

Effect of the Environment on Reproductive Health



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Overview



- Which environmental exposures are associated with reproductive toxicity?
- How do environmental exposures cause damage?

Environmental Exposures



- Pharmaceutical agents
 - diethylstilbestrol
- Pesticides
 - dichloro-diphenyl-trichloroethane (DDT), methoxychlor (MXC)
- Flame retardants
 - polybrominated diphenyl ethers (PBDEs)
- Plasticizers
 - phthalates, bisphenol A
- Environmental contaminants
 - dioxins, polychlorinated biphenyls (PCBs)

Pharmaceutical Agents: Diethylstilbestrol (DES)

"Really?"

Yes...

des PLEX
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

recommended for routine use
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^{1,2,4}

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 effectuation of estrogen.

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

REFERENCES

1. Canalis, E. M., et al.: *Am. J. Obst. & Gynec.* 45:1296, 1955
2. Gilman, J., and Kaplan, A.: *N. Y. St. J. Med.* 50:1923, 1956
3. Karmaky, E. J.: *South. M. J.* 45:1146, 1952
4. Pelen, E. J.: *Med. Times* 82:925, 1954; *Am. J. Surg.* 87:45, 1954
5. Ross, J. W.: *J. Nat. M. A.* 43:30, 1951; 43:253, 1952

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



desplex
live
desplex
healthy
desplex
babies
desplex

EFFECTIVE Over 96 per cent live delivery in 1200 patients... including 540 habitual aborters.¹
SAFE No side effects in pregnant patients... in either low or massive dosage.²

COMPREHENSIVE

A Formulation Proved By Extensive Clinical Experience, 1, 2, 3, 4

— Each desplex tablet contains 25 mg. of rapid-acting ultra-micronized diethylstilbestrol U.S.P., with protective and effectuating amounts of vitamin B complex and vitamin C.

— For further information and a generous trial supply of desplex, write to:

FRANK L. HALEY, M.D., — Medical Director
Grant Chemical Co., Inc.
New York 10, N.Y.

REFERENCES

1. Pelen, E. J.: *Med. Times* 82:925, 1954; *Am. J. Surg.* 87:45, 1954
2. Karmaky, E. J.: *South. M. J.* 45:1146, 1952
3. Gilman, J. and Kaplan, A.: *N. Y. St. J. Med.* 50:1923, 1956
4. Ross, J. W.: *J. Nat. M. Assoc.* 43:30, 1951; 43:253, 1952

After extensive clinical experience with des, Karnaky¹, Gilman 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.

References

1. Karnaky, E. J.: *Amer. J. Obst. & Gyn.* 53:517, 1947
2. Gilman, J. and Koplowitz, A.: *New York State J. Med.* 50:1923, 1950; *J. Nat. M. A.* 43:25, 1952
3. Ross, J. W.: *J. Nat. M. A.* 43:25, 1952

DES Story



- 1966-1969
 - 8 women between 15-22 developed vaginal cancer (should be 0)
 - 7 of the 8 women were born to mothers who took DES during pregnancy
- 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
- DES grandsons



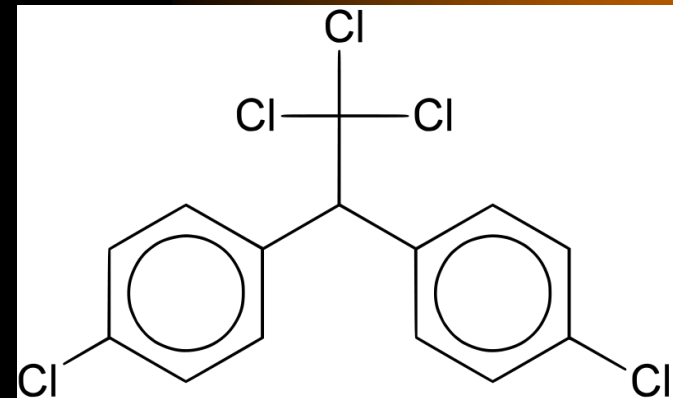
What did we learn from the DES story?



- 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
- We must take precautions when using DES

