The Relationship of Environment and Human Health

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Environmental Toxins Impact Us All

• Environmental toxicants are industrial or naturally occurring, organic or inorganic, chemicals that harm human health across the lifespan and more so during critical developmental windows.

Endocrine Disruptors

Endocrine Society defines as **an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.**


"All substances are poisons; there is none which is not a poison. The dose differentiates a poison and a remedy."

Paracelsus (1490-1541)
Endocrine Society
Second Scientific Statement

“Endocrine disrupting compounds contribute to outcomes related to impaired reproduction, neurodevelopment, thyroid function, metabolism, and increased propensity for hormone-sensitive cancers.

Unfortunately, it is difficult to directly relate chronic disease burden to exposures in humans. The increased prevalence of such diseases underscores the need to invoke precaution in introducing new (and usually untested) chemicals into the environment.”


Assessment of Risk Complex

- Exposed to many EDCs in environment - understanding how they act alone and together is crucial but difficult to study.
- Lifelong exposures to EDCs, particularly during critical windows may lead to considerable adverse consequences to human health.
- One of most sensitive stages in human development takes place in-utero and first 3 years of a child's life.
- While limits/restrictions for some EDCs have been made for children's products – there is still considerable exposure and little focus on limits during pregnancy.

"In our every deliberation, we must consider the impact of our decisions on the next seven generations."

Iroquois Confederacy
EDC and Reproduction

- Increased prevalence of hormone-sensitive cancers (e.g. breast, prostate), impaired fertility, early puberty, decreased sperm counts, genital malformations, and unbalanced sex ratios at least partially attributable to increased EDC exposures.


EDC and Reproduction

Epidemiological prospective cohorts using biomarkers for exposures over past 16 years: EDC exposures impact reproductive potential in women. Exposure to EDCs decrease:

1. Estradiol levels (BPA)
2. Antral follicle count (BPA, phthalates, parabens)
3. Oocyte quality (BPA, phthalates, PCBs, triclosan*)
4. Implantation (BPA, phthalates, PCBs)
5. Embryo quality (BPA, PCBs, triclosan*)
6. Rate of clinical pregnancy and live births (phthalates, parabens).

Triclosan banned by FDA in antibacterial hand soaps in 2017


Premature Ovarian Insufficiency

- 25% of premature ovarian insufficiency cases have unknown etiology.
- Review 97 relevant human and animal studies: phthalates, BPA, pesticides and tobacco most reported substances having negative impact on ovarian function with increased follicular depletion leading to an earlier age of menopause onset.

**Bisphenol A**

- First synthesized 1891, known to mimic estrogen since 1930s.
- In hard, rigid plastics, metal food cans; plastic water pipes, thermal receipts, etc.
- Banned in baby bottles and cups in 2012.
- Reproductive toxicity category 1B (‘May damage fertility’) in EU.
- Associated with disruption of: female reproduction (cystic ovaries, altered uterine morphology, fertility), mammary gland development, cognitive function and metabolism (increased insulin resistance).
- Mechanism of action is complex but available evidence shows that disruption of estrogenic pathway is central and consistently involved in these four effects.


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**Prenatal Exposure BPA**

- Chemical signaling (hormone) vitally important in fetal development.
- Fetus likely exposed to free BPA, readily crosses placenta.
- Fetal sex determined genetically but gonadal hormones important for differentiation of male/female phenotypes. EDCs mimicking or blocking natural sexual hormones may interfere with development.
- Exert epigenetic effects that may be passed to subsequent generations.

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**Canned Foods**

- Randomized crossover study 20 healthy volunteers given canned or fresh food. One day wash out and then interventions reversed.
- Urine samples collected immediately before meals and then 2 h, 4 h, and 6 h after meals.
- Mean BPA concentrations at 2 h, 4 h, and 6 h after meals were 152%, 206%, and 79% higher, respectively, than mean BPA concentrations before meals. Returned to baseline by 24 hours.

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**BPA and Dental Restorations**

- Systematic review 20 studies show that BPA levels increase in saliva one hour after composite resins and dental sealants.
- One week after treatment, level in saliva only marginally higher than before treatment and no statistically significant level in urine.

