

Emerging Environmental Chemicals: Implications for Human Health



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Wyoming Chronic Disease Conference

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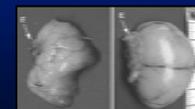
DDT – Harbinger of Future Problems

- Novel organochlorine insecticide synthesized in 1873.
- Awarded Nobel prize in 1948.
- Banned from use in U.S. in 1973
- Multiple problems identified
 - Environmental persistence
 - Lack of species selectivity
 - Biomagnification in food chain
 - High residue levels in fish and birds
 - Eggshell thinning and decreased reproductive success in birds.
 - Bioaccumulation in human adipose tissues and plasma



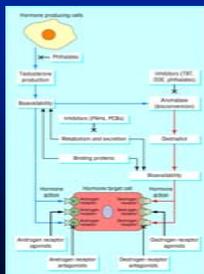
DDT – An Endocrine Disruptor

- Feminizing effects in males
- Combs and wattles failed to develop in male roosters
- Testicles 18% of normal size
- Compound shown to mimic effects of estrogen. (anti-androgenic)
- If DDT is estrogenic, could exposure to women increase risk of breast cancer?
- Are other effects such as developmental impairment and reproductive toxicity seen?



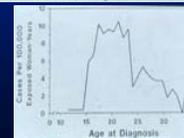
What is an endocrine disruptor?

- A compound that interferes with the Synthesis, Secretion, Transport, Binding, Action or Elimination of hormones.
- Mechanism of Action
 - Estrogenic
 - Androgenic
 - Anti-Estrogenic
 - Anti-Androgenic



Human Endocrine Disruptor

- DES used to prevent miscarriage and premature delivery from 1941-1971.
- 5 to 10 million women and their male and female children exposed.
- Cluster of vaginal clear cell adenocarcinoma identified (Herbst et al., New Eng J Med, 1971).

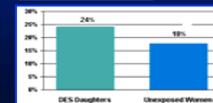


Diethylstilbestrol (DES)

- Clear cell adenocarcinoma - vaginal and cervical
- Reproductive tract structural differences
- Pregnancy complications –
 - Ectopic & pre-term delivery
- Infertility



Infertility Rates for DES Daughters vs. Unexposed Women*



Palmer, 2001



Examples of Endocrine Disrupting Pesticides

Pesticides		Insecticides	
Herbicides		S-HCH	(120)
2,4-D	(98,99)	Carbaryl	(100)
2,4,5-T	(100)	Chlordane	(121)
Alachlor	(95,101)	Dicofol	(20)
Amitrole	(102,103)	Dieldrin	(113)
Atrazine	(104-106)	DOT and maraboltas	(30)
Metribuzin	(107)	Endosulfan	(122; A. Soto, unpublished)
Nitrofen	(10)	Heptachlor and H-epoxide	(113)
Trifluralin	(108,109)	Lindane (γ-HCH)	(123)
Fungicides		Metbomyl	(107)
Benomyl	(110)	Methoxychlor	(5,124)
Hexachlorobenzene	(111-114)	Mirex	(A. Soto, unpublished)
Manczels	(108)	Oxychloridane	(121)
Maneb	(115,116)	Parathion	(125)
Metiram-complex	(117)	Synthetic pyrethroids	(126)
Tributyl tin	(118,119)	Toxaphene	(A. Soto, unpublished)
Zincb	(116)	Transnonachlor	(121)
Ziram	(95)	Nematocides	

Environ Health Perspect. 1993;October; 101(S): 378-384

Dibromochloropropane (DBCP)

- Used widely as a nematocide
- Workers at a California mfg plant found to be infertile (Whorton, 1977)
 - Azoospermia
 - Oligospermia
 - Increased gonadotrophin levels (FSH, LH)



'Teeny Weenies'

- Lake Apopka chemical spill – DDT, dicofol, agricultural runoff
- Decrease in juvenile alligator population
- Reduced penis size, lower levels of testosterone, increased estrogen and anatomical defects in males
- Increased estrogen levels, oocyte and follicle abnormalities in females



