dietary-induced obesity increased the spermatozoal toxicity of glycidamide in the absence of oxidative stress.

Source(s) of support:
Reference(s):
Rapid Method of Sperm DNA Extraction for Epigenetic and Genetic Studies

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Background and Objective: There is a growing interest in elucidating the role of sperm epigenetics and genetics on reproductive success and the trajectory of health outcomes over the lifecourse. Massive reorganization of chromatin structure during spermatogenesis occurs where the majority of histones are replaced by protamines enabling tight compaction of the sperm nucleus. The condensed nucleus of sperm; however, is resistant to lysis by buffers from commercially available column-based DNA purification kits due to the formation of disulfide bridges between protamines. To overcome this, traditional methods for sperm DNA extraction have used reducing agents, such as dithiothreitol (DTT) and 2-mercaptoethanol (βME), with proteinase K to cleave disulfide bridges and degrade nucleoproteins using incubations at 56°C ranging from 2–24 hours. Our objective was to develop a rapid method for extracting high quality DNA from human sperm for downstream DNA methylation and genetic analyses.

Methods: Sperm from semen samples provided by three human volunteers were isolated using a one-step 90% gradient (PureCeption). Sperm cells were homogenized with 0.2mm steel beads for 5 minutes at room temperature on a Disruptor Genie (Scientific Industries) in the presence of a commercially-available guanidine thiocyanate lysis buffer (Zymo gDNA lysis or Qiagen RLT) supplemented with 50 mM TCEP. After homogenization, sperm DNA were extracted using Quick-gDNA MiniPrep (Zymo Research) or AllPrep (Qiagen) silica-based column kits. DNA methylation analyses of imprinted loci were assessed using the MassARRAY platform (Sequenom).

Results: Our method resulted in yields > 90% (2.7 pg/sperm cell) and high quality DNA (260/280 > 1.8). DNA yields did not differ between immediate extraction and after four weeks of homogenate storage at 4°C (37.5 ± 2.7 ng/μl and 38.7 ± 2.8 ng/μl, respectively). DNA methylation analyses revealed similar methylation levels at baseline and 4 weeks of storage for the imprinted loci: SNURF (1.43 ± 1.02% and 1.55 ± 0.95%), PEG10 (3.69 ± 0.66% and 4.28 ± 1.52%), and H19 (88.93 ± 3.24% and 91.78 ± 2.00%).

Conclusion: Our 5 minute room temperature homogenization protocol resulted in > 90% yield of high quality sperm DNA without the use of proteinase K compared to 2-24 hour incubations reported in other methods. After homogenization, DNA can be extracted by user-preferred silica-based spin columns. Unlike βME and DTT, TCEP is odorless and stable at room temperature in aqueous solutions, thereby making it the reducing agent of choice to further streamline our procedure. Our homogenization method also stabilizes nucleic acids to allow for optional storage of homogenate for future DNA extraction. This method is also amendable for sperm DNA extraction of other mammalian species. Together, our improved method has important practical implications for research in clinical settings where sample processing constraints likely exist.

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Reference(s):
The Home Observation of Periconceptional Exposures (HOPE) Study—a Prospective, Pre-conception Cohort