Pesticides

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



DDT

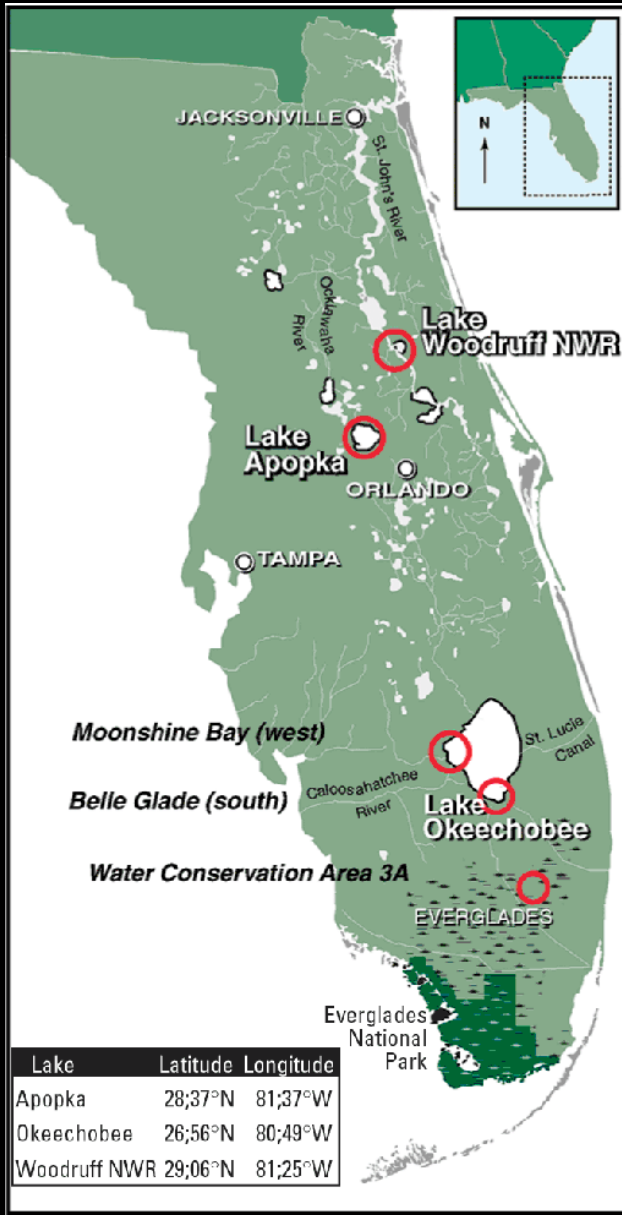


Pesticides



- 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

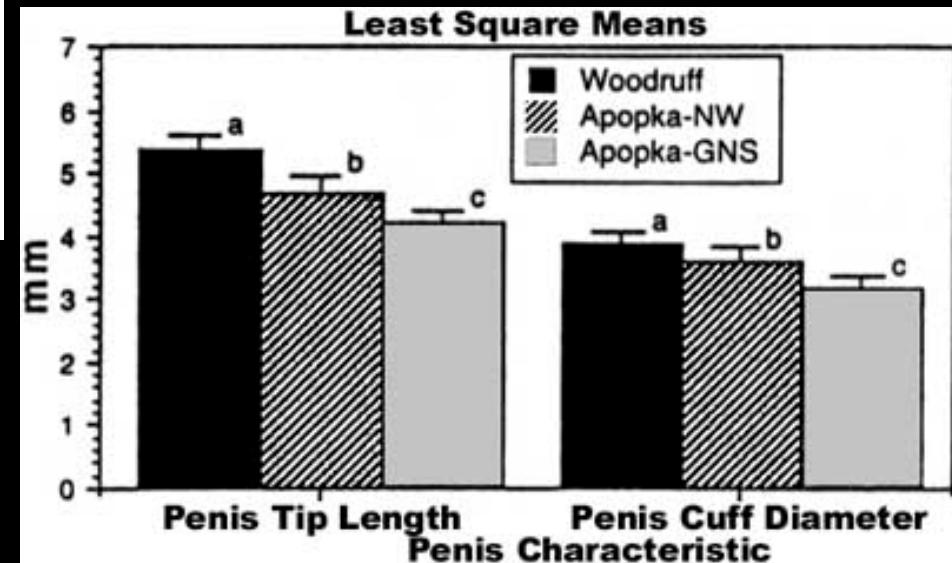
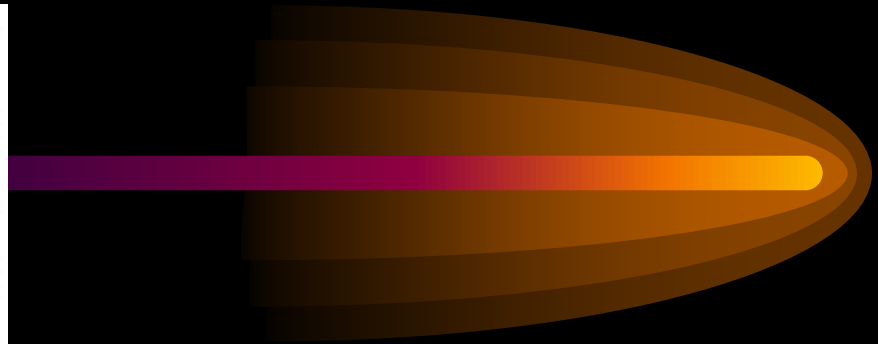
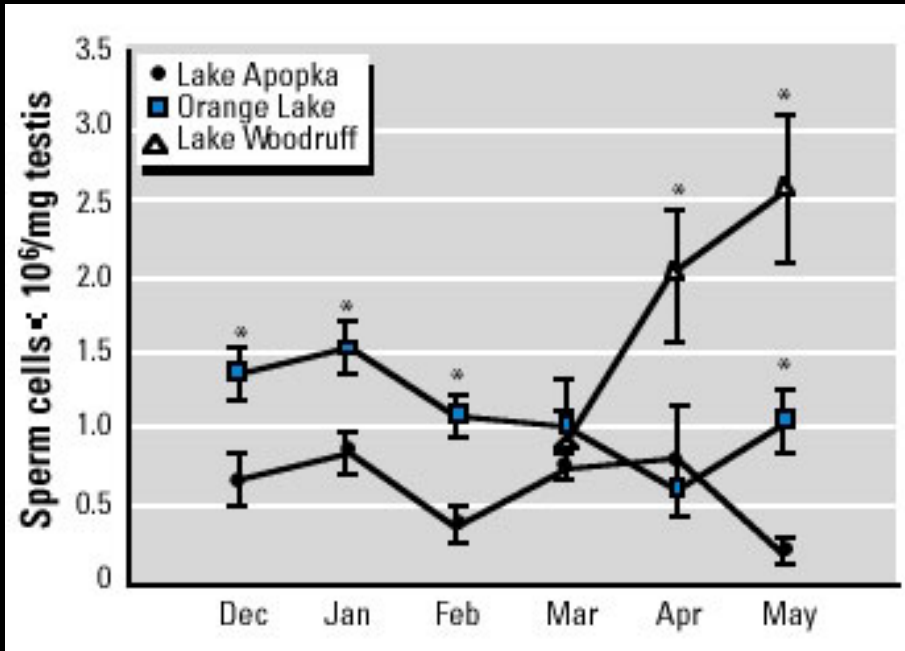


(CNN)

