An overview of environmental chemicals as contributors to diseases and disabilities

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Genes and environment are in continuous conversation.
Toxicity

• Adverse effects depend on:
  – The properties of the chemical
  – Exposure: route, dose, timing, pattern, duration
  – Susceptibility of individual or population
  – Interactions with genetic, nutritional, and social factors
Hazards, exposures, risks

- **Hazard**—a chemical or physical agent capable of causing harm; the potential to cause harm
- **Exposures**—the applied dose of a chemical agent
- **Risk**—the probability of harm. Hazard and exposure together determine risk.
Route of exposure

- Ingestion
- Inhalation
- Intravenous
- Through the skin (dermal)
- Health effect can vary with the route of exposure (e.g. asbestos)
- Toxicity may vary with dose, duration, timing, route of exposure (e.g. metallic mercury, current BPA debate)
What happens to the chemical after exposure?

- Rapidly metabolized and excreted?
- Stored? In fat? (dioxin) In bone? (lead)
  - In multiple organs? (mercury)
- “Half-life”—minutes, hours, days, years?
  - benzene—minutes some pesticides—hours
  - methylmercury—months dioxin—years
  - lead—years
- Challenge of estimating peak exposure level
PBTs

- Persistent
- Bioaccumulative
- Toxic
Mechanisms of toxicity

• Many different ways that a chemical can cause toxicity or a health effect
  – Direct damage to parts of cells or organs
  – DNA damage or mutation (e.g. benzene metabolites)
  – Alter gene expression, including epigenetics
  – Interfere with normal enzyme levels, affecting metabolism (e.g. dioxin)
  – Interfere with function of hormones or other signaling molecules
  – Induce excessive inflammation; oxidative stress
  – Etc.
Epigenetics

- Alterations that result in heritable changes in gene expression that do not involve changes in the DNA sequence
- Two types of epigenetic information (marks): Cytosine methylation (DNA); histone modifications (Protein)
- Epigenetic marks are set during development
Hormones

• Play key roles during development of specific organs, immune system, reproductive system

• Attach to specific receptors; e.g. estrogen receptor or testosterone receptor, others (e.g., BPA and multiple receptors)

• Hormone-receptor complex then attaches to DNA in the cell and activates the genes
Endocrine disruptors

- Exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.
Environmental Threats to Healthy Aging

Environmental Factors
- Food system/diet
- Toxic Chemicals
- Environmental contaminants
- Socioeconomic stressors

Altered Pathways
- Inflammation
- Oxidative Stress
- Disrupted Insulin Signaling

Endocrine disruption

Diabetes
Cardiovascular disease
Obesity
Abnormal lipids
Metabolic syndrome
Alzheimer’s
Inflammation is a dimension of diabetes, metabolic syndrome, obesity, CVD, some neurodegenerative disorders, and other chronic illnesses.

Numerous inflammatory markers involved
Oxidative Stress

INTERNAL
- Mitochondria
- Activated immune cells (phagocytes)

EXTERNAL
- Tobacco smoke
- Industrial pollutants
- Ozone, particulate
- Pesticides
- Radiation
- Anesthetics
- Organic solvents
- Some pharmaceuticals
- High oxygen
- Food*

Sufficient antioxidants keep this process in check.
Sources of oxidative stress

• Food
• Tobacco smoke
• Industrial pollutants
• Ozone, particulate air pollution
• Pesticides
• Organic solvents
• Some pharmaceuticals
Dose-response

• The shape of the dose response curve is essential for predicting toxicity and health effects.

• Dose-response curve can vary for different health effects from the same chemical; e.g. the dose response curve for “death” from exposure to a pesticide will differ from the curve for impacts on the developing brain.