Guillette LJ, et al. (1994). "Developmental Abnormalities of the Gonad and Abnormal Sex Hormone Concentrations in Juvenile Alligators from Contaminated and Control Lakes in Florida." Environmental Health Perspectives 102(8):680-688

Alligator Phallus Size



- Reproduced in lab with DDD and DDE



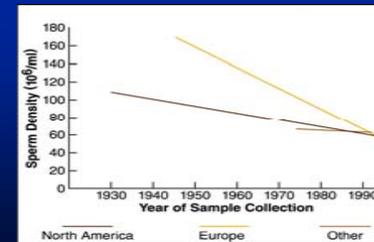
Guillette LJ, et al. (1996). "Reduction in Penis Size and Plasma Testosterone Concentrations in Juvenile Alligators Living in a Contaminated Environment." General and Comparative Endocrinology 101:32-47

Sperm Concentration Decline

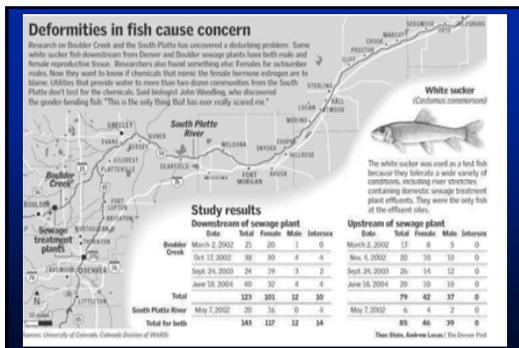
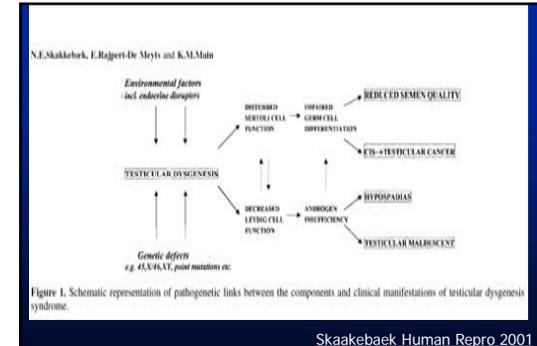
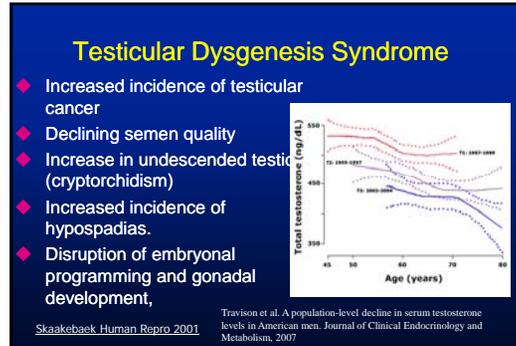
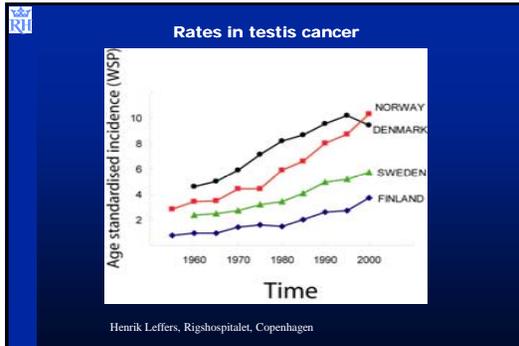
"Every man sitting in this room today is half the man his grandfather was, and the question is, are our children going to be half the men we are?"