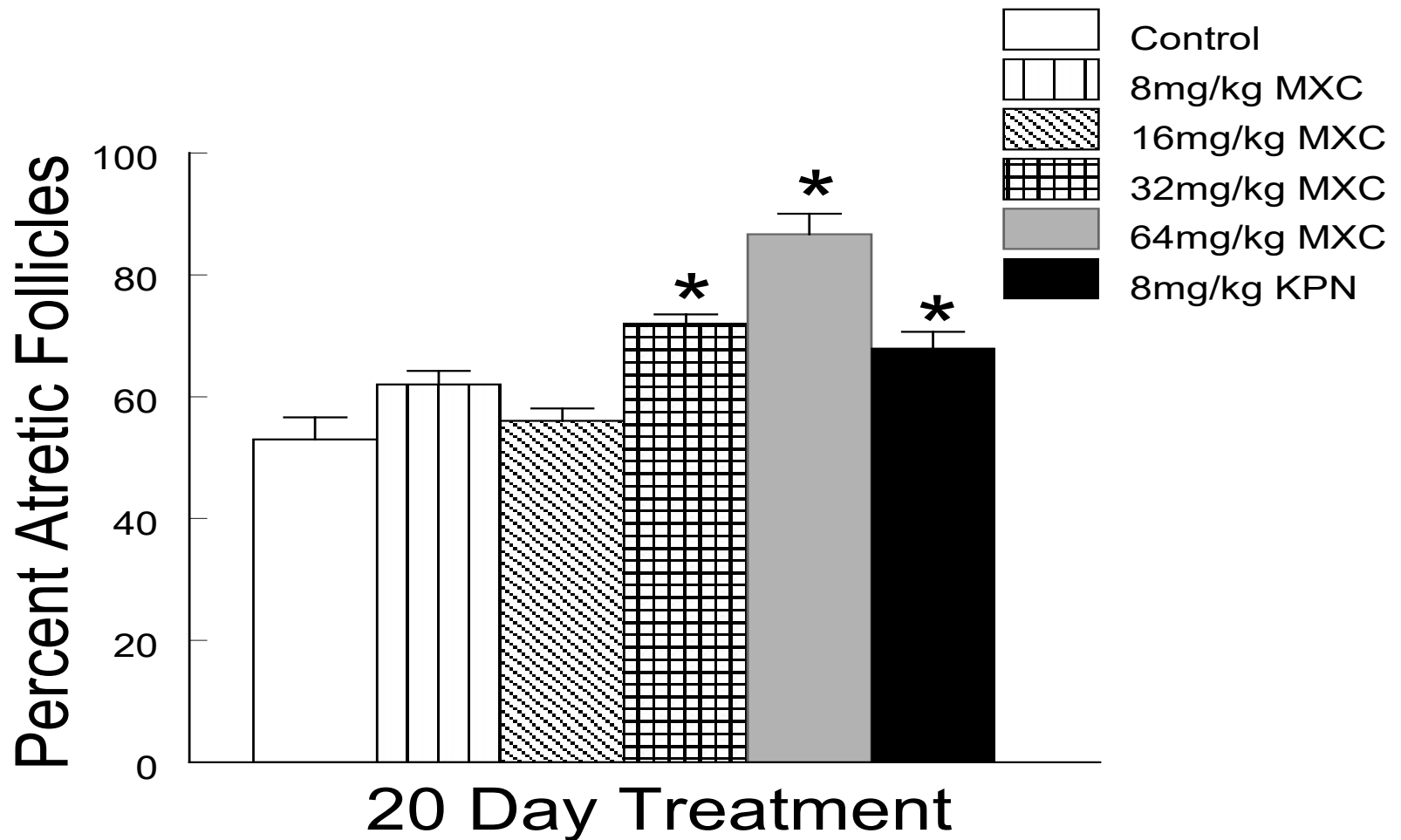


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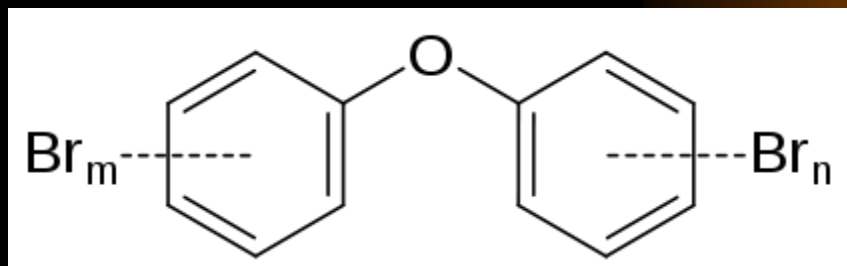
Lake Apopka Disaster



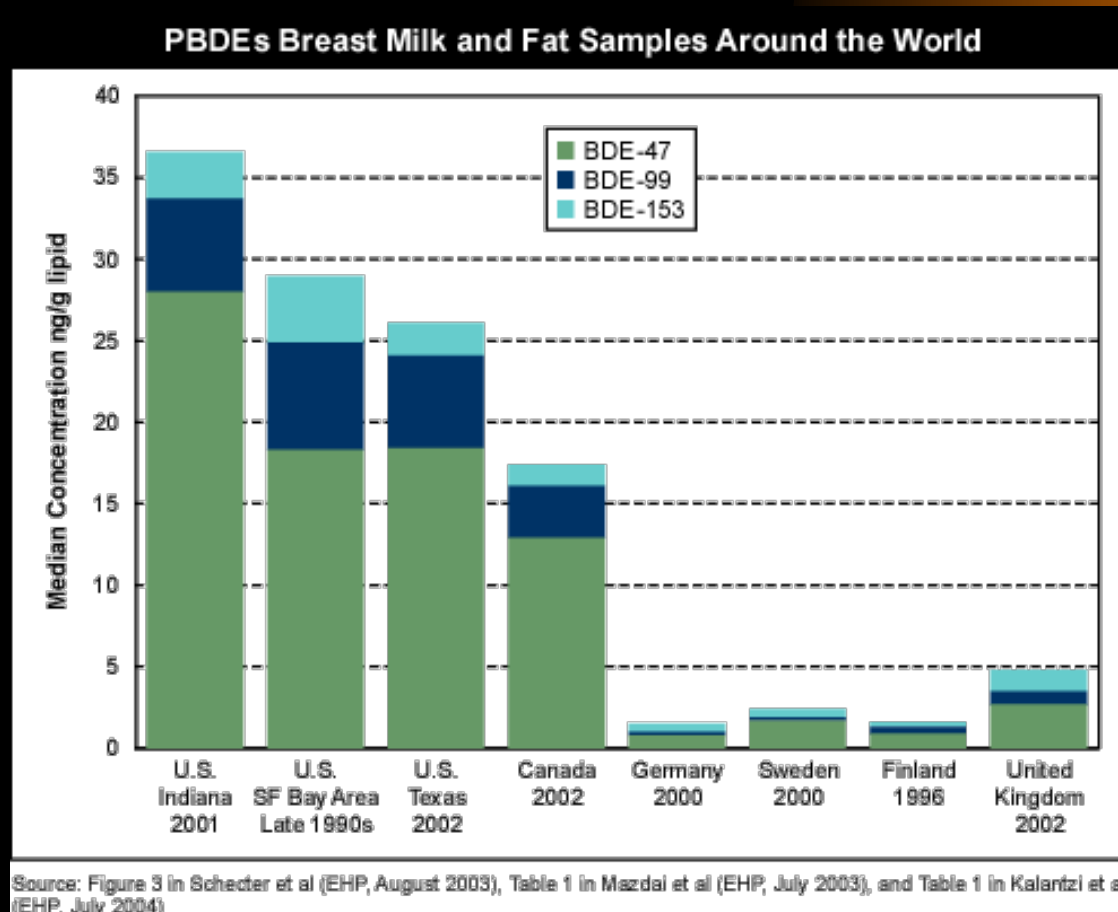
Effect of MXC on Antral Follicles



Flame Retardants



Flame Retardants



Flame Retardants

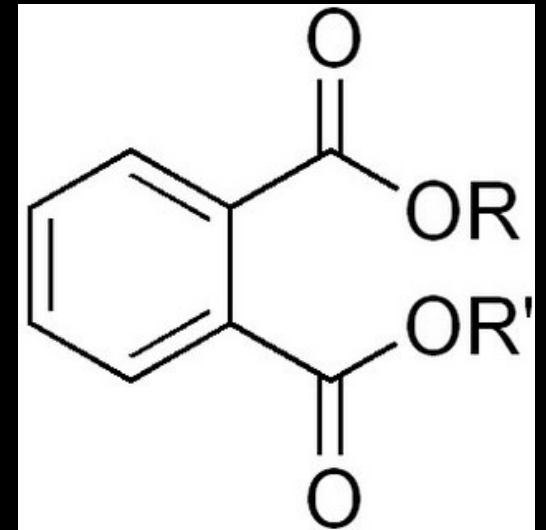


Reduced eggshell mass
Delayed egg laying
Reduced fledging success
Consistent with peregrine data