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A prospective, pre-conception cohort of couples (women 18–35, men 18–40) without known infertility were recruited in Utah beginning in early 2012. To date 147 couples have enrolled. Recruitment is ongoing. We perform individual-level biomonitoring among male and female partners timed to the fertile window. The contaminants selected for analysis, Bisphenol A (BPA) and disinfection by products (DBP), are ubiquitous, involuntary exposures, but the method could be used to study any time-varying exposure. Women observe cervical mucus to identify the fertile window and an estimated day of ovulation or conception (EDO/C). Both participants collect daily first-morning urine samples during the fertile window, after which males discontinue but females collect for the remainder of the cycle. BPA and DBP are measured in each urine sample with the remainder stored in a bio-repository unless the participant has denied consent to store specimens for future use. We plan to analyze the relationship between exposures and the outcomes of semen quality among males and time to pregnancy for the couple. Couples continue daily fertility charting until pregnancy is achieved or until 38 weeks after the second cycle of specimen collection. Eighty-five (63%) couples have achieved pregnancy thus far. Our method of timing exposure assessment to the periconceptional period is inexpensive and portable. Couples learn the method from a simple educational brochure with available support from study staff. The protocol could be easily expanded to other sites and to target other periods of development during pregnancy. To date, ~5000 urine samples have been submitted. Among men, 1037 urines were expected and 838 (81%) collected with the majority corresponding correctly to the fertile window (654, 78%). Among women, 3243 samples were expected and 2742 (85%) submitted, primarily during the collection period (2580, 94%). On average, each woman collects 17±5 and each man collects 6±2 samples per cycle. Preliminary results of 2614 urine samples (1996 female, 618 male) show a geometric mean of BPA as 2.52 ng/mL (95% CI, 2.27–2.79) and median of 2.40 ng/mL. Geometric mean BPA levels were higher among men at 2.78 ng/mL (95% CI, 2.39–3.22) compared to women at 2.44 ng/mL (95% CI, 2.15–2.77). Both males and females collect saliva specimens at EDO/C+2 days, and male partners collect a semen specimen at home during intercourse between the end of the fertile window and onset of next menses. Saliva collection compliance was high among both men (206, 96.7%) and women (207, 97.1%). Semen collection was also highly compliant with 90% (n=193) of expected specimens submitted. In preliminary analyses, for every unit increase in BPA geometric mean, the odds of abnormal sperm concentration increased by 1.18 (95% CI 1.01–1.37), and men in the highest BPA tertile (≥4.67 ng/mL) had a 3.30 (95% CI 1.02–10.70) increased odds of abnormal sperm heads compared to men in the low BPA tertile (≤1.90 ng/mL).

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Reference(s):
Placental arsenic concentrations in relation to both maternal and infant biomarkers of exposure in a US cohort

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Arsenic crosses the placenta and may have adverse consequences in utero and later in life. The placenta has critical functions in nutrient and waste transport between mother and fetus and in hormonally regulating the progression of pregnancy. Little is known about arsenic concentrations in the placenta and how they relate to maternal and infant exposures, particularly at the levels of exposure seen in the US.

We measured total arsenic concentrations in 765 placental tissue samples from women enrolled in the New Hampshire Birth Cohort Study. Approximately 9% of NHBCS participants have drinking water arsenic above the current 10 µg/L maximum contaminant limit. We compared placenta arsenic concentrations to the arsenic concentration of second trimester maternal urine (total and individual species, excluding arsenobetaine), maternal post-partum toenails and infant toenails. We also examined associations between placental arsenic and household drinking water arsenic.

We found a wide range of arsenic concentrations in placenta (0 – 18.4 ng/g wet weight), with a median of 0.76 ng/g. Placenta arsenic concentrations were positively associated with arsenic concentrations in maternal urine (P<0.0001), toenails (P<0.05) and infant toenails (P<0.05). Placental arsenic concentrations were related to arsenic concentrations in household drinking water (P<0.0001). Placental biopsy tissue is a reliable biomarker of maternal arsenic exposure during pregnancy, even at low exposure levels.

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Reference(s):
High fat olive oil, not butter, has a protective role in bisphenol A-induced impaired spermatogenesis

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Increase in the incidence of male reproductive problems within the last few decades are too rapid to be explained by genetic factors alone, and suggest environment/lifestyle may play roles in their development. Since exposure to Bisphenol A (BPA) is ubiquitous and consumption of high-fat diets is deeply ingrained in our culture, prenatal exposure to both BPA and high levels of dietary fats is a legitimate public health concern. Also, obesity, aging, xeno-oestrogens, inflammatory cytokines and poor dietary choices all cause increases in intracellular E2 in adult males. Our objective was to study the relative contributions and interactions between high fat butter (HFB) or olive oil (HFO), and BPA diets, on rat spermatogenesis. We hypothesize that gestation is a critical window for dietary fatty acids-BPA interaction, that reprogram spermatogenesis, resulting in subtle changes in germ cell differentiation in adulthood. Moreover, these changes may go unnoticed until critical secondary exposures occur, to unmask their effects.