[Lou Guillette to the U.S. Congress](#)

Sperm density decline



Swan et al EHP 1997



Atrazine

Most commonly used herbicide in the US

Most frequently detected pesticide in surface water

2nd most commonly detected pesticide in drinking water

Occupational risk to applicators & families

- Previously Observed Effects**
- Toxicological Studies**
- ◆ Altered Estrus Cycle (rats)
 - ◆ Delayed Puberty (rats)
 - ◆ Breast Tumors (rats)
 - ◆ Gonadal Dysgenesis (tadpoles)
 - ◆ Hermaphroditism (frogs)
 - ◆ Decreased Sperm Counts (fish, rodents)
 - ◆ Pregnancy Loss (rabbits)
 - ◆ Prostate Inflammation (rats)
 - ◆ Immune System Impairment (rats, mice, & amphibians)
 - ◆ Erratic Swimming (fish, salamanders)

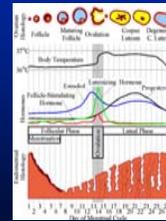
Toxicological Findings –Atrazine *Hayes et al 2002*

- ◆ Induced hermaphroditic deformities
- ◆ Demasculinized larynges in male frogs
- ◆ Decreased testosterone 10 fold



Pesticide Exposure and Menstrual Cycle Characteristics

- ◆ Mean cycle length was approx 4 days shorter at the highest quartile concentration of DDT and DDE when compared with the lowest quartile. (Windham et al. 2005)
- ◆ Women who used probable hormonally active pesticides had a 60-170% increased odds of experiencing long cycles, missed periods and inter-menstrual bleeding. (Farr et al 2004)



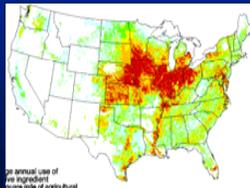
Menstrual Cycle Characteristics in Women Exposed to Atrazine in Drinking Water



Atrazine in Drinking Water and Menstrual Cycle Activity

ATZ exposure associated with changes in reproductive hormone levels

- Reduced estrogen
- Reduced progesterone
- Reduced LH (pre-ovulatory and surge)



Cragin et al., 2010

ATZ exposure associated with abnormal menstrual cycles

- Irregularity
- Increased Follicular Phase Length
- Increased Cycle Length > 6 weeks

Emerging Contaminants of Concern

- Persistent Organic Pollutants (POPs)
- Many have endocrine disrupting properties
- Traditional POPs include DDT and PCBs
- Emerging POPs
 - Phthalates (plastics, personal care products)
 - Bisphenol A
 - Polyfluorinated compounds e.g. PFOS (non-stick, non-stain products)
 - Polybrominated Diphenyl Esters (flame retardants)



PHTHALATES – EXPOSURES

- Phthalates are 'plasticizers' widely used to soften plastics such as PVC for flexibility, including children's toys. They are also used to hold color and scent in consumer and personal care products and in multiple household products.
- Di(2-ethylhexyl) phthalate (DEHP), one of the more commonly used phthalates, leaches from blood products, intravenous and dialysate bags, and tubing made with polyvinyl chloride.
- Phthalates are also present in drinking water, air, and food
- Despite rapid metabolism and elimination of most phthalates, chronic repetitive, low-level exposures from ingestion, inhalation and dermal absorption creates chronic exposure.
- Widespread exposure in NHANES sera

BISPHENOL A HEALTH EFFECTS

- Endocrinologically active as a xeno-estrogen
- Very limited human studies.
- NTP report describes 'some concern' for developmental toxicity for fetuses infants and children (2008).
 - Effects on brain, behavior and prostate gland.
 - Negligible concern for reproductive toxicity for adult men and women.
- Evidence of human health effects is inconclusive but plausible based on animal data.



PERFLUORINATED COMPOUNDS

- Grease-resistant food packaging and paper products, such as microwave popcorn bags and pizza boxes, contain PFCs.
- Perfluorooctane sulfonate (PFOS) was used until 2002 in the manufacture of 3M's Scotchgard treatment, used on carpet, furniture, and clothing.
- PFOA is used to make DuPont's Teflon product, famous for its use in non-stick cookware. If Teflon-coated pans are overheated, PFOA is released.
- PFCs are in cleaning and personal-care products like shampoo, dental floss, and denture cleaners.
- Gore-Tex clothing, known for its ability to shed water, contains PFCs.