NOAA, 2009

Fernie et al., 2009

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



- 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

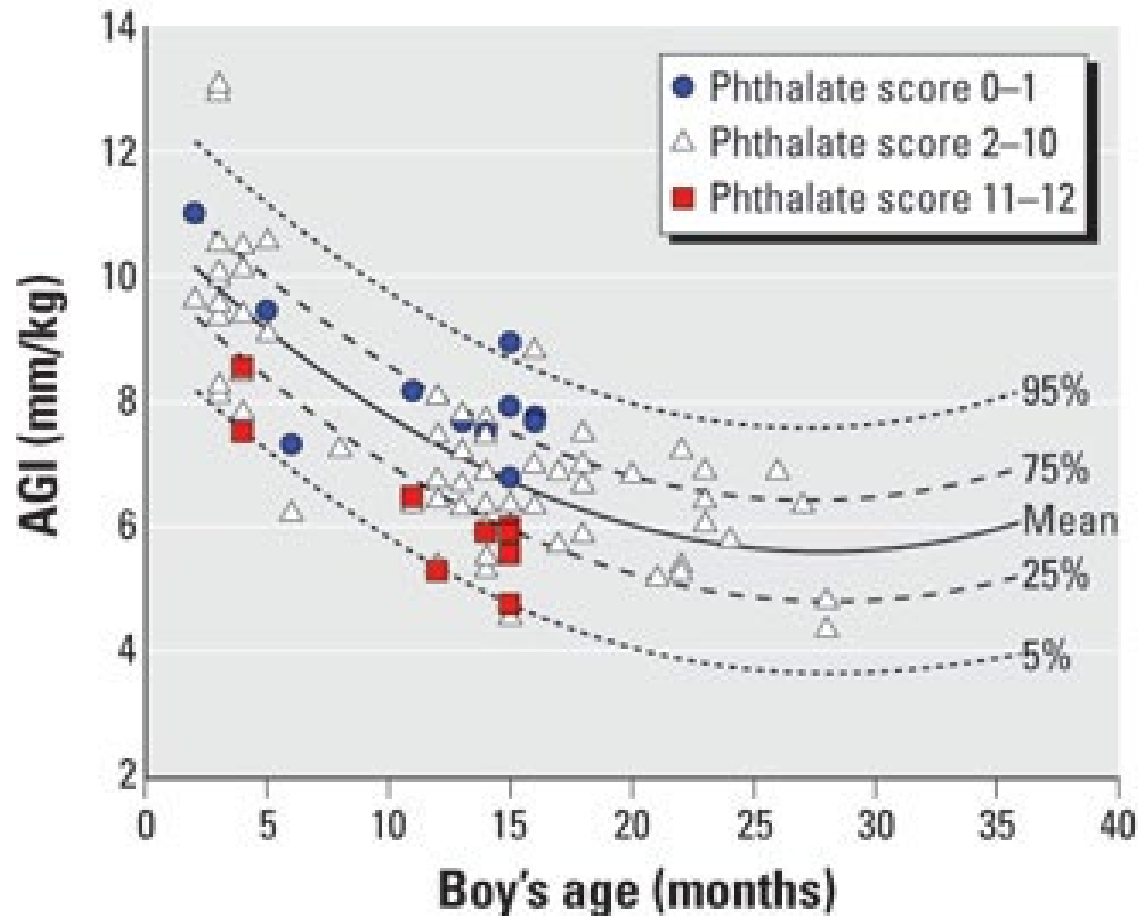
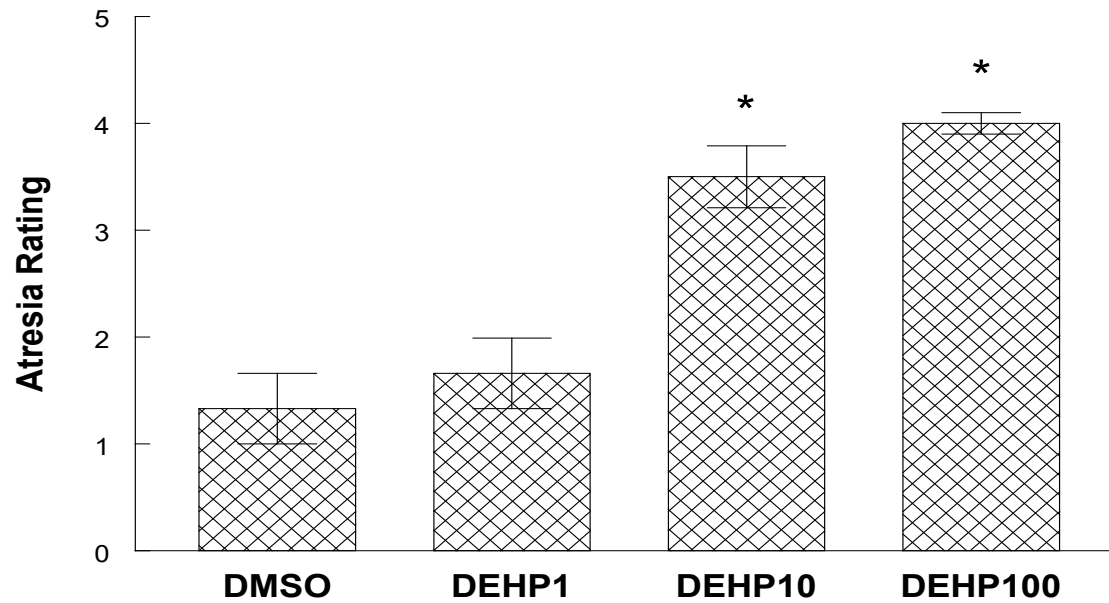
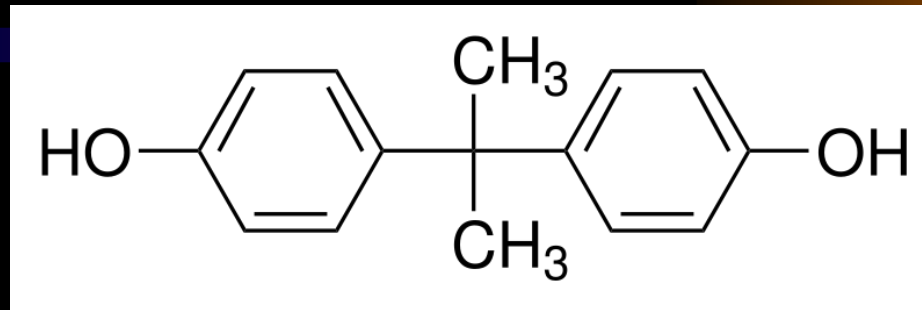


Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

Effects of Phthalates on Antral Follicles



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



TAXI RECEIPT	
HACK #	12345
MED #	9C57
TRIP #	8294
DATE:	08/01/2009
START TIME	18:53
END TIME	19:07
RATE NO.	03
STAND.	CITY RATE
MILES R1	1.48
FARE1	\$8.10
SURCHARGE	\$1.00
TOTAL	\$9.10
TIP/OTHER	\$2.00
GR. TOTAL	\$11.10

