

Effects of chronic low-dose
exposures on the endocrine, immune
& neurological systems of the
developing fetus and child

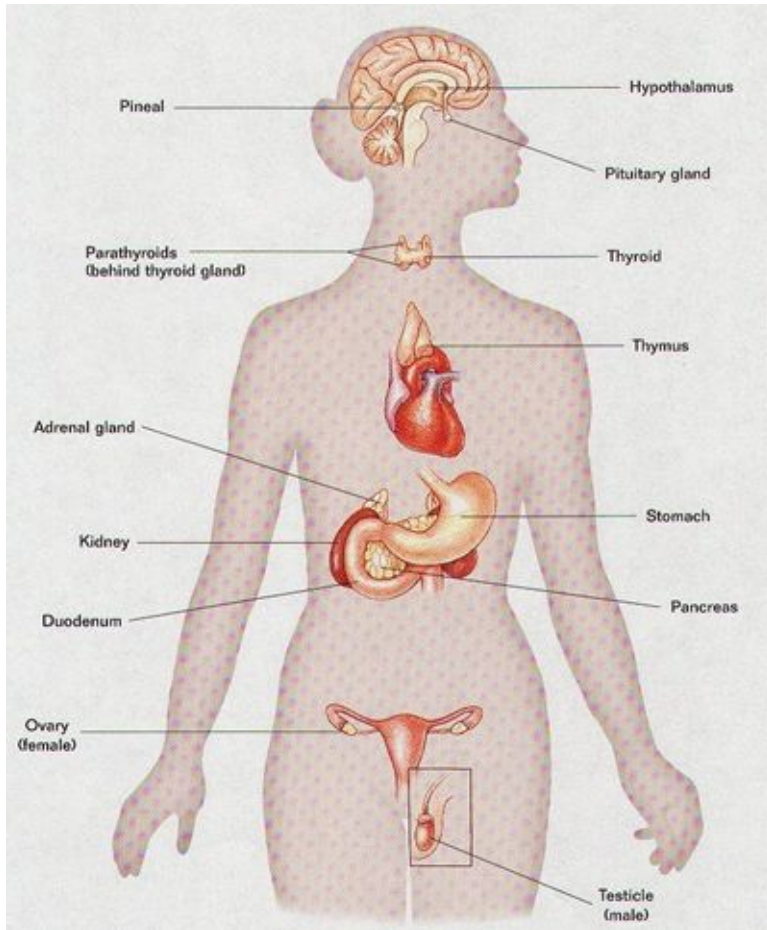
Loren Vanderlinden, PhD
Toronto Public Health
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- *An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects*
[IPCS (NIEHS, WHO), 2002]
- interfere with hormone biosynthesis, metabolism, or action leading to deviation from normal homeostatic control or reproduction [The Endocrine Society, 2009]
- “endocrine disruption” a.k.a. **“endocrine toxicity”**
- Also called – *endocrine disruptors, hormonally active chemicals, hormone mimics*

Known or Suspected Endocrine Disruptors

- Persistent Organic Pollutants (POPs)
- Some pesticides
- Metals
- Industrial chemicals – PCBs, dioxin
- Compounds found in plastics – phthalates, bisphenol A, penta- to nonyl phenols
- Perfluorinated cmpds - non-stick, stain repellants
- Flame Retardants

Key Observations



Source: www.epa.gov

- Widespread exposure, ↑ body burdens
- Exposure path food mainly
- Uncertainty in science
- Several mechanisms, effects
- Evidence of harm from animal studies
- Low doses, timing is critical
- Influence on human health isn't entirely clear

Observations in wildlife

Experimental data (**Toxicology**)