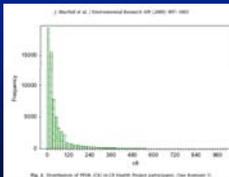


PERFLUORINATED COMPOUNDS

- Ubiquitous human exposures.
- PFOA's half-life is estimated at more than 4 years. PFOS's half-life is estimated at more than 8 years.
- PFOA is a probable human carcinogen (EPA); it causes liver, pancreatic, testicular, and mammary gland tumors in laboratory animals. PFOS causes liver and thyroid cancer in rats.
- PFCs cause liver and kidney damage, as well as reproductive problems in laboratory animals.
- Developmental delays in growth and maturation have been seen in the offspring of PFC exposed pregnant rats and mice.
- Studies by 3M of workers exposed to PFCs during manufacturing show no apparent impact on their health.
- A study of 70,000 people exposed to PFOA in drinking water in Ohio and West Virginia is underway.

PERFLUOROCTANOIC ACID IN WATER

- Increased diabetes mortality has been reported in workers exposed to perfluorooctanoic acid (PFOA)
- A study of 70,000 people exposed to PFOA 80x in drinking water in Ohio and West Virginia is underway.
- Recent paper reports no increase in diabetes or fasting blood glucose in 13,922 WV residents.
- No effect on birth weight or gestational age in OH residents



MacNeil et al., Env. Res. 2009; Nolan et al., Reprod. Toxicol. 2009

PolyBrominated Diphenyl Ethers PBDEs

- Structurally similar to PCBs (polychlorinated biphenyls)
- Widespread use as flame retardants
- Used in many consumer products



PBDEs in Consumer Products

Plastics

Computers, televisions, hair dryers, curling irons, copy machines, fax machines, printers, coffee makers, plastic automotive parts, lighting panels, PVC wire and cables, electrical connectors, fuses, housings, boxes and switches, lamp sockets, waste-water pipes, underground junction boxes, circuit boards, smoke detectors

Textiles

Back coatings and impregnation of home and office furniture, industrial drapes, carpets, automotive seating, aircraft and train seating

Polyurethane foam

Home and office furniture (couches and chairs, carpet padding, mattresses and mattress pads) automobile, bus, plane and train seating, sound insulation panels, imitation wood, packaging materials

PBDE Exposure

- PBDEs migrate out of products into the environment – persistent and bioaccumulative pollutants.
- Atmospheric transport – found in arctic sediment, mussels, fish, seals, bears.
- Found in house dust and mother's breast milk
- PBDEs have health effects at low doses
- Banned by the European Union in 2006
- Highest levels world wide found in North America



Health Effects of PBDEs

- Similar to PCBs (Polychlorinated biphenyls) which are known to affect endocrine function, cause delayed neurological development
- Animals studies indicate that PBDEs
 - Affect thyroid hormone levels
 - Neurobehavioral toxicity
 - Affects development - alters behavior
 - Impairs memory and learning
 - Delay sexual development

Human PBDE levels over time

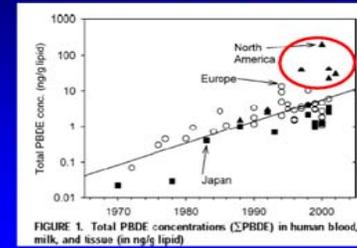
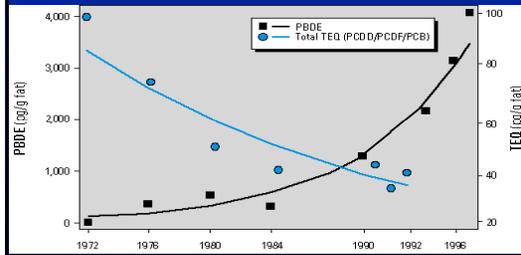