We performed a study, where Taconic Sprague-Dawley rats were exposed in utero to normal diet (no-soy diet-16% kcal fat), BPA (25 µg/kg bw/day), HFB (HFB - 39% kcal fat), HFO (HFO – 39% kcal fat), HFB+BPA and HFO+BPA. The dose of 25 µg/kg bw/day BPA was based on an initial pilot dose-response experiment. We found that adult males prenatally exposed to BPA, HFB± BPA, and HFO ± BPA had qualitatively normal spermatogenesis (Sp/sis) within the testis. However, when treated with testosterone and 17β-estradiol (T+E2) for 20 weeks (mimic aging), the BPA, HFB and HFB+BPA exposed males, and not unexposed rats, exhibited impaired Sp/sis (consisting of germ cell degeneration). Moreover, we found that males exposed to HFO + (T+E2) did not show impaired Sp/sis. Surprisingly, HFO protected the testis from BPA induced impairments in Sp/sis. On T+E2 treatment, 100% of unexposed rats had normal Sp/sis. However, only ~40% of the male rats exposed to HFB, BPA and HFB+BPA showed presence of spermatozoa in seminiferous tubules (STs). While the numbers of rats exhibiting impaired Sp/sis remained the same among these groups, the severity of phenotype changed. The HFB+BPA exposed males showed the presence of focal ST atrophy, where STs were lined by sertoli cells and a few spermatogonia. STs were also examined for estrogen receptor (ER)-α, ER-β, androgen receptor, aromatase, BRDT and protamine-1 (prm-1) by IHC. Loss of ER-β expression in round spermatid was observed for the BPA, HFB and HFB+BPA exposed males, but not in the presence of HFO. Moreover, abnormal association of prm-1 with meiotic / mitotic spermatocytes was observed. Our results suggest that while HFB and BPA diet alone can lead to a blocks in spermatocyte differentiation into round spermatids and spermatid elongation, the HFB/BPA diet results in a significant number of STs blocked at earlier stages of Sp/sis (atrophy). Moreover, HFO can protect the testis from harmful effects of BPA.

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Reference(s):
Fetal growth and maternal glomerular filtration rate: a systematic review

Background. Chemicals used in commerce are ubiquitous in the prenatal environment and research has found that these exposures are associated with a wide range of adverse health outcomes in both humans and animals, including impaired prenatal growth. Glomerular filtration rate (GFR) may influence concentrations of biomarkers of exposure and their etiologic significance in observational studies of associations between environmental contaminants and fetal growth. It is unknown whether the size of a developing fetus may affect maternal GFR such that a small fetus leads to reduced plasma volume expansion (PVE), reduced GFR and subsequent higher concentrations of biomarkers in maternal serum—i.e. the reverse causality hypothesis.

Objectives. To answer the question: ‘Is there an association between fetal growth and maternal GFR in humans?’

Methods. We adapted and applied the Navigation Guide systematic review methodology for environmental health to assess quality and strength of the evidence of an association between fetal growth and GFR, either directly or indirectly via reduction in PVE. We conducted a systematic search of the literature using four online databases, assessed the risk of bias of individual studies, extracted outcome data and assessed the overall quality and strength of the evidence across all human and non-human studies according to pre-specified factors. Finally we integrated the strength ratings from the human and non-human animal evidence streams to achieve an overall strength of evidence statement for the association between fetal growth and GFR: ‘known to be associated,’ ‘probably associated,’ ‘possibly associated,’ ‘probably not associated’ or ‘not classifiable’

Results. We identified 35 relevant studies: 31 human studies; 2 non-human observational studies and 2 experimental non-human studies. We rated the human and non-human observational studies as ‘low’ quality and the experimental non-human studies as ‘very low’ quality. We found evidence of an association between increased fetal growth and increased PVE but there was limited or inconsistent evidence on the relationship between fetal growth and PVE, and PVE and GFR. Overall we rated all three evidence streams as ‘inadequate’, predominately based on the small number, size and quality of studies on GFR. We rated the association between fetal growth and GFR as ‘not classifiable’ according to pre-specified and transparent definitions.

Conclusions. There is currently no evidence to support the plausibility of a reverse causality hypothesis for associations between exposure to environmental chemicals during pregnancy and fetal growth. Further high quality, pragmatically designed and adequately powered human and non-human studies are needed in order to reach a conclusion on the association between fetal growth and GFR.

