

Endocrine Disruptors and the Reproductive System



Jodi Anne Flaws, Ph.D.
University of Illinois
Department of Comparative Biosciences
jflaws@illinois.edu
333-7933

Overview



- What is an endocrine disruptor?
- Which environmental exposures are associated with reproductive toxicity?
- How do endocrine disruptors cause damage?

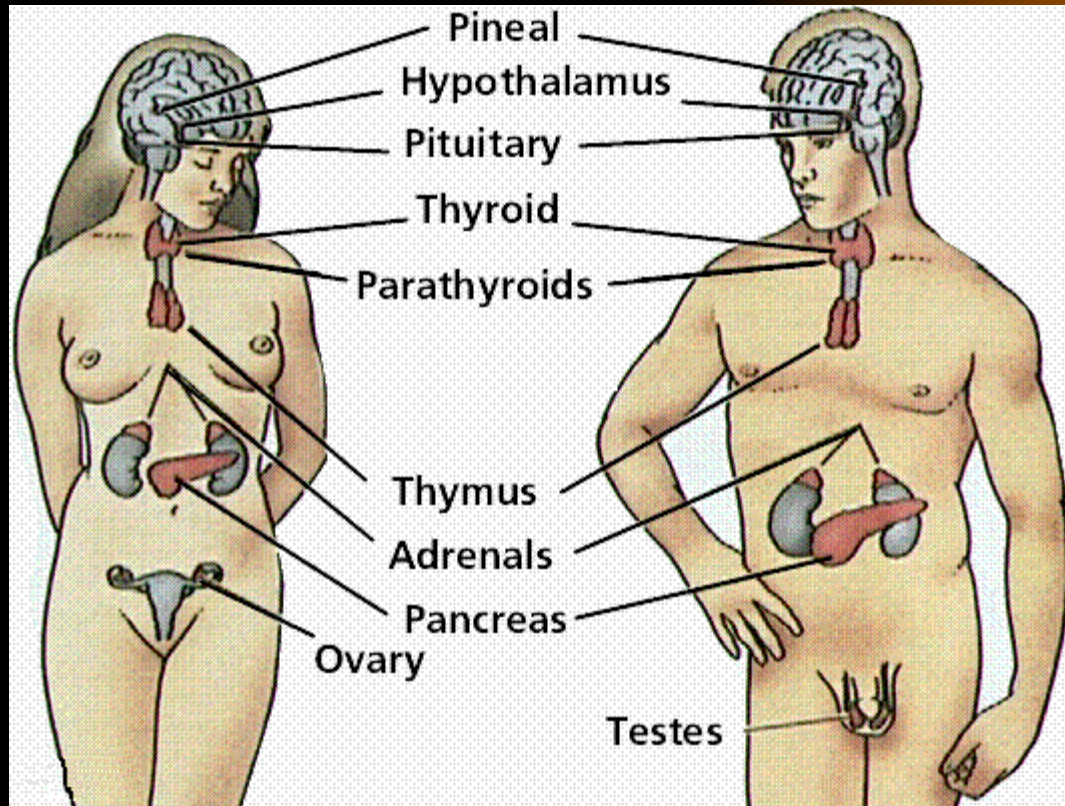
What is an endocrine disruptor?



“Exogenous agent that interferes with the synthesis, storage/release, transport, metabolism, binding, action, or elimination of natural hormones”

Cooper and Kavlock, 1997

Endocrine System



Endocrine Disruptors



- Estrogens
- Androgens
- Anti-estrogens
- Anti-androgens
- Progestogens
- Adrenal toxins
- Thyrotoxic agents
- Aryl hydrocarbons
- Retinoids

Endocrine Disruptors



- Types of endocrine disruptors
 - Pharmaceutical agents
 - diethylstilbestrol, oral contraceptives
 - Pesticides
 - dichloro-diphenyl-trichloroethane (DDT), methoxychlor (MXC)
 - Flame retardants
 - polybrominated diphenyl ethers (PBDEs)
 - Plasticizers
 - phthalates, bisphenol A
 - Heavy metals
 - lead, mercury, arsenic
 - Environmental contaminants
 - dioxins, polychlorinated biphenyls (PCBs)

Pharmaceutical Agents: Diethylstilbestrol (DES)



"Really?"

Yes...
des PLEX
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

recommended for routine pregnancies
in ALL pregnancies . . .

96 per cent live delivery with **des PLEX**
in one series of 1200 patients*—
— bigger and stronger babies, too.†

No gastric or other side effects with **des PLEX**
— in either high or low dosage^{1, 2, 3}

(Each **des PLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating to assure prompt help in emergencies. **des PLEX** tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectiveness of estrogen.)

For further data and a generous
trial supply of **des PLEX**, write to:
Medical Director

REFERENCES

1. Caspell, E. M., et al., *Am. J. Obst. & Gynec.* 45:1294, 1953.
2. Gitman, L., and Koplowitz, A., *N. Y. J. Med.* 50:3213, 1950.
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5. Ross, J. S., *J. Nat. M. A.* 43:50, 1951; 43:252, 1953.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.



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Over 96 per cent live delivery in 1200
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Grant Chemical Co., Inc.
New York 10, N. Y.

REFERENCES

1. Paffen, E. J., *Med. Times* 82:971, 1954; *Am. J. Surg.* 87:91, 1954.
2. Karnaky, K. J., *South. M. J.* 43:1746, 1950.
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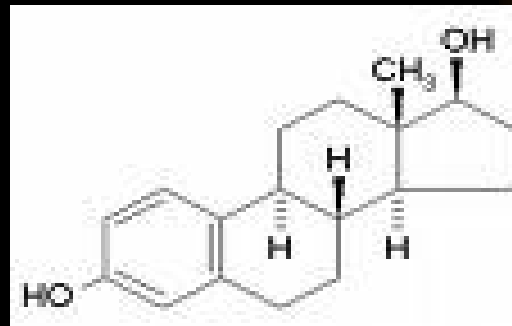
After extensive clinical experience with **des**, Karnaky¹, Gitman and Koplowitz² and Ross³ as well as countless other clinicians wholeheartedly endorse the sound therapeutic necessity for the use of **des** in threatened abortion, habitual abortion and premature labor.

In a most recent publication, Karnaky has demonstrated that **des**, in massive doses (275 milligrams daily) provides optimum therapeutic results with maximum safety.

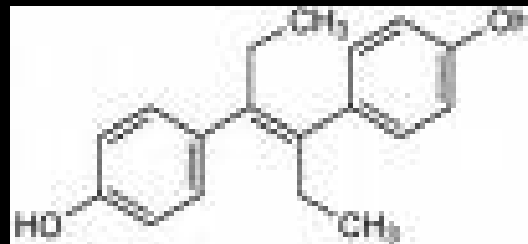
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1. Karnaky, K. J., *Amer. J. Obst. & Gyn.* 53:312, 1947.
2. Gitman, L., and Koplowitz, A., *New York State J. Med.* 50:2823, 1950.
3. Ross, J. S., *N. Nat. M.A.* 43:20, 1951.

DES versus Estradiol



Estradiol



DES

DES Story



- 1966-1969
 - 7 women between 15-22 developed clear cell adenocarcinoma of the vagina
- 1969-current
 - Serious adverse outcomes in male and female children of DES-exposed mothers
 - DES use limited; not manufactured in US

DES Events

- Females

- Abnormalities of the reproductive tract
 - Uterus, Fallopian tubes
- Infertility
- Preterm labor
- Fibroids
- Cancer
 - Vagina, Breast
- DES granddaughters

- Males

- Cryptorchidism
- Abnormal semen
- Reduced fertility
- Testicular cancer
- Hypospadias

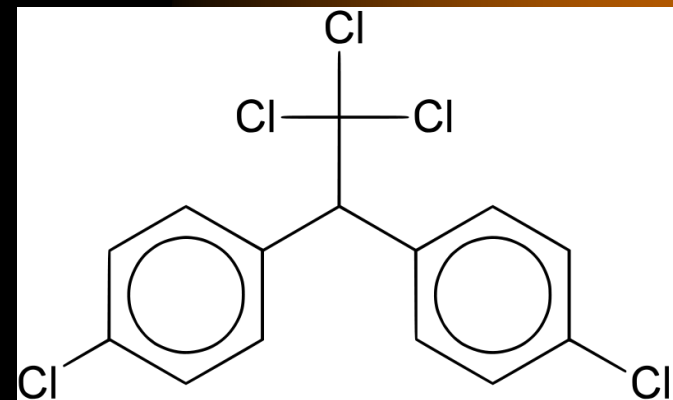


What did we learn from the DES story?

- Placenta does not always protect the fetus
 - We must use care with drugs given to pregnant women
- Not all estrogens are good for all tissues, species
- Chemicals can have delayed, long-lasting effects
- Chemicals can have transgenerational effects
- Nothing? A lot?
 - DES being used a prostate and breast cancer treatment in some countries
 - DES being used to treat dogs and cats with urinary incontinence

Pesticides

- Pesticides
 - Banned
 - Dichloro-diphenyl-trichloroethane (DDT)
 - Kepone
 - Hexachlorocyclohexane
 - Current
 - Atrazine
 - Endosulfan
 - Lindane
 - Methoxychlor



DDT

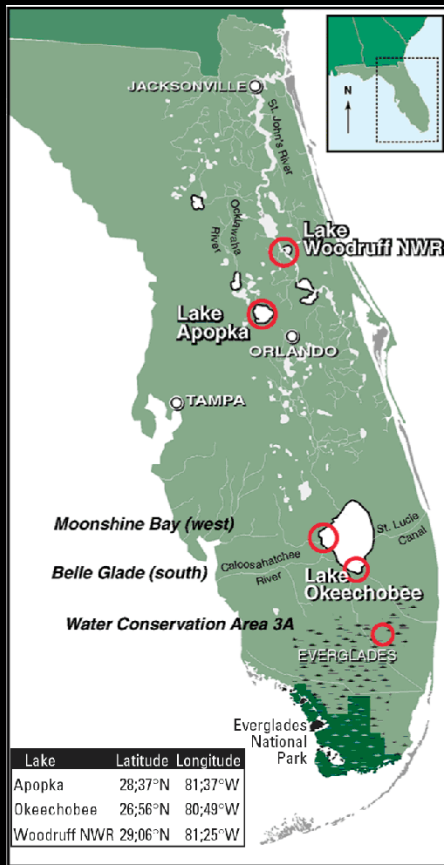


Pesticides



- Used on crops, lawns, gardens, homes, and pets
- Contaminate food and water
- Known reproductive toxicants in wildlife and humans
 - eggshell thinning in birds (DDT)
 - abnormal reproductive organs in alligators (DDE)
 - masculinization of rodents (kepone, DDT, methoxychlor)
 - spontaneous abortion in women
 - endometriosis in women
 - low conception rates in women
 - infertility in men and women
 - altered sex ratio in humans and fish (more females)