THANK YOU



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

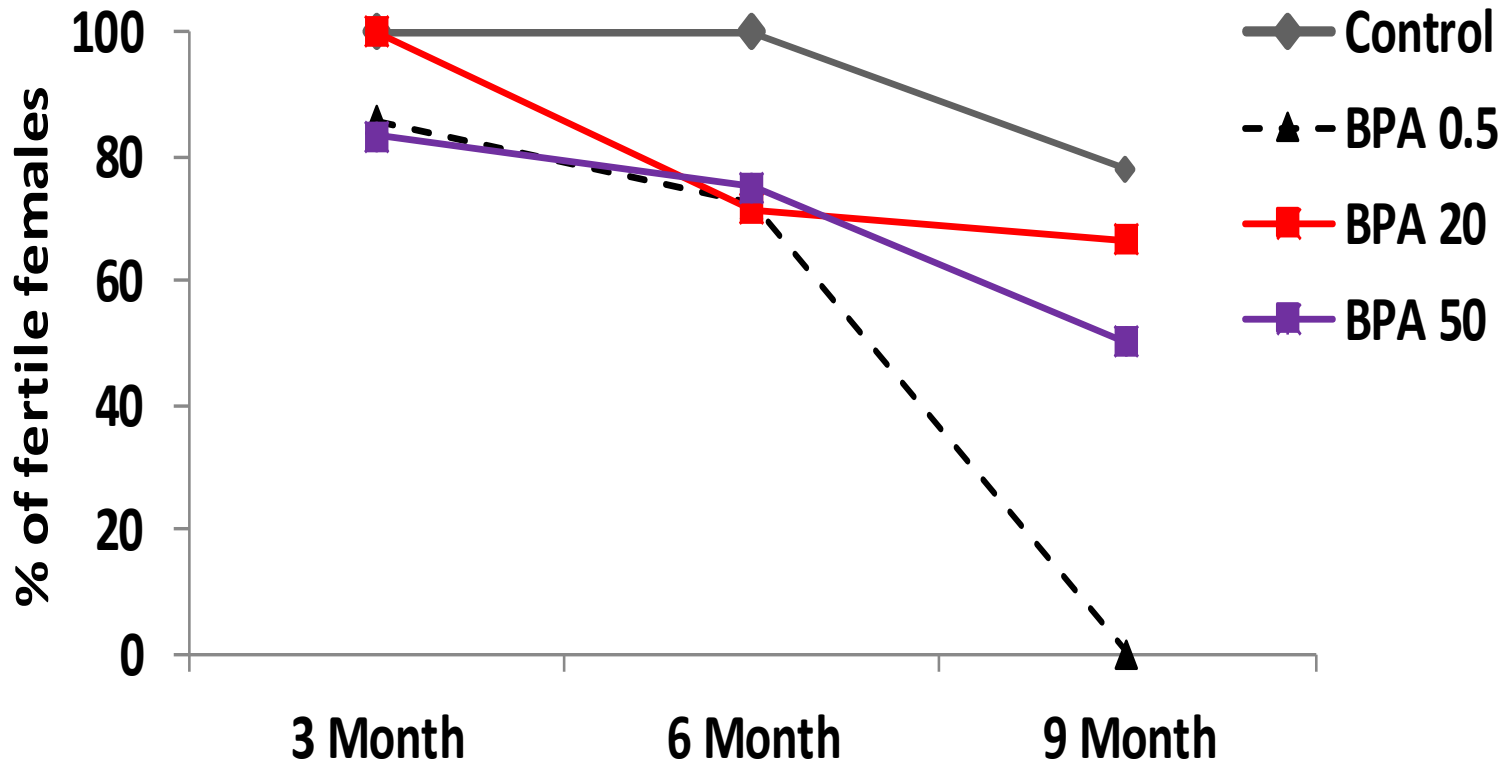


- BPA is found in 95% of human urine samples
 - it is rapidly metabolized and excreted
- BPA has been detected in ovarian follicular fluid, suggesting the follicle may be a source of BPA exposure for the early fetus
- BPA is able to rapidly cross the placenta and enter fetal organs in rats