• If we focus on acute, obvious effects we will miss more subtle or delayed effects.
Non-linear dose-response curve with “threshold”

Figure 1. Typical nonlinear, “threshold”, dose-response relationship ($R = Ad^3$).
ACUTE EFFECTS

Death Rate

LD_{50}  Usually 100%

Dose
Non-monotonic dose-response curve

vom Saal et al. 1997
A Complicating Problem…

• Humans are always exposed to multiple environmental agents
• It is difficult to decipher how exposure to many agents will influence the effects of each one
• Linking exposure and disease has to take multiple exposures into account
Unique windows of vulnerability

Childhood health, illness

NUTRITION

TOXICANTS

INFECTIONS

GENETICS

SOCIAL ENVIRONMENT

Adult health, illness

Cardiovascular disease
Diabetes
Cancer
Neurodegenerative disease
Etc.
Fetal susceptibility

• Unique biological events > unique vulnerability

• Development of brain, immune system, endocrine (hormone) system, reproductive system can be disrupted by exposure to environmental chemicals during fetal life, infancy, or childhood (chemicals that interfere with hormones and other signaling molecules)
Earlier life experiences can influence later-life health, disease

Toxic exposures (e.g. air pollution, pesticides)
Diet
Stress
Birth weight; development

Obesity, hypertension, cardiovascular disease, diabetes, cancer
Alzheimer’s, dementia; Parkinson’s disease

DES in utero: ↑ vaginal, cervical, breast cancer risk
DDT before age 14: ↑ breast cancer risk (Cohn, 2007)
Lifetime lead exposure: cognitive decline
Manifestations of abnormal development

• Fetal death

• Low birth weight; e.g. maternal smoking, air pollution, some pesticides Woodruff, Environ Res, 2009; Windham, Fertility Sterility, 2008

• Birth defects; e.g., pesticides, solvents (mixed, inconsistent evidence; challenges)

• Cancer; leukemia and maternal pesticide exposures, paternal exposure to carcinogens (inconsistent evidence) Wigle, EHP, 2009

• “Functional” abnormalities; e.g., neurodevelopment; reproductive, immune, respiratory systems, etc.

• Increased susceptibility to adult disease
Diseases with links to environmental chemicals

- Over 200 diseases or conditions with causal links to environmental chemicals
- Database at [www.healthandenvironment.org](http://www.healthandenvironment.org)
- Cancers, asthma, infertility, birth defects, heart disease, neurodevelopmental disorders, neurodegenerative diseases, etc.
- Strength of evidence classified as strong, good, limited/conflicting
- Sources: Major textbooks and supplemental literature searches
Non-Hodgkin’s Lymphoma: Documented Links

- 1,3-butadiene [Strong]
- benzene [Strong]
- Dioxins/TCDD [Strong]
- 2,4-D [Good]
- Agent Orange [Good]
- aldrin [Good]
- Aromatic amines [Good]
- captan [Good]
- Carbamates [Good]
- carbaryl [Good]
- carbon disulfide [Good]
- carbon tetrachloride [Good]
- Chlorophenols [Good]
- Chlorophenols [Good]
- Creosotes [Good]
- DDT/DDE [Good]
- dicamba [Good]
- dichlorvos [Good]
- Fungicides [Good]
- Insecticides [Good]
- Ionizing radiation [Good]
- lindane [Good]
- malathion [Good]
- MCPA [Good]
- mecoprop [Good]
- Organochlorine pesticides [Good]
- Organophosphates [Good]
- PCBs [Good]
- Pesticides [Good]
- Phenoxyacetic herbicides [Good]
- Secondhand smoke [Good]
- Solvents [Good]
- tetrachloroethylene (PCE) [Good]
- trichloroethylene (TCE) [Good]

Breast Cancer: Documented Links

- Active smoking [Strong]
- Estrogens/DES [Strong]
- ethyl alcohol (ethanol) [Strong]
- Ionizing radiation [Strong]
- Secondhand smoke [Strong]
- Aromatic amines [Good]
- B-naphthylamine [Good]
- benzidine [Good]
- ethylene oxide [Good]
- PAHs [Good]
- PCBs [Good]
- Progestins [Good]
- Solvents [Good]
- tetrachloroethylene (PCE) [Good]

Childhood Brain Cancer: Documented Links

- Ionizing radiation [Strong]
- dichlorvos [Good]
- lindane [Good]
- Pesticides [Good]
- Second-hand smoke [Good]
- Solvents [Good]

Environmental chemicals and fertility-related impacts (humans)

Bisphenol A  Miscarriage/ fetal loss
Chlorinated hydrocarbons  Menstrual irregularities
Glycol ethers  Endometriosis
Heavy metals  Reduced fertility
Phthalates  Hormonal changes
Solvents  Altered puberty onset