Lake Apopka Disaster

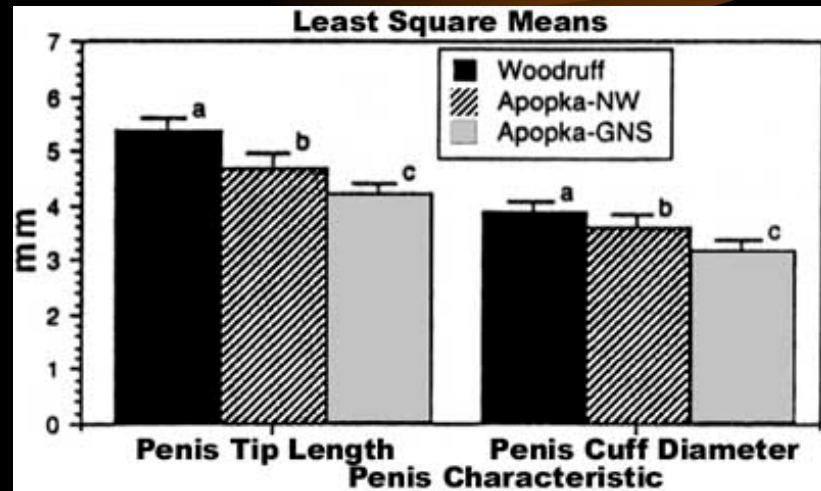
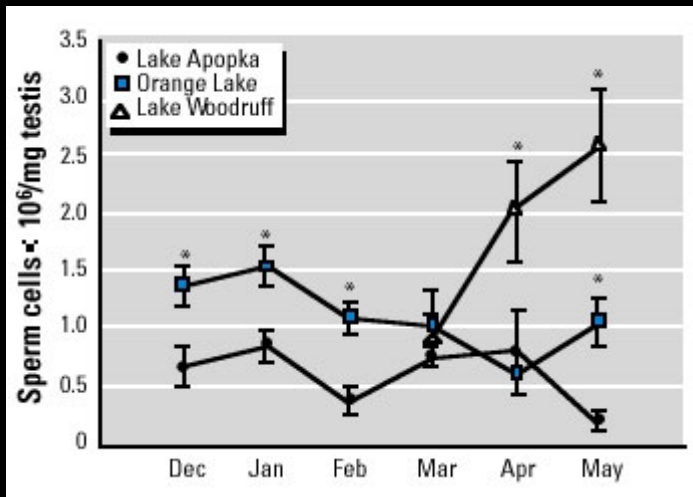


(CNN)

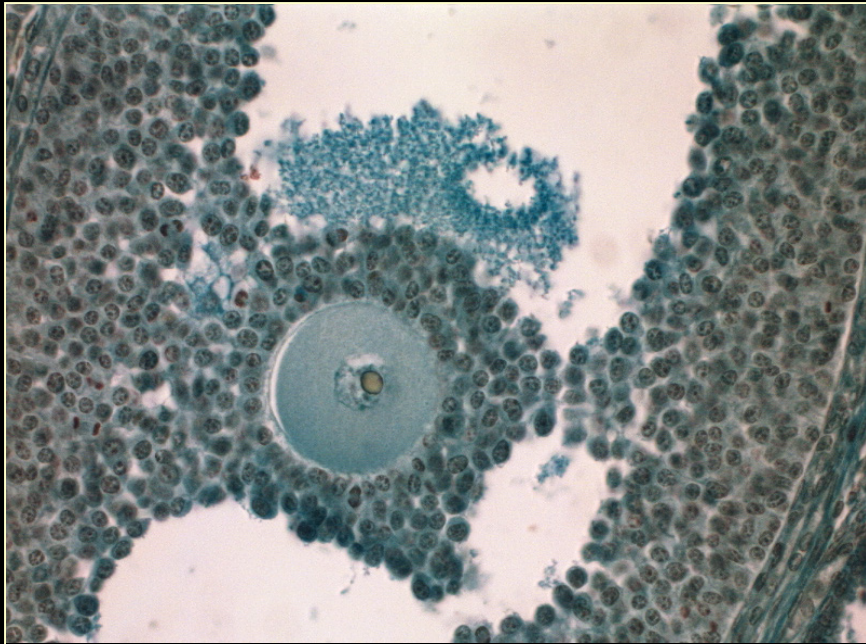


(CNN)