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Controversy Exists

- High levels in urine, blood, umbilical cord blood, amniotic fluid in US.
- National Toxicology Program CLARITY-BPA study in rats failed to find any significant adverse effects even at high exposure to BPA.
- However, NIEHS funded studies show BPA exposure in pregnancy can increase risk of obesity and behavioral problems in child, and increase asthma with early childhood exposure.
- Discrepancies in outcomes may be due to differences in animal models, labs using different experimental designs, different measurements (HPLC, GC-MS or LC-MS/MS), route and window of exposure, and experimental targets.


Columbia Center for Children's Environmental Health https://ccceh.org/?s=BPA&submit=Search Accessed October 6, 2019

BPA Analogue

- Research shows BP-B, BP-F, BP-S also act as endocrine disruptors.
- National Toxicology Program: “Our results add to a growing literature indicating that risk characterizations of BPA need to expand and should begin to consider BPA structural and functional analogues. This is especially important given that the evidence…that many of the BPA analogues are active at concentrations similar to or lower than BPA.”


Strategies for Patients

- Eat fresh or frozen foods
- Do not microwave foods/beverages in plastic containers or with plastic cling-wraps
- Hand wash plastic containers
- Use glass, porcelain and/or stainless steel containers
- Avoid cans when possible, especially acidic, salty or fatty foods (purchase in glass or cartons). Be cautious with “BPA-free”
- Use filter for tap water and carry stainless steel water bottle
- Say no to thermal paper receipts.
- Avoid plastics with recycling #3 and 7

Phthalates

- Human made chemicals used in toys, vinyl floor and wall coverings, detergents, lubricating oils, food packaging, pharmaceuticals, blood bags/tubing, and personal care products.
- CDC: 84% population have >six phthalates in system. Women higher levels of urinary metabolites than men for those phthalates that are used in soaps, body washes, shampoos, cosmetics, and similar personal care products.
- SYNTHETIC fragrances are a significant source of exposure.

https://www.fda.gov/cosmetics/ingredients/phthalates Accessed October 6, 2019
Phthalates and Motor Skills

- NIEHS Study: researchers measured 6 phthalate metabolites in urine from 209 women late in their pregnancy and children at 3, 5, and 7 years.
- Age 11, administered motor proficiency screening test to children.
- Higher exposure to phthalates before birth associated with lower motor function among girls; higher exposure in childhood associated with lower scores in boys.


Phthalates and Cognition

- Significant inverse associations seen between various maternal prenatal metabolite concentrations and child processing speed, perceptual reasoning working memory; child verbal comprehension; child perceptual reasoning.
- Among children of mothers with highest versus lowest quartile DnBP and DiBP metabolite concentrations, IQ was 6.7 and 7.6 points lower, respectively.


Phthalates

- Data from Swedish Environmental Longitudinal Mother and Child, Asthma, Allergy and the Infant Development and Environment Study (TIDES): found prenatal exposure to specific phthalates statistically significantly associated with language delay in children.
- TIDES study: 3 DEHP metabolites during 1st trimester significantly and inversely associated with shortened anogenital distance in male newborns.

**Diet and EDC Levels**

- Use of **plastic containers** associated with higher urinary phthalate metabolites, **canned food consumption** associated with higher urinary BPA concentrations.
- Foods/dietary patterns associated with **healthier food choices** (e.g., organic/grown/raised/caught foods, folic acid supplements, vegetarianism) associated with lower urinary phthalate metabolite and BPA concentrations.
- Dietary intervention: exclusive consumption of **organic foods** for 3 days: urinary DEHP metabolite concentrations decreased 53–56% and urinary BPA concentrations by 66%. Foods provided and prepared from plastic-free packaging and containers.

**Phthalates Insulin Resistance**

- Systematic review by EPA researchers: phthalate exposure at levels seen in human populations may have metabolic effects.
- Association between phthalate exposure and **diabetes** should be considered.
- Other EDC implicated in type-2 DM include BPA, PCBs, and organochlorine pesticides.