Vallombrosa Conference 2005; Chemical exposures and infertility and related disorders
http://www.healthandenvironment.org/
Multiple chemical agents
Example: Neurodevelopmental impacts
Vulnerability of the developing brain

• A highly orchestrated sequence of events
• Cell division, migration, differentiation, synapse formation, myelination, synapse pruning
• Each process can be disrupted by environmental agents with long-term, downstream effects
Neurodevelopmental toxicants: Multiple processes; mechanisms

<table>
<thead>
<tr>
<th>Process</th>
<th>Toxicants</th>
</tr>
</thead>
<tbody>
<tr>
<td>proliferation</td>
<td>radiation, ethanol, mercury, OP pesticides</td>
</tr>
<tr>
<td>migration</td>
<td>radiation, mercury, ethanol</td>
</tr>
<tr>
<td>differentiation</td>
<td>ethanol, nicotine, mercury, lead, decreased thyroid</td>
</tr>
<tr>
<td>synaptogenesis</td>
<td>radiation, ethanol, lead, triethyl tin, OP pesticides, PCBs, decreased thyroid</td>
</tr>
<tr>
<td>gliogenesis &amp; myelination</td>
<td>decreased thyroid, ethanol, lead</td>
</tr>
<tr>
<td>apoptosis</td>
<td>ethanol, lead, mercury</td>
</tr>
<tr>
<td>signaling</td>
<td>ethanol, OP pesticides, mercury, lead, PCBs</td>
</tr>
</tbody>
</table>
Long-recognized hazards

- Alcohol – hyperactivity, cognitive deficits
- Nicotine – IQ deficit, learning and attention deficits; includes environmental tobacco smoke (LBW, intrauterine growth retardation)
- Lead – impaired IQ, learning, attention; hyperactivity, impulsiveness, aggression; failure to complete school, trouble with the law
Additional neurodevelopmental hazards

• Methylmercury, arsenic, manganese
• Polychlorinated biphenyls (PCBs)
• Brominated flame retardants
• Pesticides
• Perchlorate; and, in combination with inadequate iodine
• Organic solvents (in addition to ethanol)
Prenatal exposure to PBDEs and neurodevelopment

n = 329; adjusted for multiple confounders; co-variables; effect modifiers; Bayley Scales of Infant Development; Wechsler Scale of Intelligence

Herbstman, EHP, Jan 2010
Prevalence of thyroid disease in pregnant women

- Clinical hypothyroidism occurs in about 0.3% of pregnant women
- Subclinical hypothyroidism occurs in about 3-4% of pregnant women; 120,000+ babies born annually to women with subclinical hypothyroidism (US)
What are the consequences?

Lower IQ
Attention deficit
Visual processing
Motor impairment

Severity appears to depend on the severity of TH insufficiency
Specific domains affected appears to depend on the timing of insufficiency.
Iodine deficiency

• 1/3 of people globally iodine deficient
• In the US, 30% of women of reproductive age have insufficient iodine intake
• Women with insufficient iodine status more susceptible to thyroid disruptors that block iodine uptake in gland
Thyroid disrupting compounds

- PCBs
- PBDEs (flame retardants)
- Perfluorinated compounds (PFOS, etc)
- Perchlorate, nitrate, thiocyanate (inhibit iodine uptake)
- Bisphenol A
- Triclosan
- Etc.

Exposures to many of these are ubiquitous; Why should we think there is a “safe” threshold for any one?
Developmental neurotoxicity of industrial chemicals

- Lead
- Methylmercury
- Arsenic
- PCBs
- Solvents
- Pesticides
- Manganese
- Perchlorate
- PBDEs

Grandjean, Lancet, 2006
The challenges inherent in putting it all together

• Aggregate chemical exposures
  – Similar or differing mechanisms of toxicity
  – Dose and timing of exposure

• Cumulative risk of chemical and non-chemical stressors
The framework for risk assessment of chemicals should be modified to account for uncertainty and variability in responses to exposures attributable to age, ethnic group, and socioeconomic status, as well as other attributes that affect individuals and make them a part of a vulnerable group.
Social environments

Micro-, macro-nutrients

Environmental toxicants

genetic makeup, gene expression

Health, disease, disability

Modified from: Hubbs-Tait et al. Psychological science in the public interest