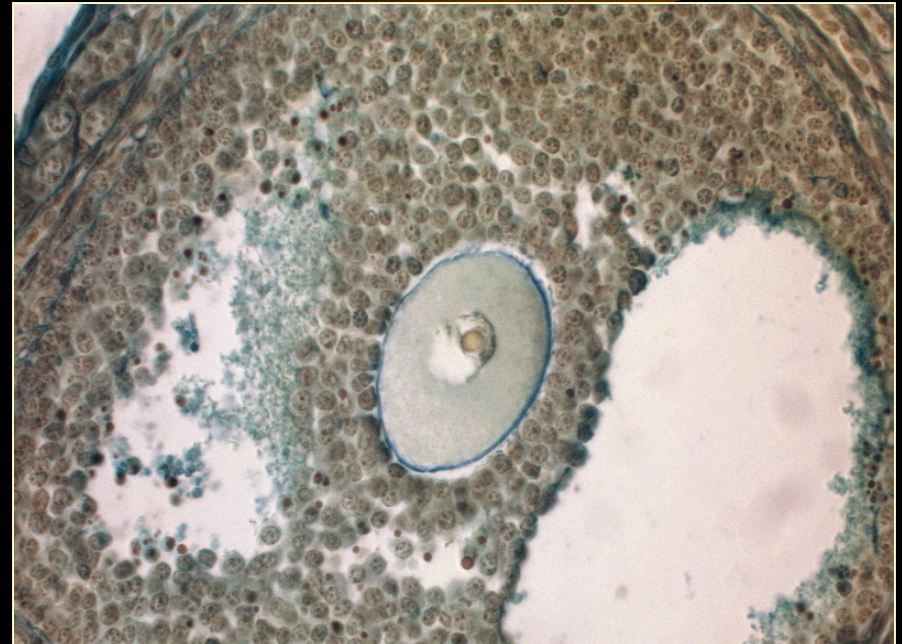
Lake Apopka Disaster



Methoxychlor

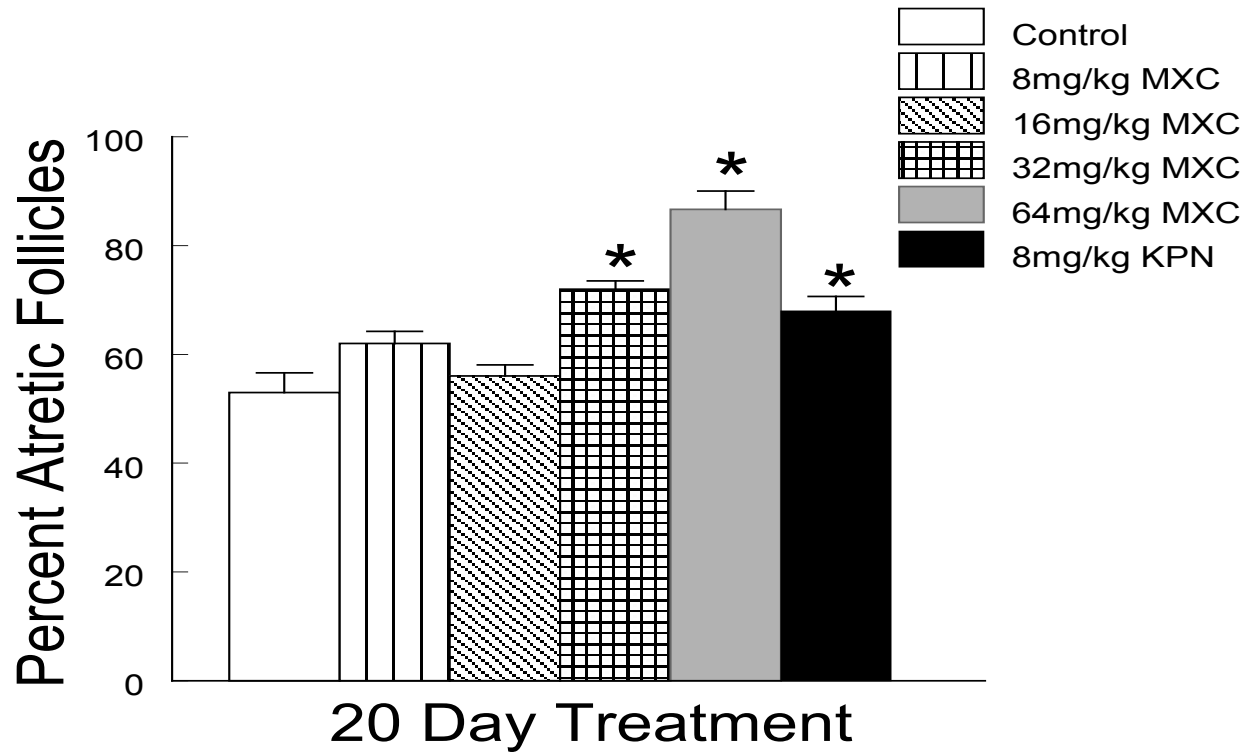


Sesame Control

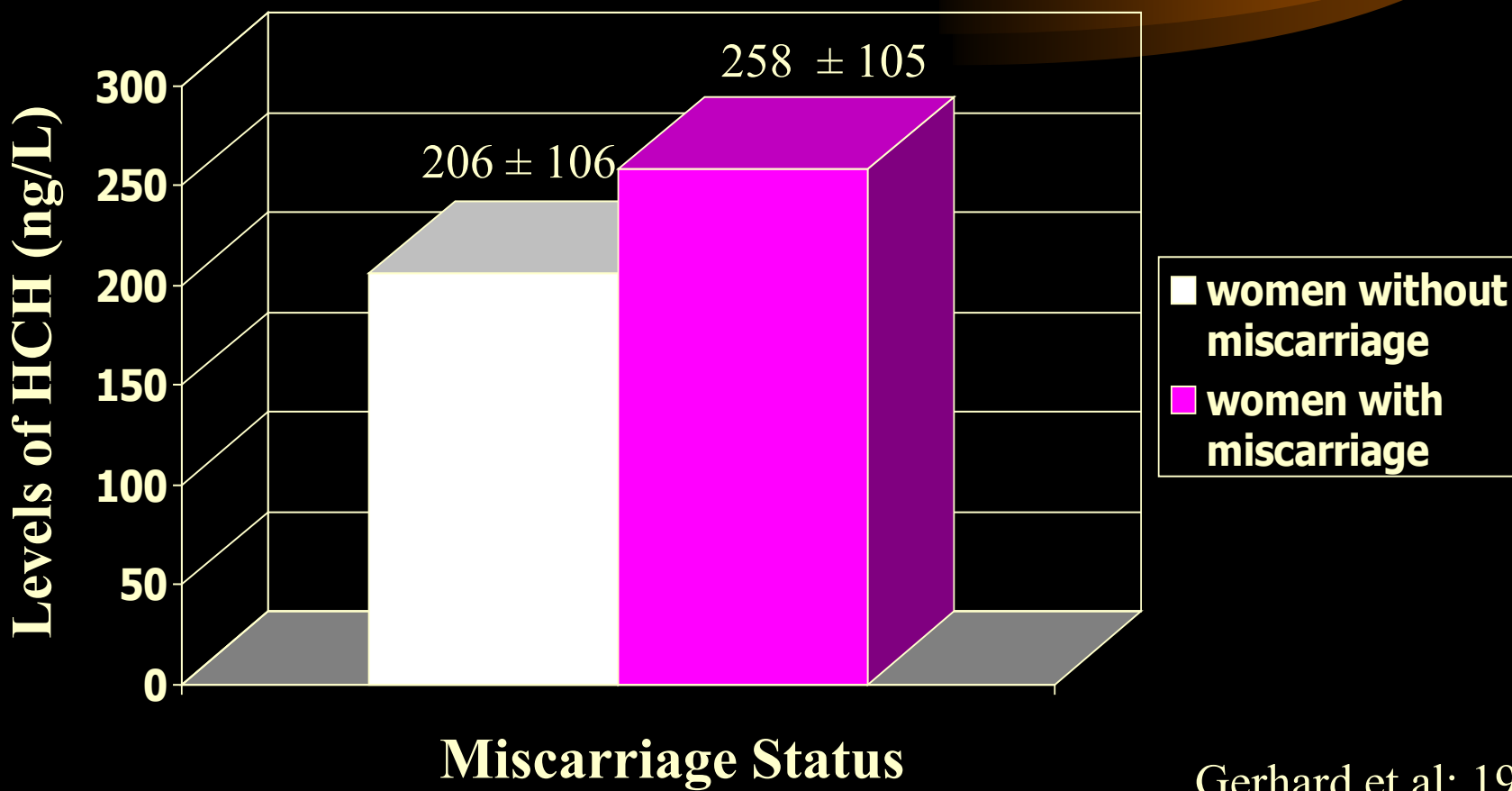


MXC (64 mg/kg/day)

Methoxychlor

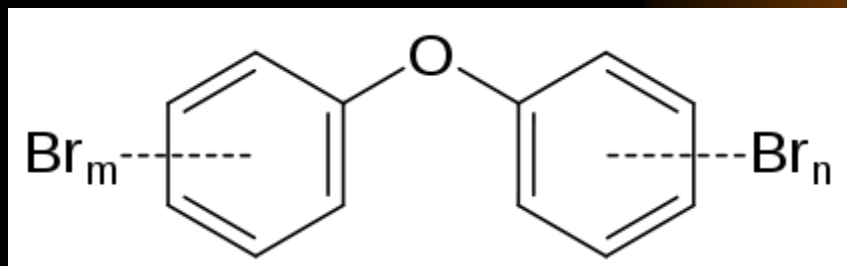


Hexachlorocyclohexane (HCH) and Miscarriage



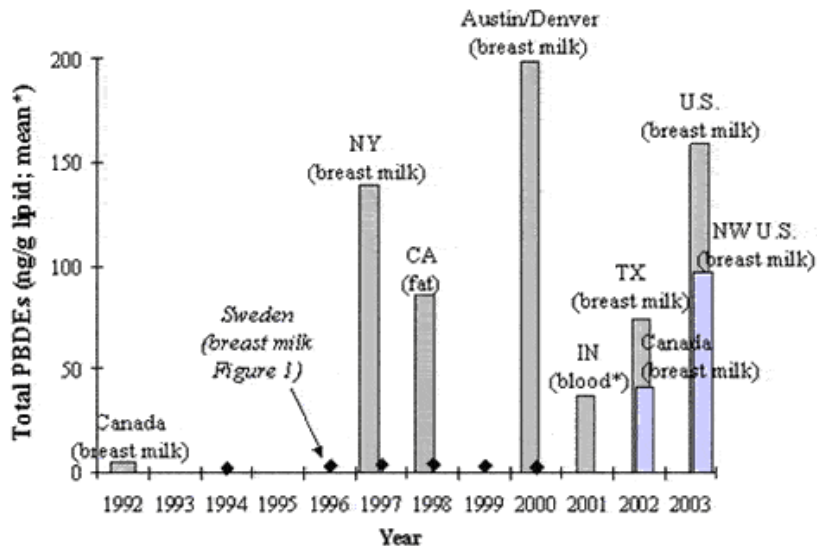
Gerhard et al; 1999

Flame Retardants



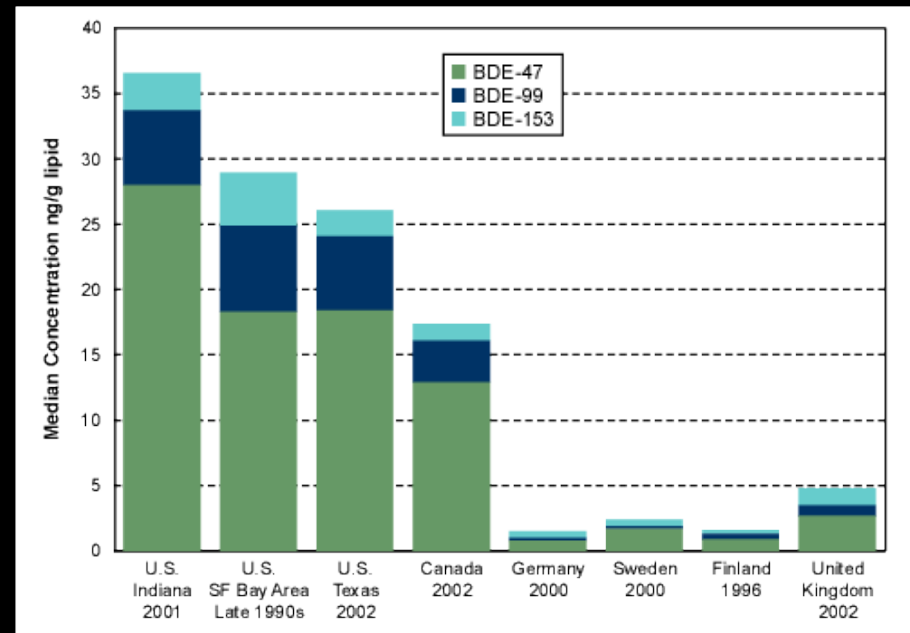
Flame Retardants

PBDE levels in human tissues from Sweden, Canada and the U.S., 1992-2003



Sources: Data from Noren and Meironyte, 2000; Meironyte, 2002; Sjodin et al., 2003; Mazdai et al., 2003 (median value*); Schecter et al., 2003; She et al., 2002; EWG, 2004; and Northwest Environment Watch, 2004.

PBDEs Breast Milk and Fat Samples Around the World



Source: Figure 3 in Schecter et al (EHP, August 2003), Table 1 in Mazdai et al (EHP, July 2003), and Table 1 in Kalantzi et al (EHP, July 2004)

Flame Retardants

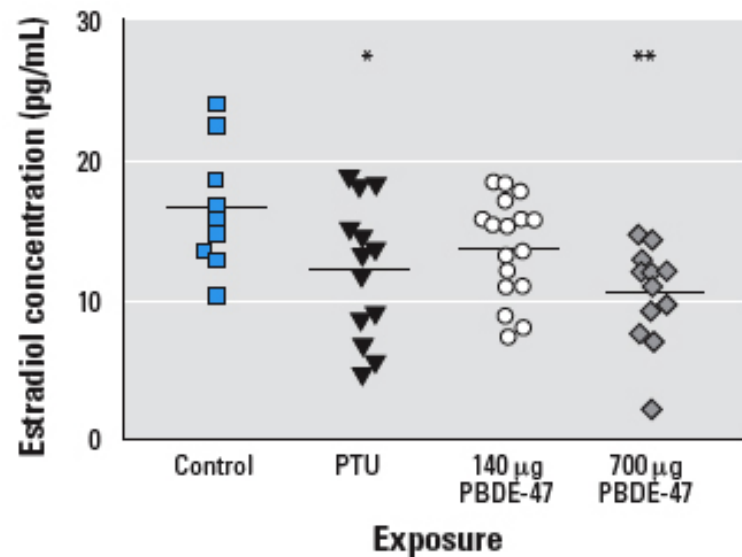


Figure 1. Individual serum estradiol concentrations (bars indicate means) of F₁ female offspring on PND38 after treatment with vehicle or PBDE-47 (140 or 700 µg/kg bw) to F₀ dams on GD6. PTU was administered on GD7–PND21.

* $p < 0.05$, and ** $p < 0.01$.

Flame Retardants

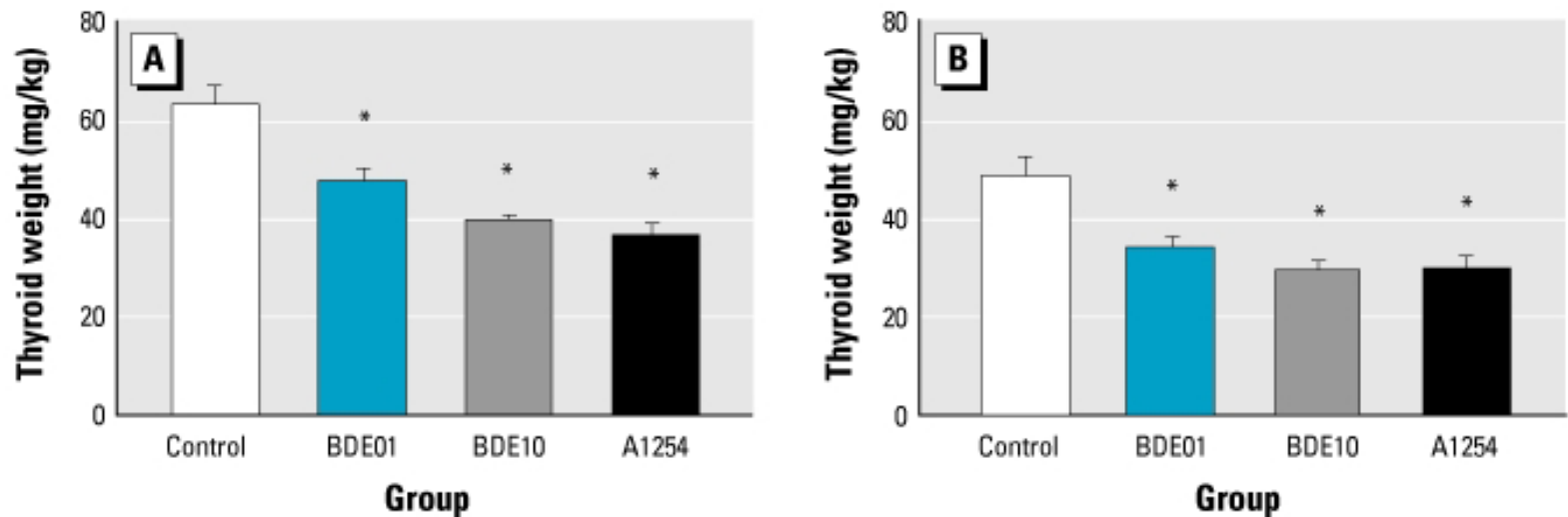
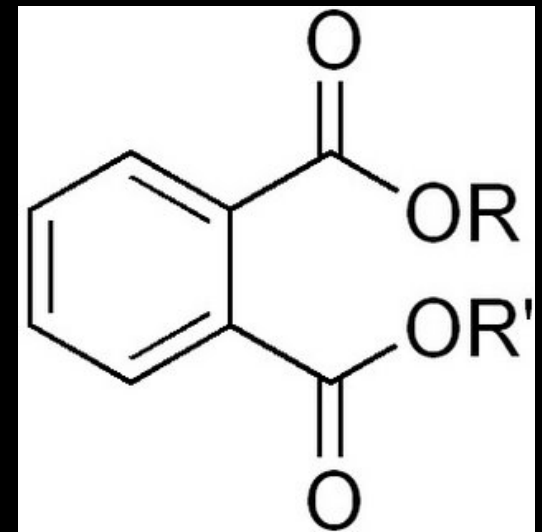


Figure 1. Thyroid weights in male (A) and female (B) adult offspring after exposure to low and high doses of PBDE-99 or A1254. Data shown are mean \pm SE ($n = 8$ /group).