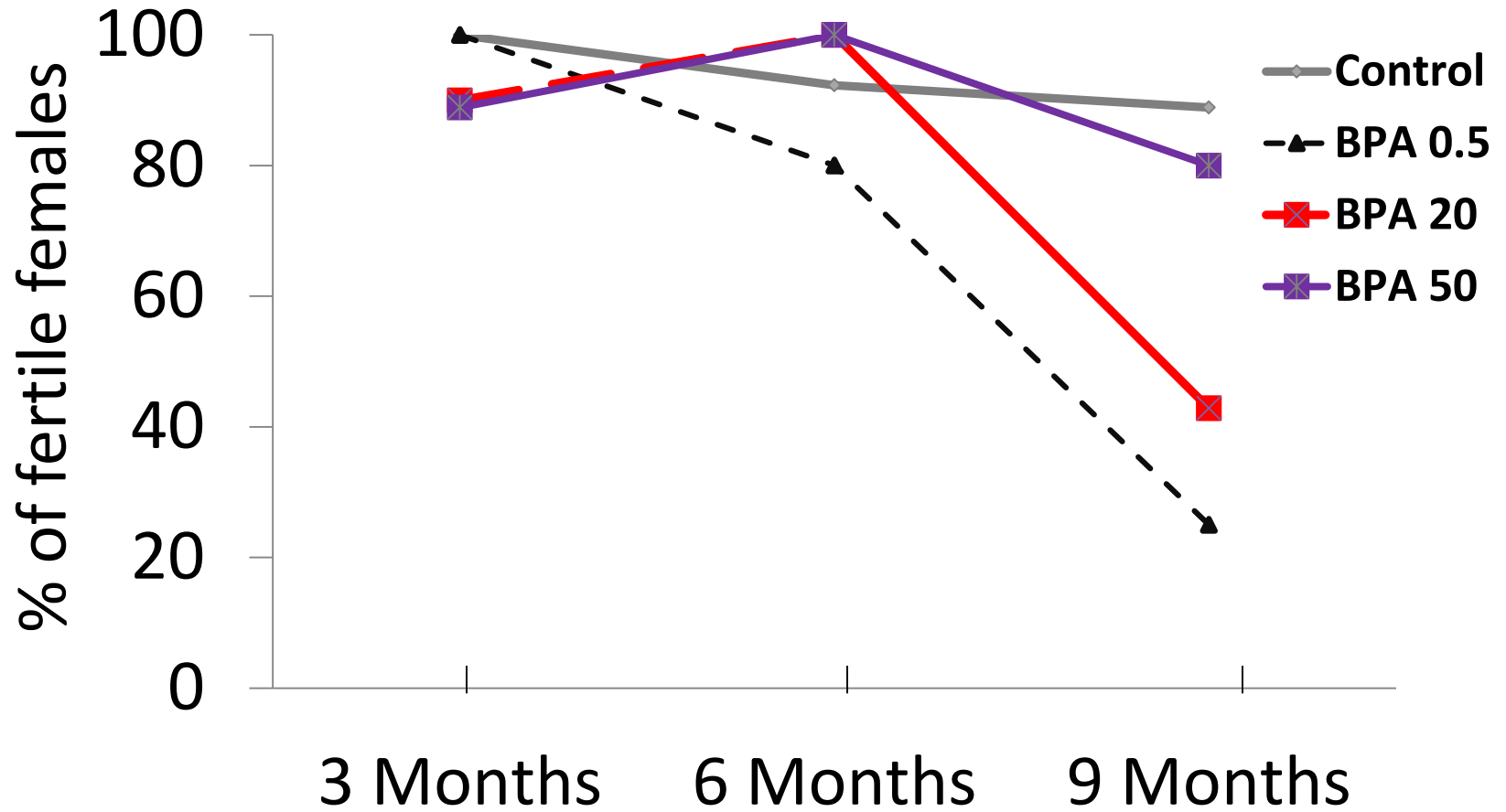
Prenatal Exposure to BPA in Rodents

- 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

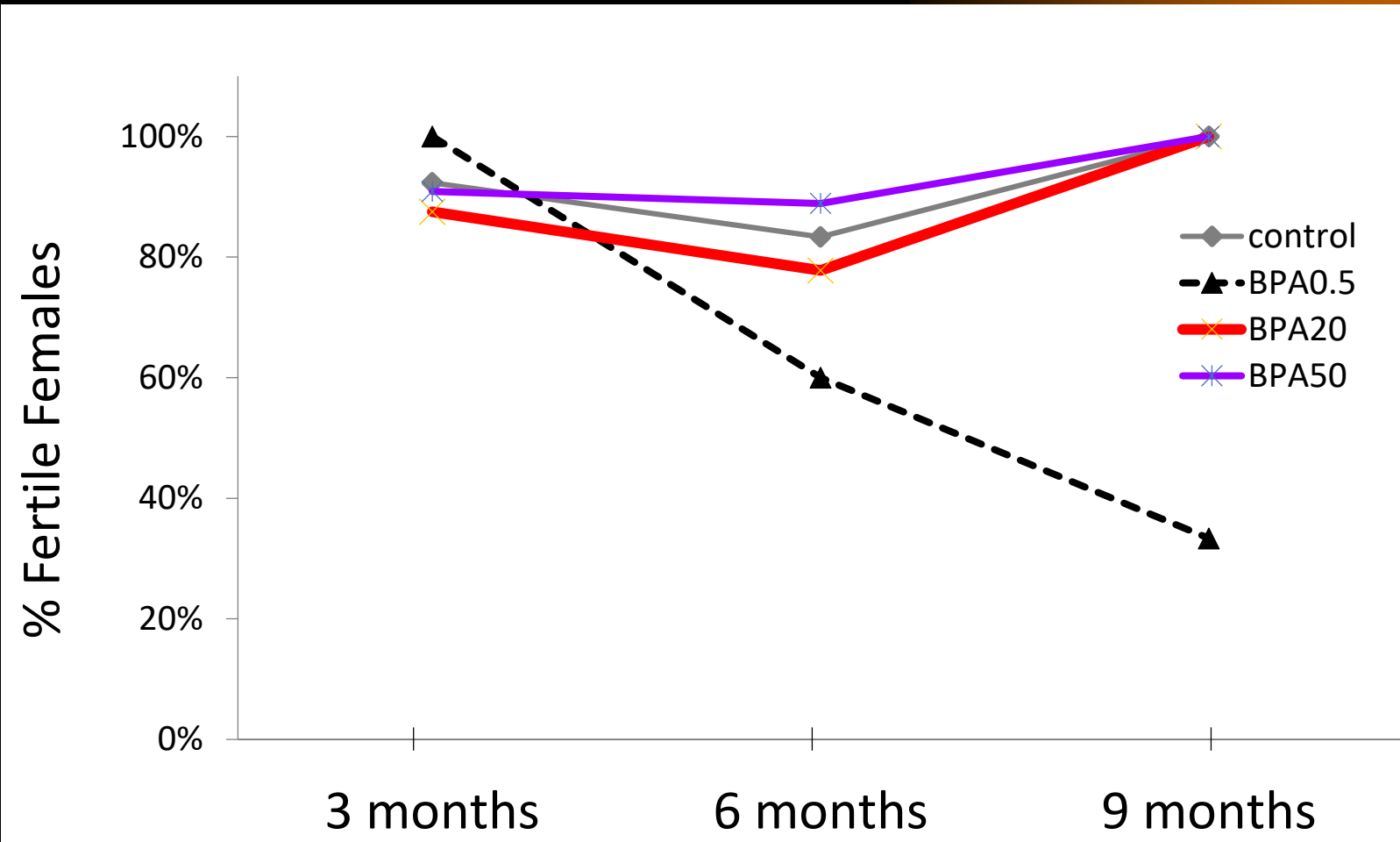
Effect of BPA on Fertility Over Time (F1)



Effect of BPA on Fertility Over Time (F2)



Effect of BPA on Fertility Over Time (F3)



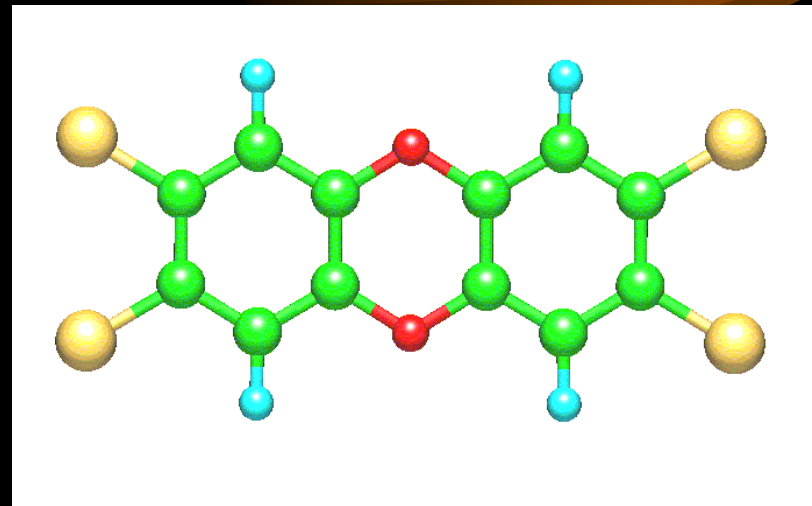
BPA



- 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



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 $p=0.03$.