**Some EDCs Act As Obesogens**

- **Can cause weight gain** via exposure to pesticides/herbicides, industrial/household products, plastics, and personal care products.
- **Highly lipophilic**, increases fat deposition that increases capacity for own retention.
- Vicious cycle of increasing obesity and retention of other lipophilic chemicals with broader range of adverse actions.
- Animal models and epidemiological studies show especially sensitive time for exposure is in utero and neonatal period.

**Reducing Exposure**

- Avoid plastics with **recycling #3 on package**
- Avoid foods with **plastic wrap/packaging**.
- Don't heat food in plastic.
- Read labels of personal care products, avoid those with phthalates or "fragrance".
- If water is from a well, **test for phthalates** and contact state health dept. if levels are high.
- Use **activated carbon filtration system** or **reverse osmosis**.
Parabens

- **Antimicrobial and preservative**, commonly used in personal care products: methylparaben (MP), propylparaben (PP), ethylparaben (EP), butylparaben (BP) and benzylparaben (BenzylP).
- **Estrogenic/anti-androgenic potential**: EU/USA/Canada limits amounts in cosmetics (0.4% single paraben and 0.8% mixtures).
- Studies in mother-infant pairs find that median concentrations of parabens are similar in both maternal blood and amniotic fluid.

Parabens and Puberty

- Center Health Assessment of Mothers and Children of Salinas: 338 children in Salinas Valley, CA followed birth to adolescence.
- In girls: peripubertal concentrations associated with earlier breast and pubic hair development, and menarche with MP; earlier menarche with PP.
- In boys: peripubertal concentrations associated with earlier genital development with PP.
- Note: study found prenatal diethyl phthalate and triclosan exposures associated with earlier menarche in girls.

Reduce Exposure

- **Read labels** for anything containing -paraben.
- Use paraben-free products.
- Consider homemade products to soothe skin: shea butter, organic sunflower seed oil, etc.
- There are “certifying” seals that consumers can also look for (e.g., Safer Choice, EWG).
Organophosphate Pesticides

- First synthesized and used as *nerve gas* in World War II.
- Their chemical structures and properties significantly modified to alter their toxicity and other physical/chemical properties but they are all neurotoxic. That's how they *work as insecticides*.
- Neurological and/or cognitive deficits described and experimental and epidemiological relationships found between pesticide exposure and Alzheimer’s, Parkinson’s, and amyotrophic lateral sclerosis diseases.


Chlorpyrifos

- Organophosphate pesticide used to *control household pests* (e.g., cockroaches, termites, fire ants).
- *Used agriculturally* to combat pests on cotton, grain, seed, nut, fruit, wine, and vegetable crops.
- Used in nurseries, food processing plants, on golf courses, and in water supplies to *combat mosquito larvae*.
- Acutely toxic to earthworms and honeybees.
- Study of indoor air and dust samples collected in homes and day cares in US found many had chlorpyrifos present, even though most had not used pesticides for one week or longer.

https://cen.acs.org/environment/pesticides/safe-exposure-chlorpyrifos-EU-regulators/97/web/2019/08Accessed 10/02/19
"The E.P.A. may argue that the science showing chlorpyrifos is unsafe is unclear... (but) under the Food Quality Protection Act, the E.P.A. must prove that there was a reasonable certainty that the pesticide would not cause harm."

Pesticide Exposure: ADHD

- Prenatal OP exposure observed a negative effect on mental development and increase in attention problems in preschool and school children.
- Children: higher urinary levels of dimethyl phosphate twice or pyrethroid metabolites were two times more likely to have ADHD, compared to children with low or undetectable levels.


**www.ewg.org**
If we are going to live so intimately with these [agricultural] chemicals—eating and drinking them—taking them into the very marrow of our bones—we had better know something about their nature and their power.”

Rachel Carson, Silent Spring

Insecticides and Cancer

- Meta-analysis of 16 studies found childhood exposure to indoor residential insecticides (nonoccupational and nonagricultural) is associated with a significant increased risk of childhood leukemia and lymphomas.
- Positive but not statistically significant association found for brain tumors.
- Integrated pest management recommended by USDA, EPA, American Public Health Association, and National PTA.

Meta-analysis of the association between childhood cancers and exposure to home pesticides during childhood. *Professional home treatments.