* $p < 0.05$ compared with control.

Plasticizers-Phthalates



Phthalates



- More than 18 billion pounds of phthalates are produced worldwide each year
- One of the top three contaminants present in human tissue (CDC report, 2005)
- Little to nothing is known about the health risks from everyday, environmental exposure

Phthalate Effects

- Have both anti-androgenic and estrogenic effects on development and sexual differentiation of the brain
- Chronic exposure in humans is associated with:
 - Decreased pregnancy rates
 - High rates of miscarriage
 - Pregnancy complications
 - Anemia
 - Toxemia
 - Preeclampsia
- Animal studies have shown that exposure inhibits ovarian and testicular synthesis of steroid hormones required for fertility

Prenatal Exposure to Phthalates

- Maternal exposure to phthalates results in a number of abnormalities of the male reproductive system
 - Reduced anogenital distance
 - Retained nipples
 - Undescended testes
 - Impaired reproductive behavior

Phthalates

Table 2. Median concentration [range ($\mu\text{g/L}$)] of six phthalate monoesters in human breast milk samples 1997–2001, collected as additive aliquots from 1 to 3 months postnatally.

Phthalate	Denmark (<i>n</i> = 65)	Finland (<i>n</i> = 65)	<i>p</i> -Value	LOD ($\mu\text{g/L}$)	Detection rate (%)
mMP	0.10 (< 0.01–5.53)	0.09 (< 0.01–0.37)	0.355	0.01	95
mEP	0.93 (0.07–33.6)	0.97 (0.25–41.4)	0.976	0.01	100
mBP	4.3 (0.6–10,900)	12 (2.4–123)	0.0001	0.05	100
mBzP	0.9 (0.2–14)	1.3 (0.4–26)	0.0001	0.05	100
mEHP	9.5 (1.5–191)	13 (4.0–1,410)	0.001	0.10	100
miNP	101 (27–469)	89 (28–230)	0.056	0.50	100

Country differences were tested by Mann-Whitney *U*-test.

Phthalates

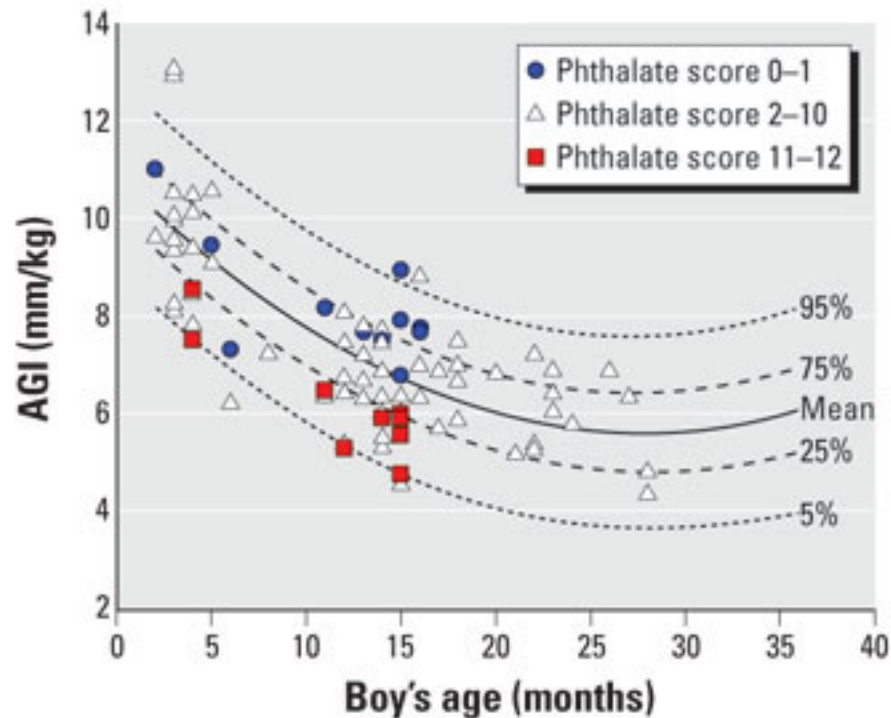
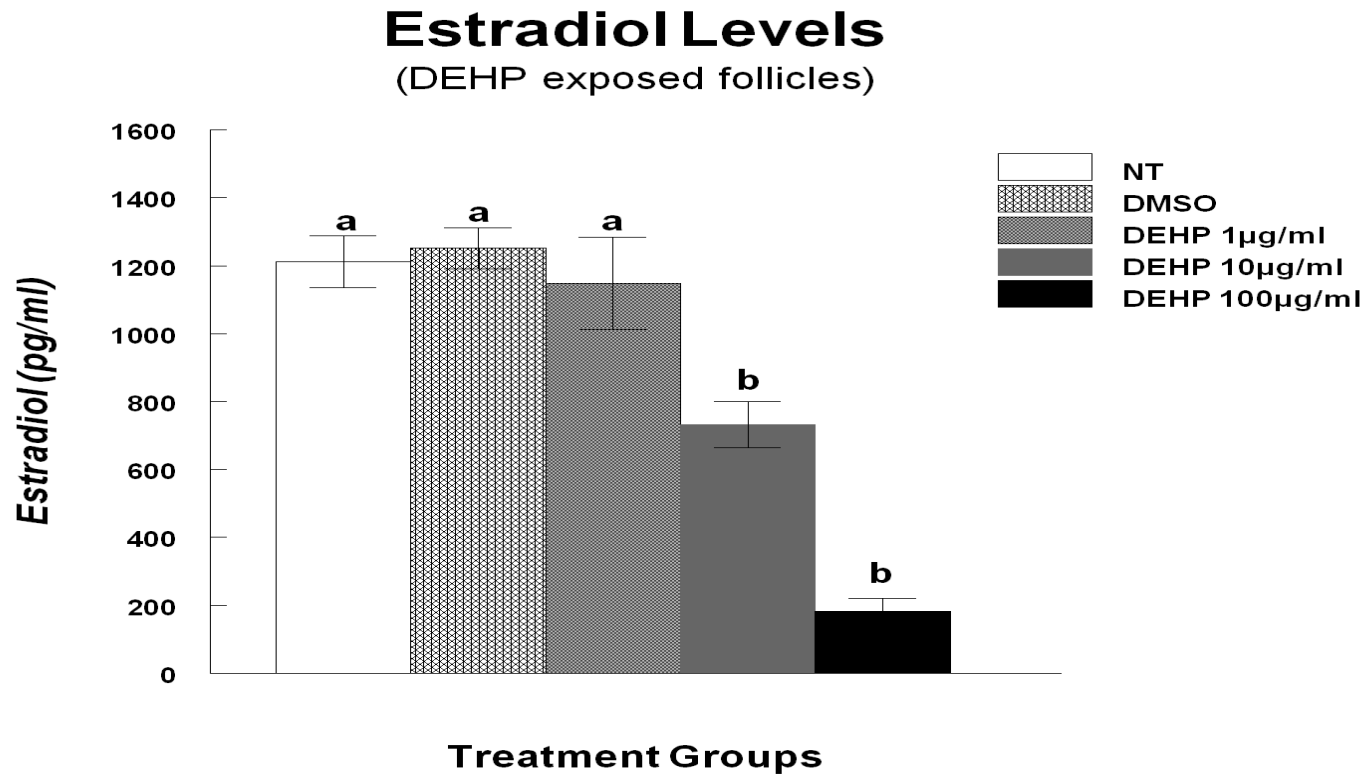


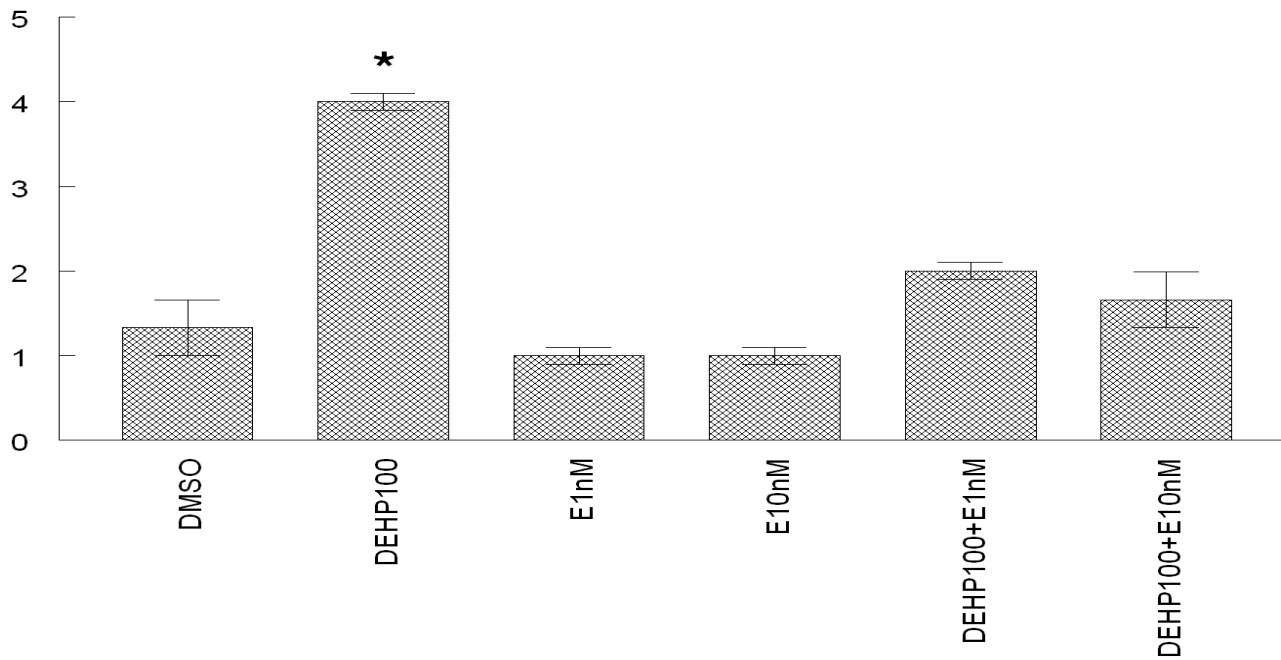
Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