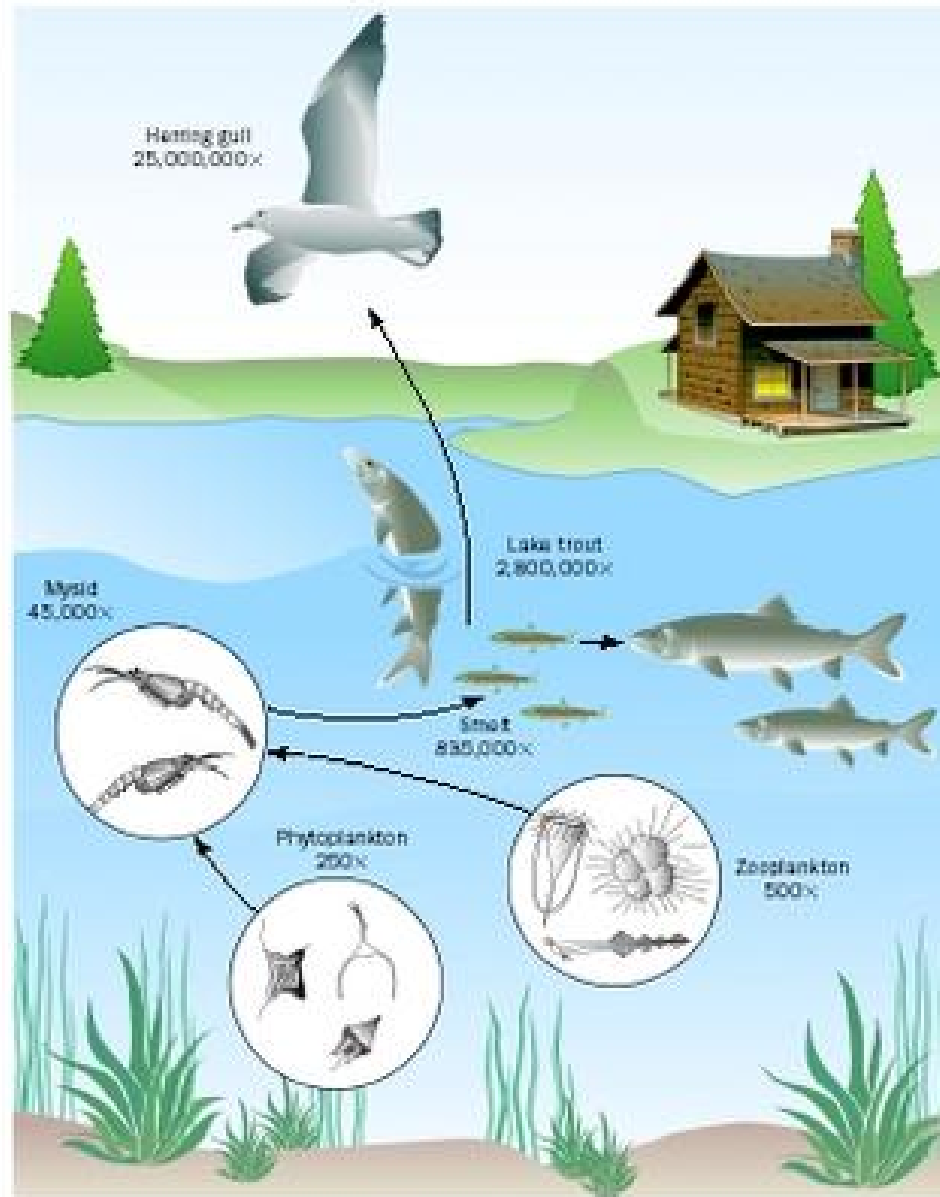
Environmental Contaminants

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



PCBs

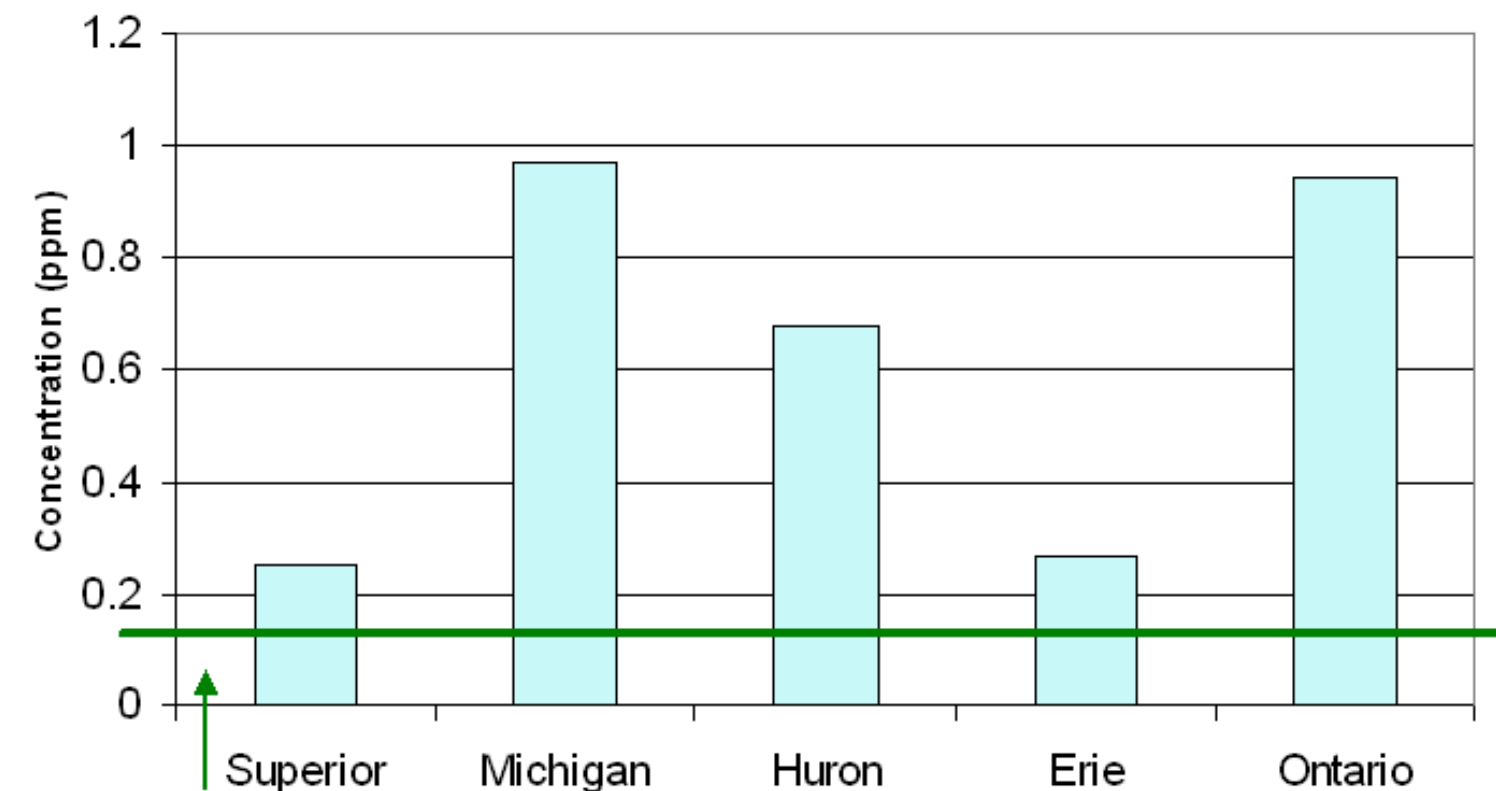
LAKE ONTARIO BIOMAGNIFICATION OF PCBs



PCBs

Total PCBs in 2005 Great Lakes Top Predator Fish

Lake trout (Walleye in Lake Erie only)



Wildlife protection value = .16ppm

Polychlorinated biphenyls (PCBs)