Paraquat Dichloride Herbicide

- Widely used on soy, corn, peanuts and alternative for weeds resistant to GLY.
- Repeated exposure in animal models induces pathological features of Parkinson's, loss of dopaminergic neurons in nigrostriatal dopamine system.
- Exposure during teen or young adult years in California increased Parkinson's risk of 200-600%, depending on overall years of exposure.
- Banned in 32 countries.


Zhang XF, Lab Invest 2016; May;96(5):496-507.
Glyphosate

- Introduced as broad-spectrum herbicide in 1974.
- Glyphosate and glyphosate-based herbicides have endocrine-disrupting effects on male reproduction at low doses.
- Two recent reviews of glyphosate's health hazards report conflicting results:
  - Review by International Agency for Research on Cancer (IARC) found glyphosate is a "probable human carcinogen".
  - Review by the European Food Safety Agency (EFSA) found no evidence of carcinogenic hazard.

Glymphosate and Cancer

- Agricultural Health Study: prospective cohort of 54,251 licensed pesticide applicators from North Carolina and Iowa, of which 44,932 (82.8%) used glyphosate, including 5779 incident cancer cases (79.3% of all cases).
- Glyphosate was not statistically significantly associated with cancer at any site in this study. Applicators in highest exposure quartile had increased risk of acute myeloid leukemia, though didn’t reach statistical significance.


Glyphosate Use Dramatically Increased

- Pregnant women in Indiana: those with highest urinary GLY levels had shorter gestational lengths (p = 0.02).
- Animal data suggest high exposures to GLY in pregnancy are associated with birth defects.
- Study in N. Carolina found increased risk of atrial septal defects in children born to mothers with higher GLY exposures.

**Foods with Glyphosate Residues**

- EFSA database: soybeans, corn, barley, lentils, linseed, mustard seed, oats, sorghum, wheat, coffee beans, tea, beet root, and mushroom with GLY residues.
- Canada: highest levels of GLY in beans, peas, lentils, grains, infant cereal and baby food, followed by juice and other processed forms of fruits and vegetables.
- GMO soy has high residues.

**Pollinators: The Honey Bee**

- Honey bee gut microbiota dominated by eight bacterial species that promote weight gain and reduce pathogen susceptibility.
- Gene encoding EPSPS in almost all sequenced genomes of bee gut bacteria, indicating susceptible to glyphosate.
- Relative and absolute abundances of dominant gut microbiota species are decreased in bees exposed to glyphosate at concentrations documented in the environment.

**Atrazine**

- Second most widely used herbicide in US and most commonly detected pesticide in surface water: it is a pervasive water contaminant.
- Endocrine disruptor, inhibiting luteinizing hormone production, increasing aromatase production. Can feminize male frogs.
- Immunotoxic effects and potential link to lymphoma.
- Banned by EU in 2004.

**Atrazine and Obesity**

- **Agricultural Health Study:** exposure during pregnancy increases risk for gestational DM.
- Chronic administration of low concentrations of atrazine in drinking water of rats decreased basal metabolic rate, and increased body weight, intra-abdominal fat and insulin resistance without changing food intake or physical activity level.
Lymphoma and Drinking Water

- Incidence of non-Hodgkin lymphoma increased rapidly in rural areas and has been consistently higher in Nebraska than US as a whole.
- Nebraska water high nitrate AND atrazine.
- Drinking water containing nitrate was associated with a nearly three-fold increase in risk for developing NHL if atrazine was also present.
- Example of difficulty in predicting cumulative effect of multiple chemical exposures.

Atrazine and Low Birth Weight

- 2017 study: association between atrazine and preterm and very preterm birth in Midwestern counties in which <10% of population uses well water.
- 14,445 live births in Ohio communities enrolled in EPA Atrazine Monitoring Program: significantly increased odds of low birth weight associated with atrazine exposure, particularly during 1st and 2nd trimesters.

EWG’s Tap Water Database

Since 2010, water utilities’ testing has found pollutants in Americans’ tap water, according to an EWG drinking water quality analysis of 30 million state water records.


EWG’s Updated Water Filter Buying Guide

What’s most important to you in a water filter?