Phthalates

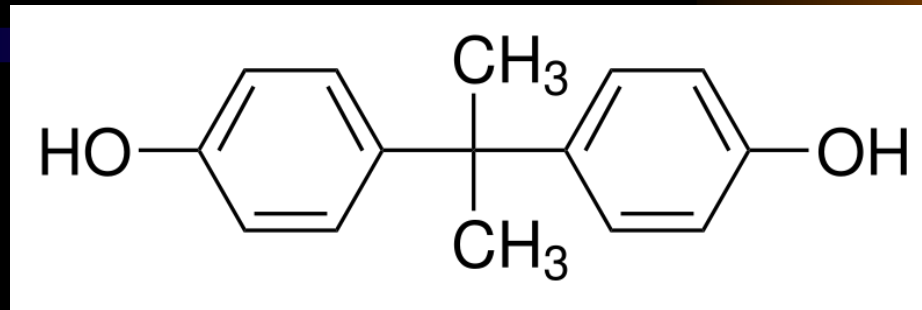


Phthalates

Atresia rating
(DEHP)



Bisphenol A (BPA)



- BPA was originally synthesized in 1891 and intended for use as a chemical estrogen to help prevent miscarriage
- Diethylstilbestrol (DES) was a more potent estrogen and used instead of BPA
- BPA was then employed by plastics manufacturers, and remains so today

BPA is Everywhere



Plastics is the country's third-largest manufacturing industry, producing nearly \$379 billion worth of goods each year (Society for the Plastics Industry).

BPA



- BPA is released from polycarbonate plastics and resins by:
 - Exposure to light
 - Heating
 - Aging
 - Coming into contact with acids and bases in cleaning products

BPA



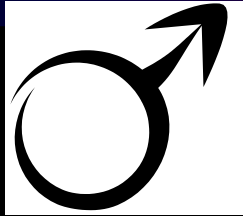
- BPA is found in 95% of human urine samples
 - it is rapidly metabolized and excreted
- BPA has been detected in ovarian follicular fluid, suggesting the follicle may be a source of BPA exposure for the early fetus
- BPA is able to rapidly cross the placenta and enter fetal organs in rats

Effects of BPA



- BPA is an endocrine disrupting chemical:
 - Anti-androgenic effects
 - Antagonistic effects on thyroid hormone receptor
 - Agonist and antagonistic effects on estrogen receptors
 - Effects depend on the receptor subtype and cell type

Gender Specific Effects of BPA



- Reduced sperm production
- Altered prostate development
- Increased susceptibility to prostate cancer



- Altered mammary glands
- Decreased fertility
- Chromosomally abnormal oocytes

Prenatal Exposure to BPA in Rodents

- BPA causes long-term adverse effects
 - Multiple cystic follicles in the ovary
 - Altered cyclicity
 - Impaired ovulation in adult life
 - Altered sexual differentiation of reproductive tissues
 - Early puberty onset
 - Weight gain
 - Decreased anogenital distance
 - Premature breast development

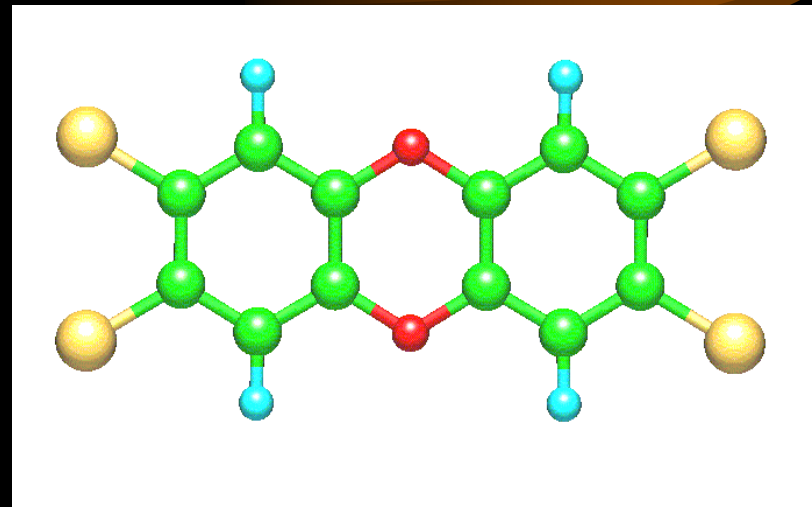
BPA



- BPA not banned in the US, but bans are being proposed
- FDA has approved BPA as a food additive, but this has been extensively criticized
- Marketing for baby bottles has been changed
 - BPA free or glass bottles

Environmental Contaminants

- Dioxins (TCDD)
 - paper bleaching
 - pesticide manufacturing



Dioxins



- Humans

- reproduction

- possible birth defects
- change in sex ratio (more females than males)
- endometriosis

- other

- chloracne

- Animal models

- reproduction

- malformations
- decreased sperm count
- delayed puberty
- endometriosis

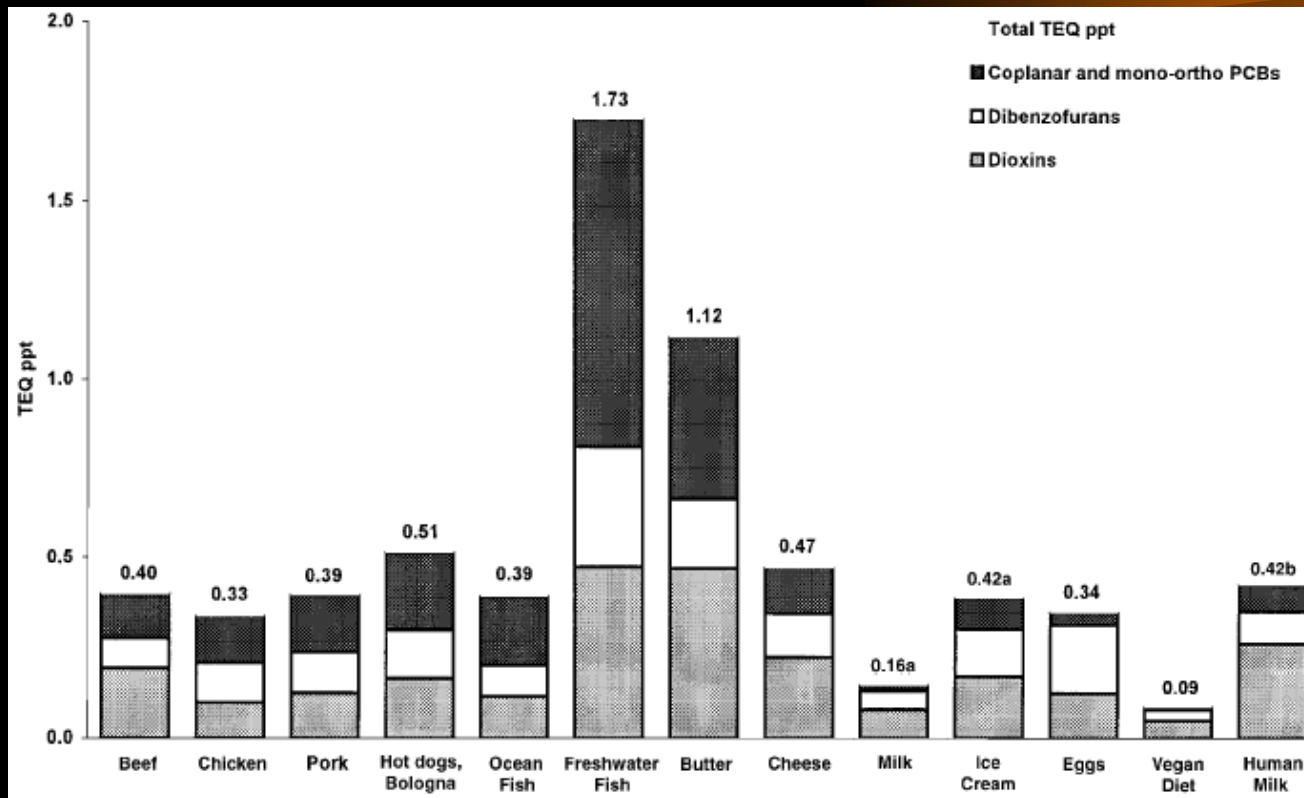
- behavior

- demasculinized sexual behaviors
- decreased reflexes
- increased locomotor activity

- other

- wasting syndrome

Dioxins



Dioxins



BEFORE



AFTER

Yushchenko endured dioxin poisoning, likely by political foes, which, along with nearly killing him, left his skin severely disfigured.

WILLisms.com



TCDD and Sex Ratio

Father's concentrations of TCDD (ppt)	Mother's concentrations of TCDD (ppt)	Number of children		Total children	Sex ratio (95% CI)
		Male	Female		
Unexposed*	Unexposed*	31	20	51	0.608 (0.47–0.74)
>15	>15	96	121	217	0.442† (0.38–0.51)
>15	Unexposed*	81	105	186	0.436† (0.36–0.51)
Unexposed*	>15	120	100	220	0.545 (0.48–0.61)
Total		328	346	674	0.487

*People living outside A, B, and R zones on July 10, 1976, and people living in these zones with serum TCDD concentrations less than or equal to 15 ppt. †Different from expected sex-ratio value of 0.514 at $p=0.03$.