FIGURE 1. Total PBDE concentrations (ΣPBDE) in human blood, milk, and tissue (in ng/g lipid)

Hites 2004

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PBDEs Breast Milk - Sweden



(Nords and Morsmard, 1995)

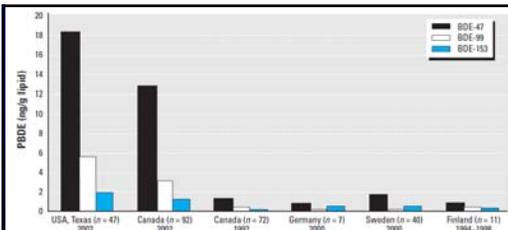
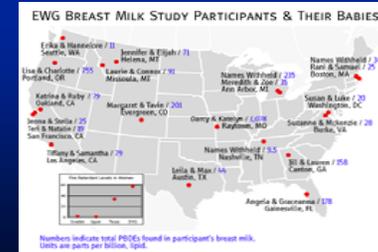


Figure 3. Median concentrations (ng/g lipid) of BDE-47, BDE-99, and BDE-153 in human milk from different countries. Data from Ryan et al. (2002) and Ryan and Patry (2001) for Canada, from Schroeter-Kermani et al (2000) for Germany, from Noren and Menonye (2000) for Sweden, and from Strandman et al. (2000) for Finland.

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Schechter et al.

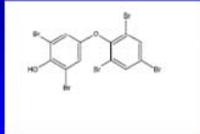
PBDEs in Breast Milk (ppb)



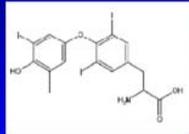
Numbers indicate total PBDEs found in participant's breast milk. Units are parts per billion, ppb.

From EWG - Toxic Fine Residues in Breast Milk from American Mothers - <http://www.ewg.com/toxic/breastmilk/us.php>

PBDE metabolites resemble thyroid hormone (T4)



An OH-BDE



Thyroid hormone (T4)

Thyroid hormones (THs) are critical for fetal brain development

- <20 wks, fetus receives all TH across the placenta
- Small changes in THs during fetal life can affect brain development
- Need to study TH disruption in early pregnancy



Adapted from: www.robysnest.com/images/placenta.jpg

Thyroid Hormones play critical roles in health

- Metabolism and body temperature regulation
- Normal growth and development
- Brain development
- Cardiovascular system
- Hearing
- Skeletal growth
- Hair and skin

7 months
T₄ treatment



Boy with Hashimoto's disease

Slide from Dr Caren Helbing (University of Victoria)

Public health implications of thyroid disruption

Many conditions are *hypothesized* to be linked to thyroid disruption *in utero*

- ADHD
- Autism
- Poor motor skills
- Learning disorders
- Reduced IQ, reading ability, language development

Soldin 2003, Haddow 1999

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Human Health Effects of PBDEs

- Limited human data
 - In 405 male sport fish consumers from the Great Lakes
 - PBDEs related to T4, thyroglobulin antibodies; inversely related to T3, TSH (Turyk et al., EHP 2009)
 - No evidence of thyroid disease in this cohort associated with PDBE exposures

How to reduce toxin exposures in the home

- Avoid foam-containing furniture & baby products meeting the "California Furniture Flammability standard TB117"
- Consider non-foam mattresses & furniture (natural latex, wool)
- Reduce exposure to indoor dust
- Open your windows (home & car), spend time outside
- Wash hands before eating
- Eat low on the food chain
- Switch to non-toxic cleaning products
- No plastic in the microwave or dishwasher
- Choose non-plastic containers to store fatty foods
- Avoid micro-waved popcorn & fast food wrappers
- Use BPA-free bottles, sippy cups, water bottles
- Avoid toys containing lead, phthalates, BPA
- Choose non-toxic materials during home renovations