- Better-tasting water
- Most effective filter
- Removes lead

www.ewg.org/tapwater/
Water

- One billion people lack access to potable water.
- Two billion lack access to adequate sanitation, over 3 billion people suffer from waterborne disease annually, many of whom die.
- The earth’s water supply is shared, and finite.
- No pollution or contamination takes place in isolation, and the health of the world’s waters has an enormous impact on the health of people everywhere.

Mercury

- Bacteria in water can transform inorganic mercury into bio-active, organic form, called methylmercury, which concentrates to very high levels in fish.
- US Geological Survey of 291 freshwater streams between 1998-2005 found 100% of the larger fish tested positive for significant mercury exposure.
- Majority of mercury entering US rivers stems from emissions from coal mining. The emissions enter the air and then are precipitated back into water systems.


FDA Advice

- Women of childbearing age and young children:
  - NO swordfish, shark, king mackerel, or tilefish.
  - Eat 12 ounces (340 g) fish and shellfish low in mercury per week.
  - Omega 3 crucial for optimal neurological development in the fetus and infant.
  - Take a prenatal vitamin with DHA.

Seafood Calculator

www.ewg.org/research/ewg-s-consumer-guide-seafood/seafood-calculator
To Reduce Exposure

- What is water source (may contain pesticide from shallow groundwater)? Recommend granulated active carbon filtration (or reverse osmosis)
- Know if your community has implemented a registry or alert system to notify individuals when planned pesticide applications are being done.
- Be an advocate for integrated pest management in homes, schools, day care center and businesses. Know how to recommend to patients.
- Dust, vacuum, and ventilate home often.
- Counsel patients about dietary modifications: purchase organic, wash produce, peel off outer layers leafy veggies, remove peels, trim fat/skin from meat/poultry/fish.

Knowing is not enough, we must apply.
Willing is not enough, we must do.
—Goethe

Pharmaceuticals in the Environment

Over 200 different pharmaceutical agents, including antibiotics, NSAIDs, analgesics, lipid-lowering drugs, estrogens, anti-depressants and others, have been detected in aquatic and terrestrial environments around the world, including areas as remote as the Antarctic.

Pharmaceuticals in Water and Soil

- Over four billion pharmaceutical prescriptions filled last year in US and is expected to increase in coming years.
- Continually increasing trends in prescription usage means that active pharmaceutical ingredients have an ever-growing presence in the natural environment.
- Pharmaceuticals are nearly ubiquitous in most environmental media as a result of improper disposal and normal human excretion.


**Antibiotics in the Environment**

- Antibiotics highly successful pharmaceuticals used in human and veterinary therapy.
- Large amounts wind up in municipal wastewater due to human excretion or improper disposal.
- Run off sludge and water from animal feedlots contribute large amounts into ecosystem.
- US: 2 million people infected with antibiotic resistant organisms and 23,000 people die each year as a direct result (CDC)

**Multi-Antibiotic Resistance in Streams**

- Screening 427 *Escherichia coli* strains isolated from 11 locations on nine streams draining into Savannah River against panel of antibiotics.
- >40% of strains demonstrated resistance to 10 or more antimicrobials, suggesting environmental multi-antibiotic resistance.
- Among multi-antibiotic-resistant isolates, several demonstrated resistance to all structural classes of antimicrobial agents tested, including frontline antibiotics such as gatifloxacin and ciprofloxacin.


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“(Our bodies) are not distinct from the bodies of plants and animals, with which we are involved in the cycles of feeding and in the intricate companionships of ecological systems and of the spirit….. It is therefore absurd to approach the subject of health piecemeal with a departmentalized band of specialists… Our fragmentation of this subject cannot be our cure, because it is our disease.”

Wendell Berry, The Unsettling of America
"Whatever befalls the earth befalls the sons of the earth. Man did not weave the web of life; he is merely a strand in it. Whatever he does to the web, he does to himself."

Resources

- ToxTown: https://toxtown.nlm.nih.gov/
- National Institute of Environmental Health Sciences Brochures and Fact Sheets: https://www.niehs.nih.gov/health/materials/index.cfm