Environmental Contaminants

- Polychlorinated biphenyls (PCBs)
 - banned in 1970s
 - electrical transformers
 - capacitors
 - hydraulic fluids
 - plasticizers
 - adhesives
 - persist in fish



Polychlorinated biphenyls (PCBs)



- Humans

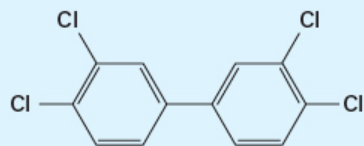
- reproduction
 - intrauterine growth retardation
 - hyperplasia in tissues
 - birth defects
- neurologic, behavior
 - impaired short-term memory
 - delayed psychomotor development
- thyroid
 - altered activity

- Animal models

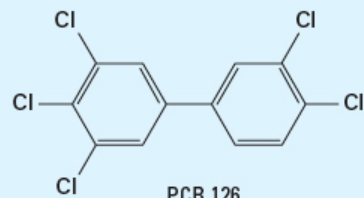
- reproduction
 - small litter size
 - abortions
 - early puberty
- neurologic, behavior
 - altered sex differentiation
 - cognitive deficits
- thyroid
 - altered activity

PCBs

A

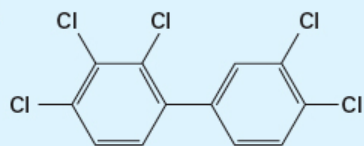


PCB 77

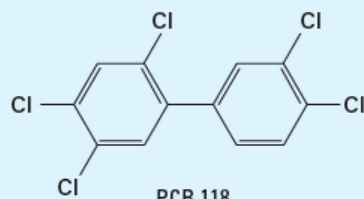


PCB 126

B

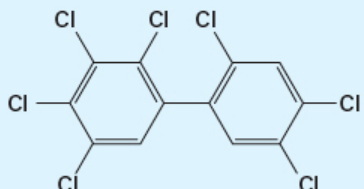
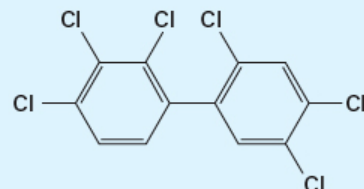


PCB 105

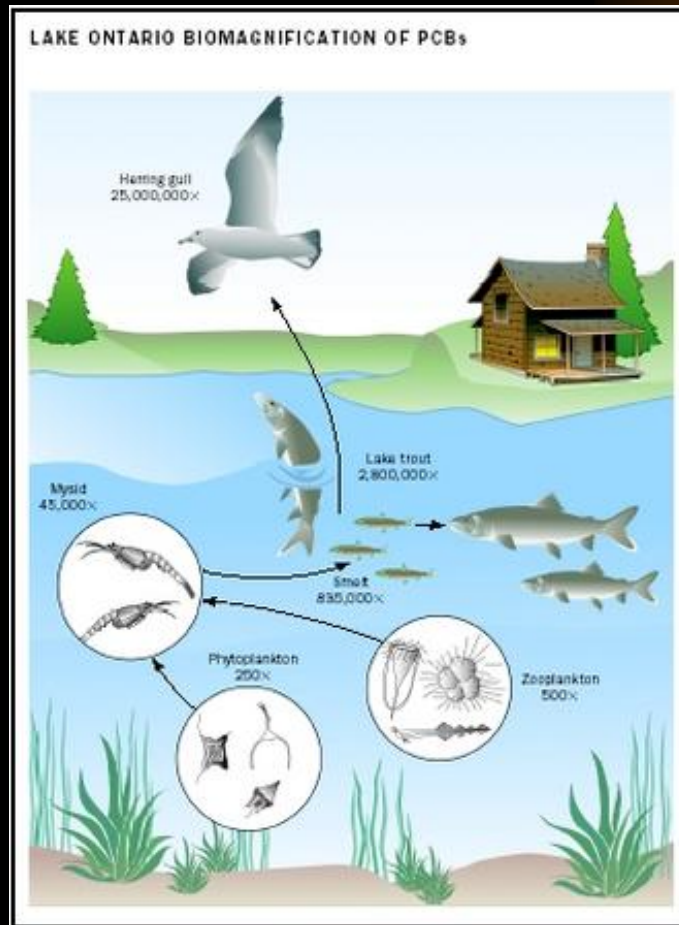


PCB 118

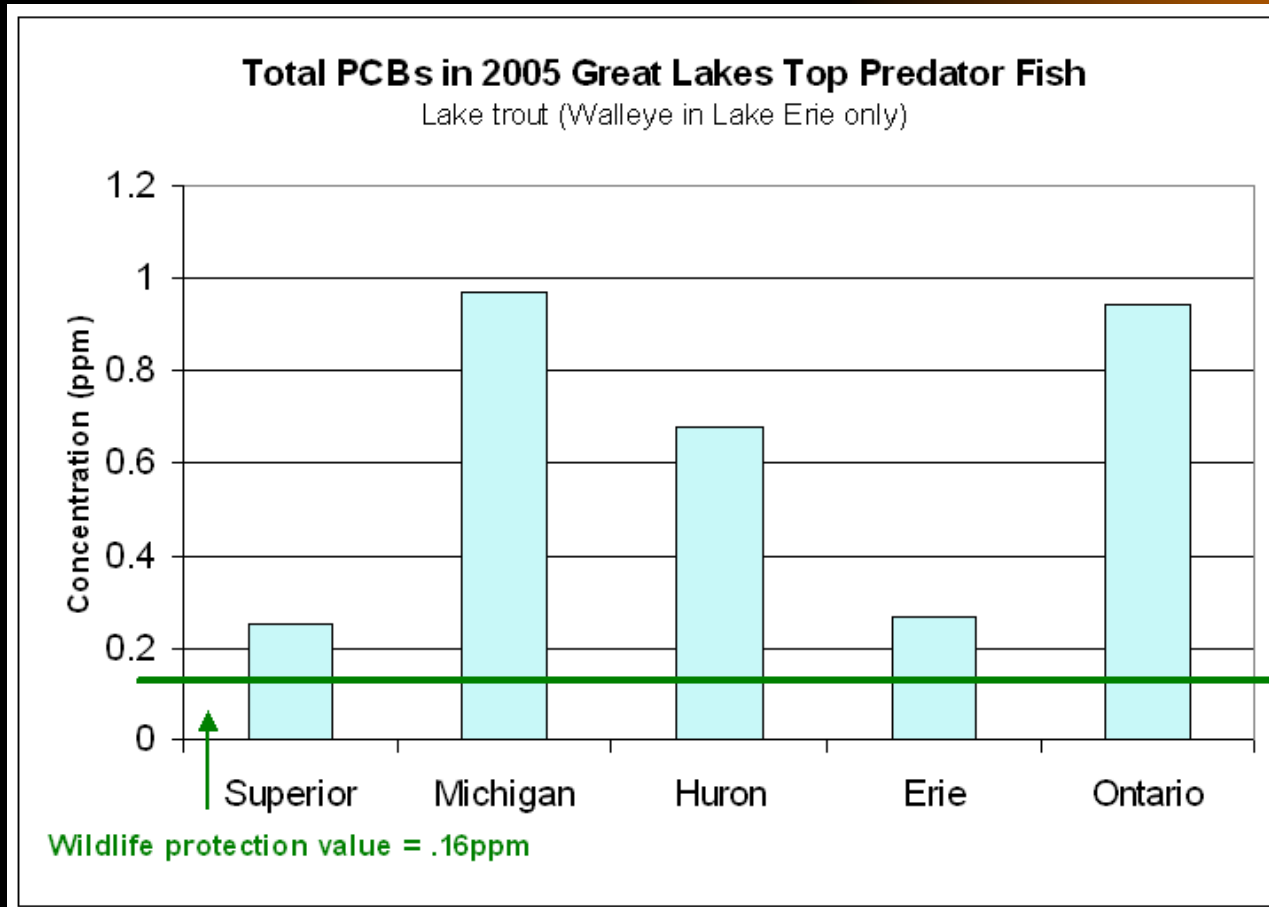
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PCBs

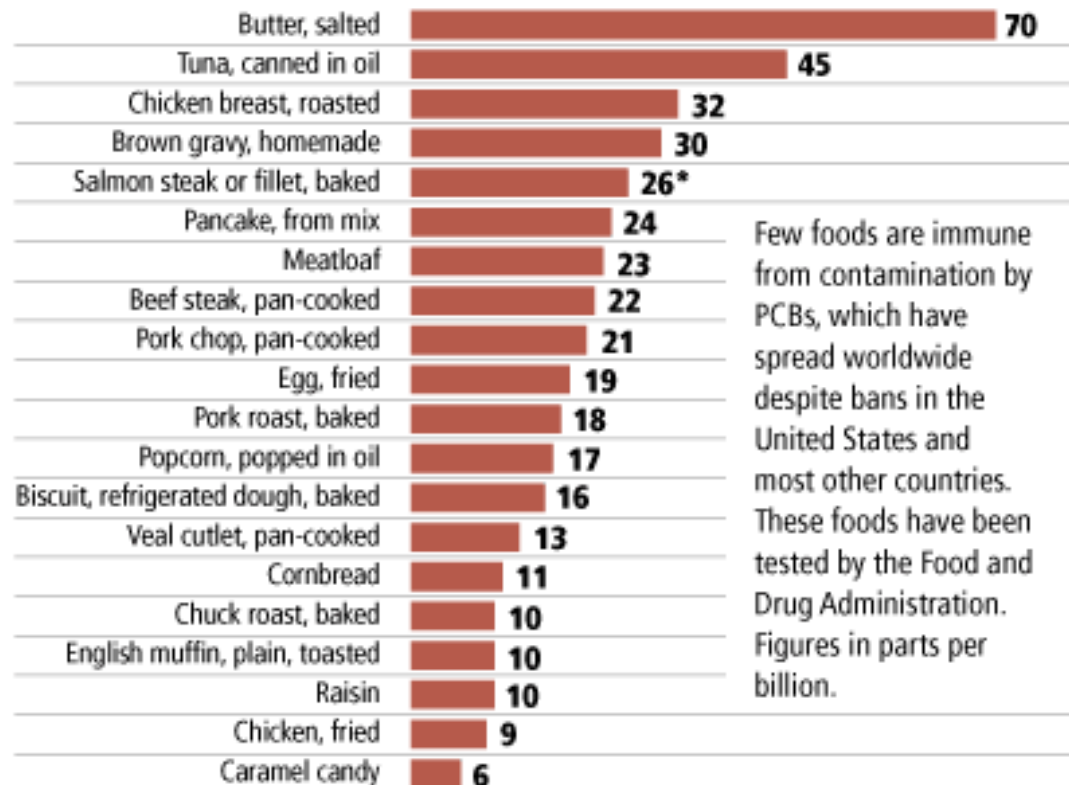


PCBs



PCBs

PCB LEVELS IN OTHER FOODS



Few foods are immune from contamination by PCBs, which have spread worldwide despite bans in the United States and most other countries. These foods have been tested by the Food and Drug Administration. Figures in parts per billion.

*Puget Sound salmon tested higher.
Source: FDA

SEATTLE POST-INTELLIGENCER

PCBs

Table 3. Summary of epidemiologic results on perinatal PCB or dietary fish exposure in relation to neurodevelopmental outcomes.^a

Outcome	Age outcome measured	Location of population studied (reference)	Effect of ↑ PCB intake	Exposure measure used	
				Fish	Measured PCBs
Neonatal reflexes	60 hr	Michigan (119)	Hyporeflexia	✓	
	60 hr	Michigan (119)	None		✓
	72 hr	North Carolina (120)	Hyporeflexia		✓
	14 days	Netherlands (121)	None ^b		✓
	36 hr	New York (122)	Abnormal reflexes	✓	
Neonatal muscle tone	60 hr	Michigan (119)	None	✓	
	72 hr	North Carolina (120)	Hypotonia		✓
	14 days	Netherlands (121)	Hypotonia ^c		✓
	36 hr	New York (122)	None	✓	
Psychomotor development ^d	6 months	North Carolina (123)	Delayed		✓
	36 months	North Carolina (124)	None		✓
	3 months	Netherlands (125)	Delayed		✓
	42 months	Netherlands (126)	None		✓
Mental development	6 months	North Carolina (123)	None		✓
	3 months	Netherlands (125)	None		✓
IQ	11 years	Michigan (127)	Decreased		✓
Visual recognition memory	7 months	Michigan (128)	Decreased		✓
Short-term memory	4 years	Michigan (129)	Decreased		✓
	4 years	North Carolina (130)	None		✓

Abbreviations: IQ, intelligence quotient; PCBs, polychlorinated biphenyls. ^aRepresentative findings are shown from each study; for brevity all results from each study are not included. ^bA relation with "neonatal optimality score," comprising reflex and tone components, was found for breast-fed children with PCBs measured in breast milk. However, with PCBs in cord blood as the exposure measure in the entire study group, including children who were not breast fed, however, a relation was not present. ^cTrue only in breast-fed children, with PCBs measured in breast milk. ^dDutch neurologic exam findings for children (not neonates) are classified with psychomotor development results in this table.