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**Associations between urinary phenol and paraben concentrations and markers of oxidative stress and inflammation among pregnant women in Puerto Rico**

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Phenols and parabens are used in a multitude of consumer products resulting in ubiquitous human exposure. Animal and in vitro studies suggest that exposure to these compounds may be related to a number of adverse health outcomes, as well as potential mediators such as oxidative stress and inflammation. We examined urinary phenol (bisphenol A (BPA), triclosan (TCS), benzophenone-3 (BP-3), 2,4-dichlorophenol (24-DCP), 2,5-dichlorophenol (25-DCP)) and paraben (butyl paraben (B-PB), methyl paraben (M-PB), propyl paraben (P-PB)) concentrations measured three times during pregnancy in relation to markers of oxidative stress and inflammation among participants in the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) project. Serum markers of inflammation (c-reactive protein (CRP), IL-1β, IL-6, IL-10, and tumor necrosis factor-α (TNF-α)) were measured twice during pregnancy (n=105 subjects, 187 measurements) and urinary markers of oxidative stress (8-hydroxydeoxyguanosine (OHdG) and isoprostane) were measured three times during pregnancy (n=54 subjects, 146 measurements). We used linear mixed models to assess relationships between exposure and outcome biomarkers while accounting for within individual correlation across study visits. After adjustment for urinary specific gravity, study visit, maternal pre-pregnancy BMI, and maternal education, an interquartile range (IQR) increase in urinary BPA was associated with 21% higher OHdG (p=0.001) and 29% higher isoprostane (p=0.0002), indicating increased oxidative stress. IQR increases in BP-3, B-PB, and P-PB were also significantly associated with 17%, 27%, and 20% higher isoprostane after adjustment for covariates, respectively. An IQR increase in triclosan (TCS) was associated with 31% higher serum concentrations of IL-6 (p=0.007), a pro-inflammatory cytokine. In contrast, IQR increases in BP-3 and B-PB were significantly associated with 16% and 18% lower CRP, a measure of systemic inflammation. Our findings suggest that exposure to BPA, select parabens, and TCS during pregnancy may be related to oxidative stress and inflammation, potential mechanisms by which exposure to these compounds may influence birth outcomes and other adverse health effects, but additional research is needed.

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**Reference(s):**
Reproductive Environmental Health Education for OB/GYN Specialists

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Reproductive Environmental Health Education for OB/GYN Specialists

Background.— Environmental health affects reproduction, however, current OB/GYN residency curricula do not address environmental health. This knowledge gap has resulted in missed opportunities for patient education and anticipatory guidance. We designed an elective rotation in Reproductive Environmental Health & Justice (REHJ), in conjunction with the University of California San Francisco Pediatric Environmental Health Specialty Unit (UCSF PEHSU) to address this knowledge gap.

Objective.— The purpose of this elective is to provide OB/GYN Residents/Fellows with experience in all aspects of reproductive environmental health. During the rotation at the UCSF P(R)EHSU, Fellows will learn to bring scientific analysis and medical knowledge to reproductive environmental health issues, and to communicate about these issues in a culturally-appropriate way to a broader audience, including the general public, the media, and the broader health care community. An additional objective is to develop competencies for the specialty of Reproductive Environmental Health and appropriate measures (performance indicators) for the achievement of these competencies.

Methods.— The proposed rotation was modeled on the extant Pediatric resident/fellow rotation at the UCSF Pediatric Environmental Health Specialty Unit, using the current PEHSU faculty and clinic resources, in collaboration with UCSF OB/GYN faculty, for proposed REHJ rotation. Proposed competencies for fellows in Reproductive Environmental Health were drafted with input from competencies proposed by the Institution of Medicine, Ambulatory Pediatric Association, and the American College of Occupational and Environmental Health.

Results.—An elective rotation, devised as a month-long block in the context of a 3-year fellowship in Maternal Fetal Medicine or a 4-year residency in Obstetrics and Gynecology, is proposed. Twenty-seven Reproductive Environmental Health competencies are proposed. The competencies are presented from 3 separate perspectives: academic, individual patient care, and community advocacy. The first fellow has completed the rotation, culminating in an abstract on maternal and fetal lead levels submitted to a national OBGYN meeting.

Conclusion.—A Reproductive Environmental Health & Justice elective for OBGYN residents and MFM fellows is intended to promote the dissemination of importance environmental health concepts in the OB/GYN community. These competencies are intended to assist in structuring the training experience, achieving consensus with respect to expectations of fellows and faculty, providing opportunities for fellows to assess their own needs or gaps in training, and improving the health of communities through education and anticipatory guidance.