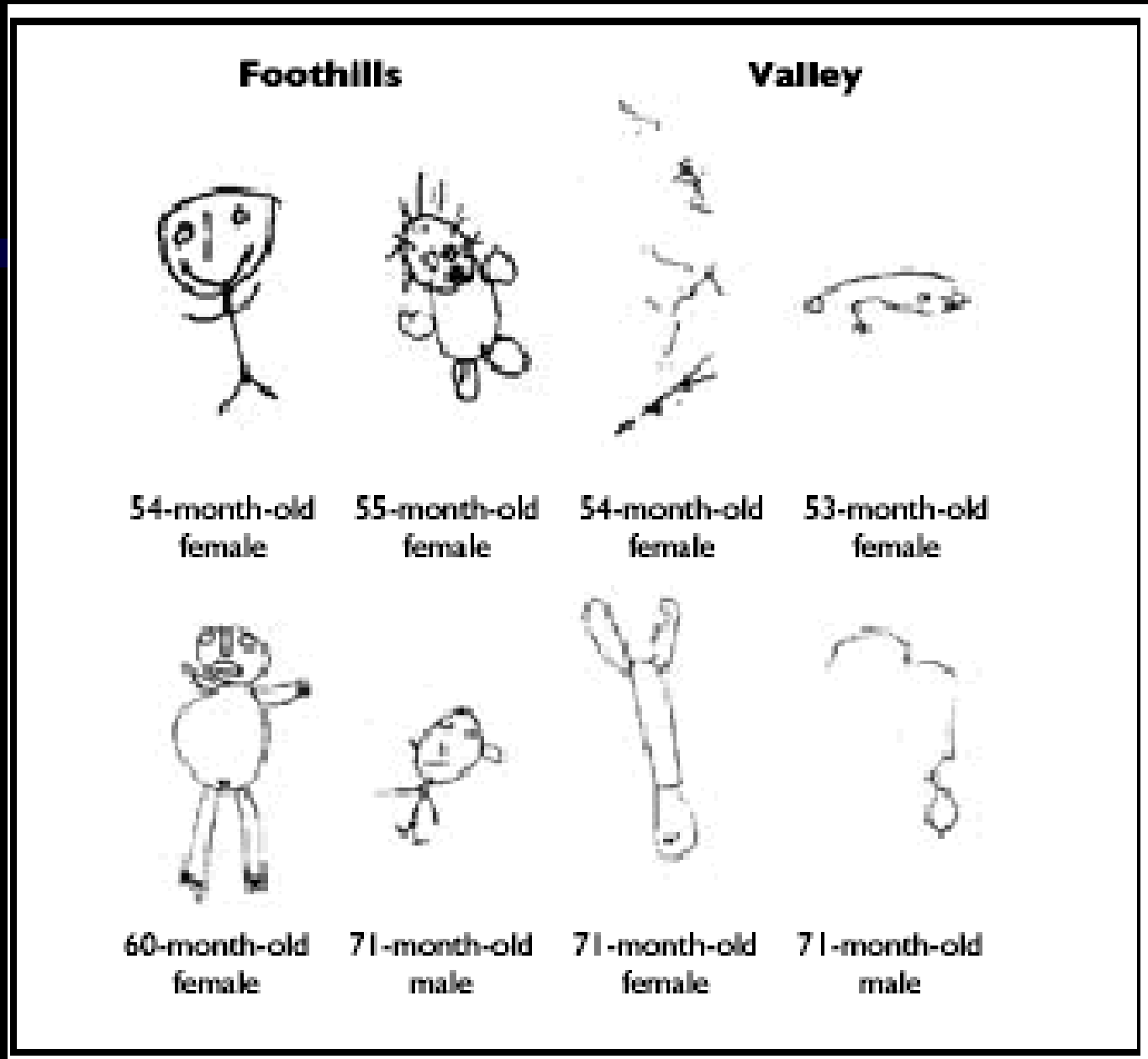
- Humans

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

- Animal models

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

PCBs

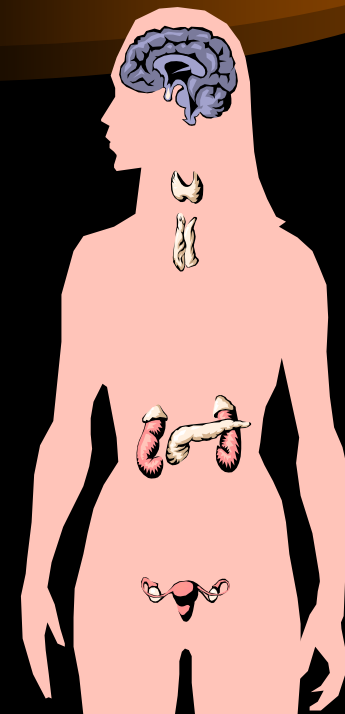


*How do agents disrupt the
reproductive system?*

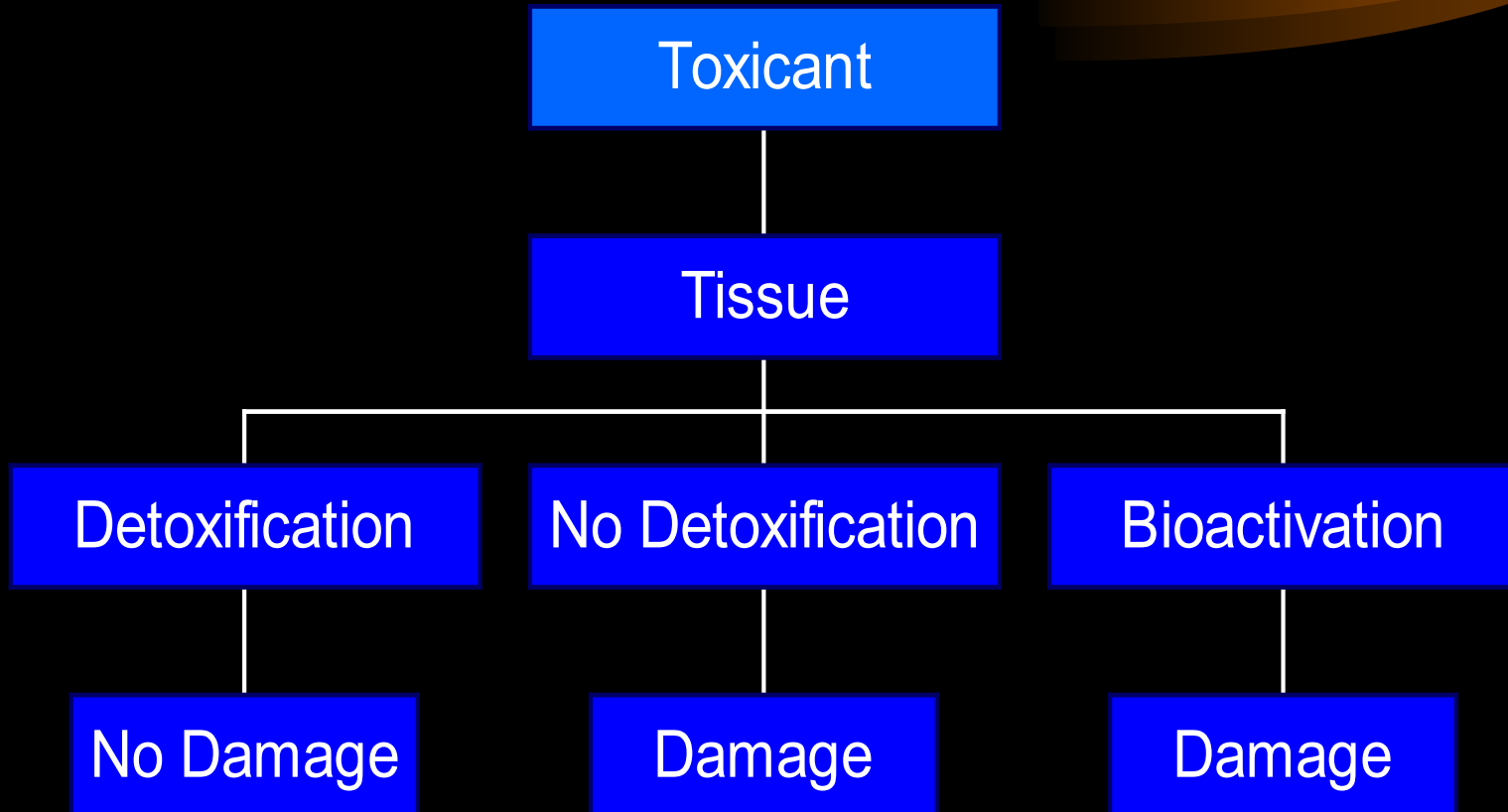


Mechanisms of Damage

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



Mechanisms of Toxicants



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 environmental chemicals
- Environmental chemicals 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