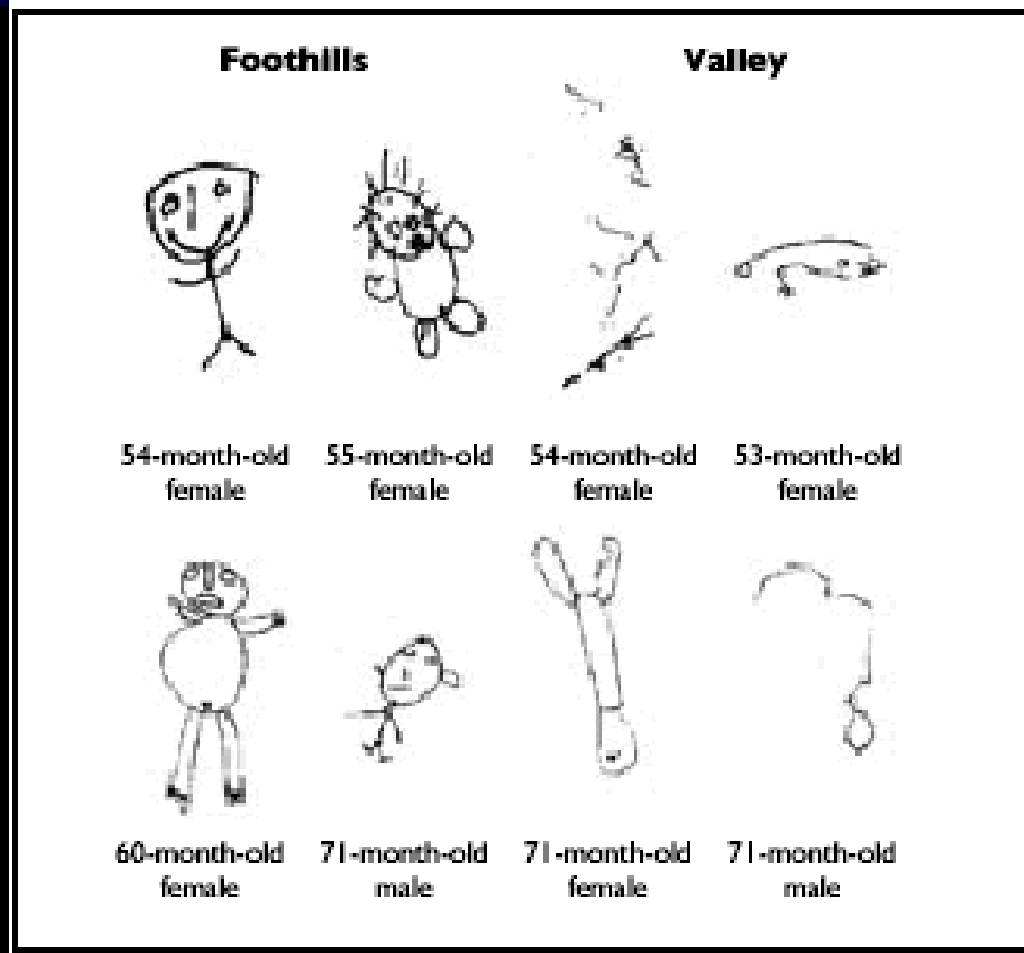
PCBs

Table 3. Neuropsychological outcomes of human PCB studies.^a

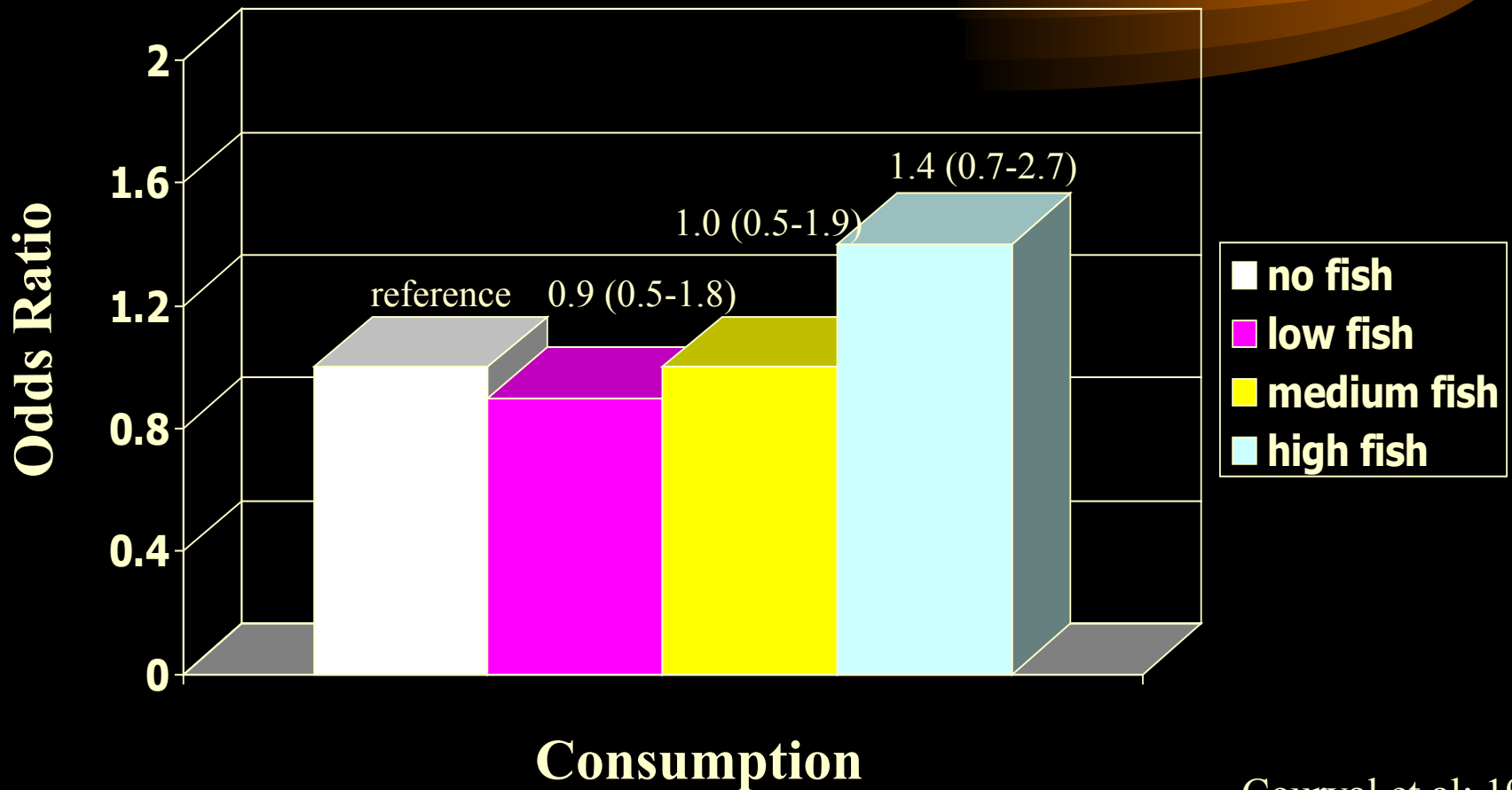
Test	Age	Outcome	Exposure variable	References
Congener-specific studies				
Oswego cohort				
NBAS	Birth	↓ Autonomic ↓ Habituation	7–9 chlorinated PCBs 7–9 chlorinated PCBs	Stewart et al. (2000)
Fagan	6 months 12 months	↓ Fixation time ↓ Fixation time	Cord blood PCBs, 7–9 chlorinated PCBs Cord blood PCBs	Darvill et al. (2000) Darvill et al. (2000)
German cohort				
Fagan	7 months	No effect	In Σ PCBs (138, 153, and 180) breast milk	Winneke et al. (1998)
Bayley scales	7 months	↓ MDI		Winneke et al. (1998)
	18 months	No effect		Walkowiak et al. (2001)
	30 months	↓ MDI		Walkowiak et al. (2001)
Kaufman ABC	42 months	↓ Mental processing composite index	In Σ PCBs (138, 153, and 180) breast milk	Walkowiak et al. (2001)
Faroe Islands cohort				
Boston Naming Test		↓ Performance	Cord blood PCBs	Grandjean et al. (2001)
Auditory function		↑ Auditory thresholds	Cord blood PCBs	Grandjean et al. (2001)
Noncongener-specific studies				
Michigan cohort				
Birth size/growth	Birth	↓ Birth weight ↓ Head circumference ↓ Gestational age	Cord blood PCBs Cord blood PCBs Cord blood PCBs	Fein et al. (1984)
	5 months	↓ Body weight	Cord blood PCBs	Jacobson and Jacobson (1988)
Bayley scales	5 months	No effect		Jacobson and Jacobson (1986)
Fagan	7 months	↓ Fixation time	Cord blood PCBs	Jacobson et al. (1985)
McCarthy scales	4 years	↓ Verbal memory ↓ Numerical memory ↓ Visual discrimination ↓ Short term memory	Cord blood PCBs, breast milk PCBs Cord blood PCBs, breast milk PCBs Breast milk PCBs Cord blood PCBs	Jacobson et al. (1990a) Jacobson et al. (1992)
Birth size/growth	4 years	↓ Body weight ↓ Activity	Total cord PCBs Child's total PCBs	Jacobson et al. (1990b)
WISC-R	11 years	↓ Full-scale IQ ↓ Verbal IQ	Prenatal PCBs Prenatal PCBs	Jacobson and Jacobson (1996)
North Carolina cohort				
NBAS	Birth	↓ Muscle tone ↓ Activity ↓ Reflexes	Breast milk PCBs Breast milk PCBs Breast milk PCBs	Rogan et al. (1986b)
Bayley scales	6 months	↓ PDI	Breast milk PCBs	Gladen et al. (1988)
	12 months	↓ PDI	Breast milk PCBs	Gladen et al. (1988)
	18 months	No effect		Rogan and Gladen (1991)
	24 months	↓ PDI	Breast milk PCBs	Rogan and Gladen (1991)
McCarthy scales	3–5 years	No effect		Gladen and Rogan (1991)

Abbreviations: ↓, decrease; ↑, increase; Bayley scales, Bayley Scales of Infant Development; Fagan, Fagan Test of Infant Intelligence; Kaufman ABC, Kaufman Assessment Battery for Children; McCarthy scales, McCarthy Scales of Children's Abilities; NBAS, Brazelton Neonatal Behavioral Assessment Scale; Wisc-R, Wechsler Intelligence Scales for Children-Revised. ^aDutch cohort is summarized in Table 2.