KEY WORDS: competency-based education; reproductive environmental health

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Reference(s):
Inhalation of concentrated ambient particulate matter by pregnant mice leads to adverse obstetric outcomes associated with particular exposure windows

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Epidemiologic studies suggest a strong causal link between exposure to airborne particulate matter (PM) during pregnancy and preterm birth (PTB) and low birth weight (LBW). However, these studies are often in disagreement regarding which particular time points are most sensitive or whether such effects are cumulative. Previously, we showed that inhalation exposure of timed-pregnant mice to concentrated PM2.5 (CAPs) collected from Tuxedo, NY (a “clean” site representing a regional background for the mid-Atlantic East Coast of the US), throughout pregnancy (6 hr/d from gestational day (GD) 0 through GD16) at a concentration of ~160 μg/m3 resulted in PTB and LBW. Using the same exposure paradigm, mice were assigned to one of four exposure windows (Win) corresponding to specific events during development (Win 1 –GD 0 - 5; Win 2-GD 6 -14; Win 3-GD 14 - 17; and, Win 4 GD 0 - 16). Mean daily CAPs concentrations for each exposure window was 178, 193, 171, and 173 μg CAPs/m3 for Win 1-4, respectively. CAPs exposure induced PTB ranging from 0.4 days for Win 2 to 0.6 days in Win 4 compared to time-matched controls corresponding to ~1 wk preterm in humans. Maternal exposure to CAPs resulted in LBW in neonates from dams assigned to Win 1, 2, and 4 with decreased weights (~10%) compared to pups born to filtered air (FA)-exposed mothers. Exposure to CAPs during Win 3 alone resulted in decreased (~8%) placental weights, with no changes being observed in litters exposed during other times. These experimental data provide feasibility for the epidemiological association between PM exposure and PTB/LBW and show experimentally for the first time that there are particularly sensitive times during gestation where PM exposure can result in adverse obstetric outcomes. Alterations in fetal development and growth are associated with lifelong effects such as increased risk for learning and behavioral difficulties, along with later life susceptibilities to disease (e.g., type 2 diabetes). Modeling these effects in mice may help develop intervention strategies for both the pregnant woman and child, both in utero and postnatally, in order to mitigate these adverse effects. Supported by March of Dimes and the NYU NIEHS Center Grant ES000260.

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Reference(s):
Maternal exposure to iodine excess throughout pregnancy and lactation induces hypothyroidism in adult male rat offspring

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Iodide transport into the thyroid is a rate-limiting step in the biosynthesis of thyroid hormones (THs). In the first trimester of gestation, the fetus depends on the maternal transfer of THs, which are important in promoting normal placenta and fetal development. The iodide transfer to the fetus and newborn throughout the second and third trimesters of pregnancy (P) and during the lactation (L) guarantees normal fetal TH production, which accounts for progressive fetal growth and development. Therefore, adequate maternal iodine intake during these periods is required for normal fetus development. The drastic consequences of iodine deficiency (ID) during P and L on fetus development are well described; however, the effects of iodine excess (IE) during these periods are still controversial. Recent data from the World Health Organization (WHO) indicated that iodine intake has greatly increased in several countries. Therefore, this study examined the consequences of maternal exposure to IE during P and L on the pituitary-thyroid axis and THs metabolism of adult male rat offspring.

Methods: Female Wistar rats were treated or not with IE (5X the physiological dose) in drinking water throughout P and L. Male offspring were given normal water and fed with standard chow diet from the end of L period (PND21) until adulthood (PND90). At PND90 the male rats were killed and the pituitary, thyroid, kidney and liver were excised. Gene expression was evaluated by Real-Time PCR and Western Blotting. Morphological changes of thyroid gland were investigated by histological analysis. Serum concentration of T3, T4 and TSH were assessed by multiplex assays. The expression/activity of the deiodinase 1 (D1), which is responsible for peripheral T3 generation and metabolism was also analyzed. Results: The adult male rat offspring exposed to IE during P+L presented decreased expression of genes related to THs synthesis (TSHR, NIS, TPO, Tg). In agreement, the treatment reduced the expression of Pax8 and TTF1, which are transcription factors involved in thyroid development and differentiation. Pituitary expression of αTSH and βTSH were increased by IE exposure. On the other hand, GH expression, which is positively regulated by T3, was decreased. In accordance, serum concentration of T3 and T4 were reduced and TSH levels were increased. Kidney and liver D1 expression and activity were decreased by IE treatment. The thyroid structure analysis revealed large follicles surrounded by increased amount of connective tissue in IE exposed animals. Conclusions: The exposure to IE during pregnancy and lactation periods induces primary hypothyroidism in the adult male offspring. Moreover, the treatment decreased the generation of T3 from T4 in the adult life. This supposedly leads to serious repercussions on growth, development and metabolism, indicating that IE during these critical periods of development may be as harmful as ID to the offspring.

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Reference(s):