PCBs



PCBs and Normal Time to Conception

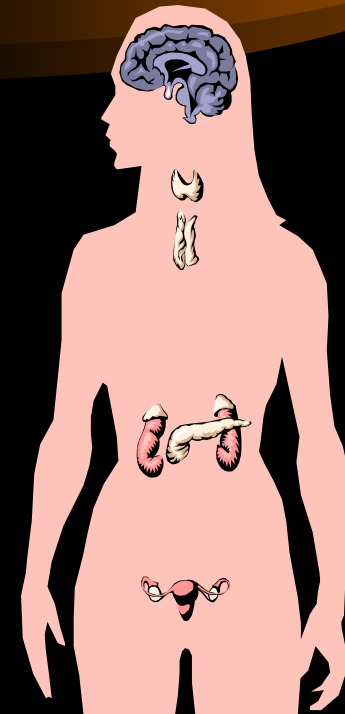


*How do agents disrupt/modulate
the endocrine system?*

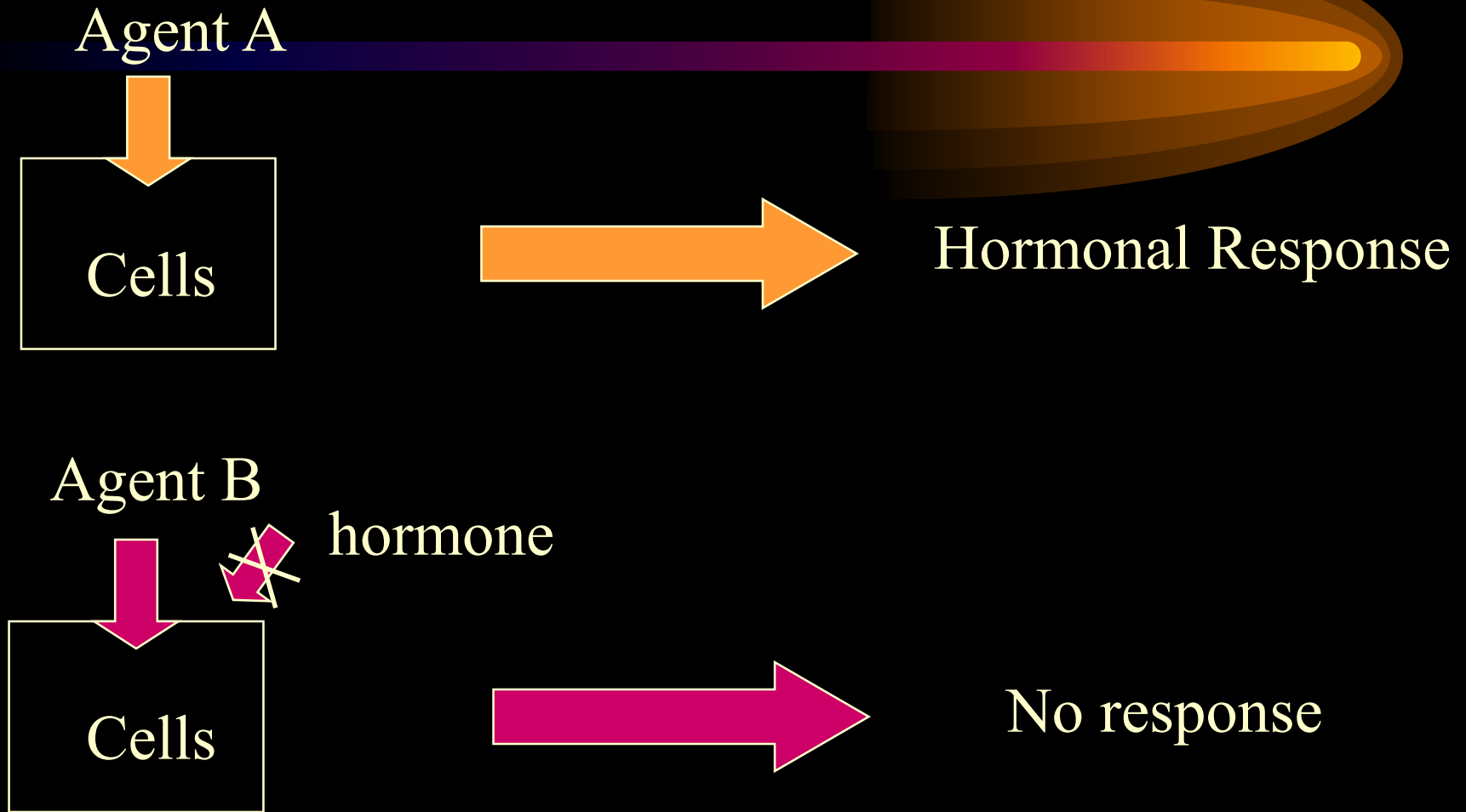


Mechanisms of Damage

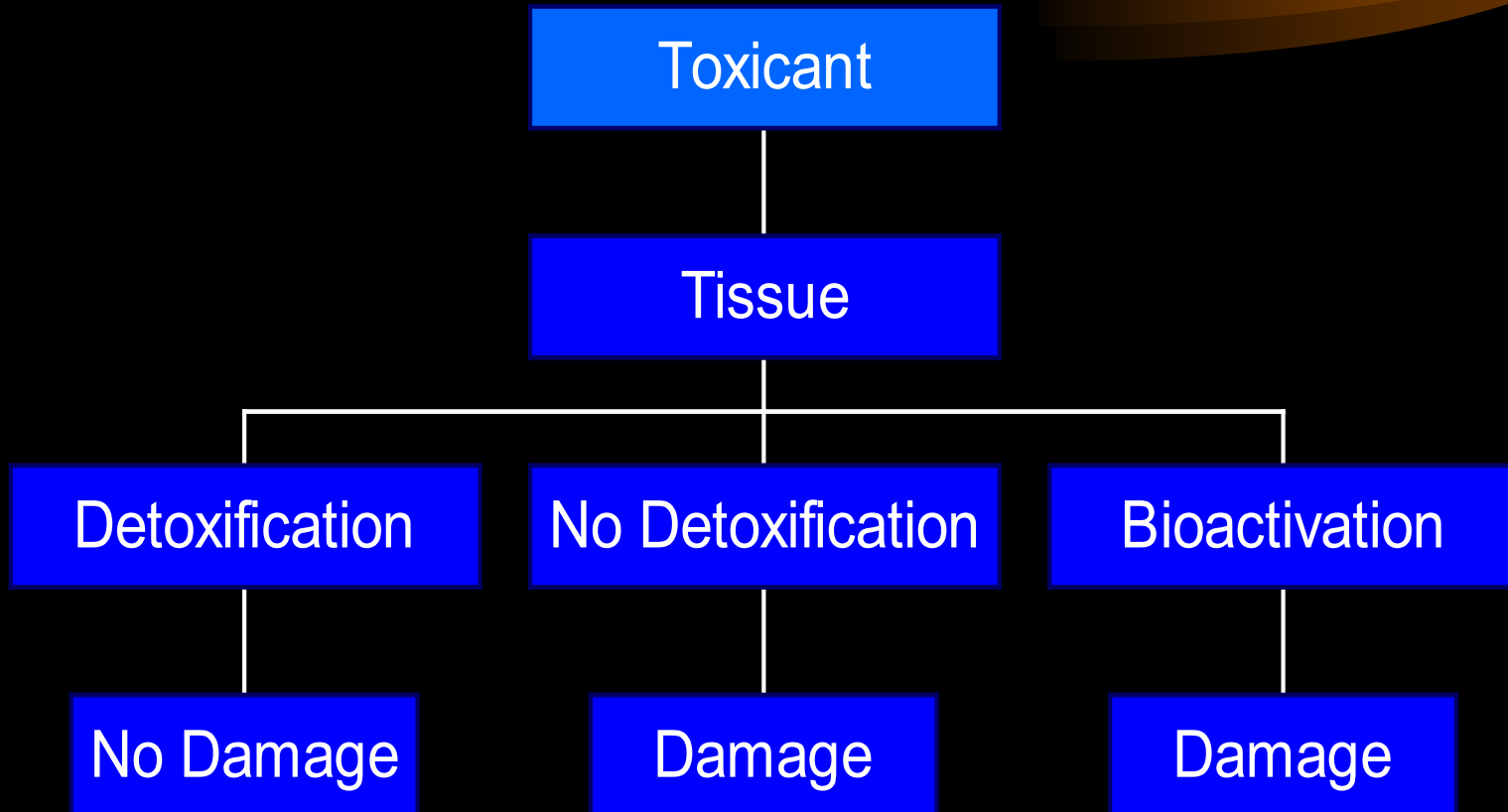
- Endocrine Disruption
 - mimic hormones
 - block hormones
 - trigger inappropriate hormone action



Mechanisms

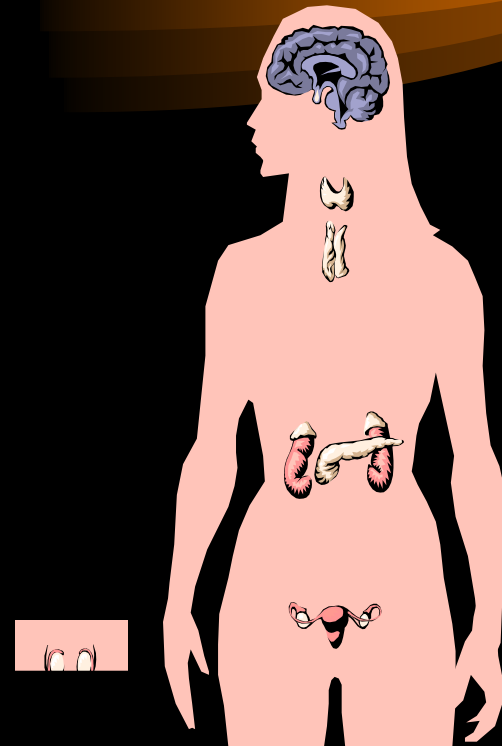


Mechanisms of Toxicants



Mechanisms of Damage

- Damage reproductive tissues
 - ovary
 - uterus
 - oviducts
 - cervix
 - vagina
 - testes
 - epididymis
 - prostate



What can we do to avoid endocrine disruption?



- Awareness
- Screen and Regulate chemicals
 - prevention
- Regulate food and water
 - prevention
- Mechanistic studies
 - treatment

Summary



- We are exposed to many endocrine disrupting agents
- Endocrine disruptors may affect reproduction in wild-life and humans
- We need more studies to determine which chemicals affect reproduction and how such chemicals act
 - Prevention
 - Treatment
 - Policies