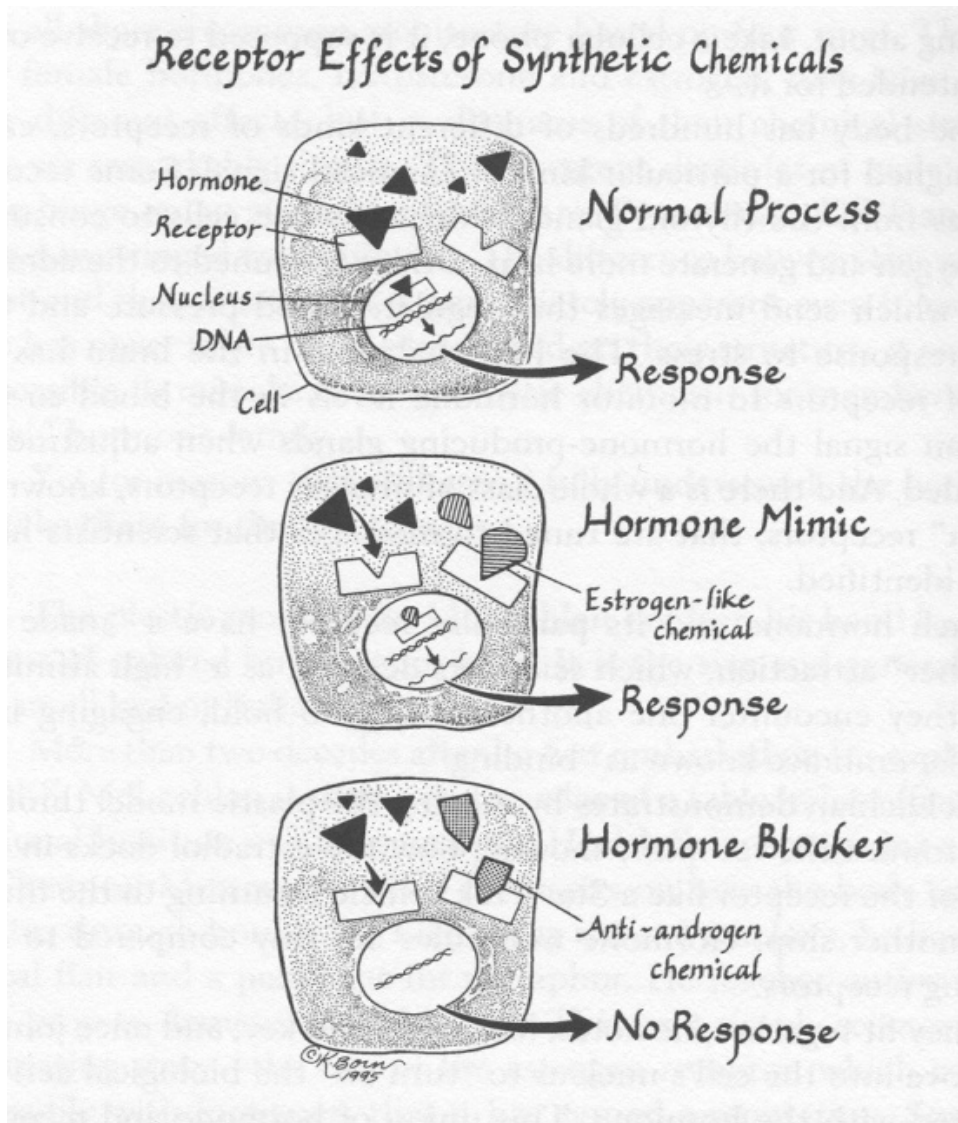
- Animal studies
- *In vitro* studies

Human population studies* (**Epidemiology**)

- Studying people with unusual/high exposures
- Patterns of health problems (“Ecological” studies)
- Worldwide time trends in health effects
- Some population studies

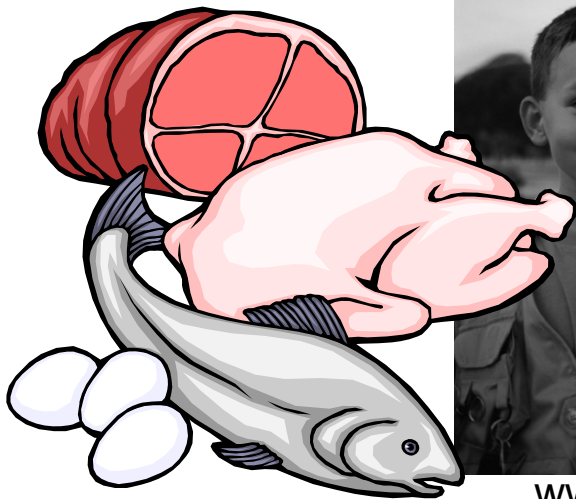
(*least data here)

Mechanisms of Action



- Alter hormone functioning
- Act as hormone mimics, antagonists (inhibitors)
- Alter transport or secretion or breakdown of hormones
- Effects on more than androgens → thyroid hormones, glucocorticoid, retinoid, others.

Exposure Risk Factors



www.cape.ca

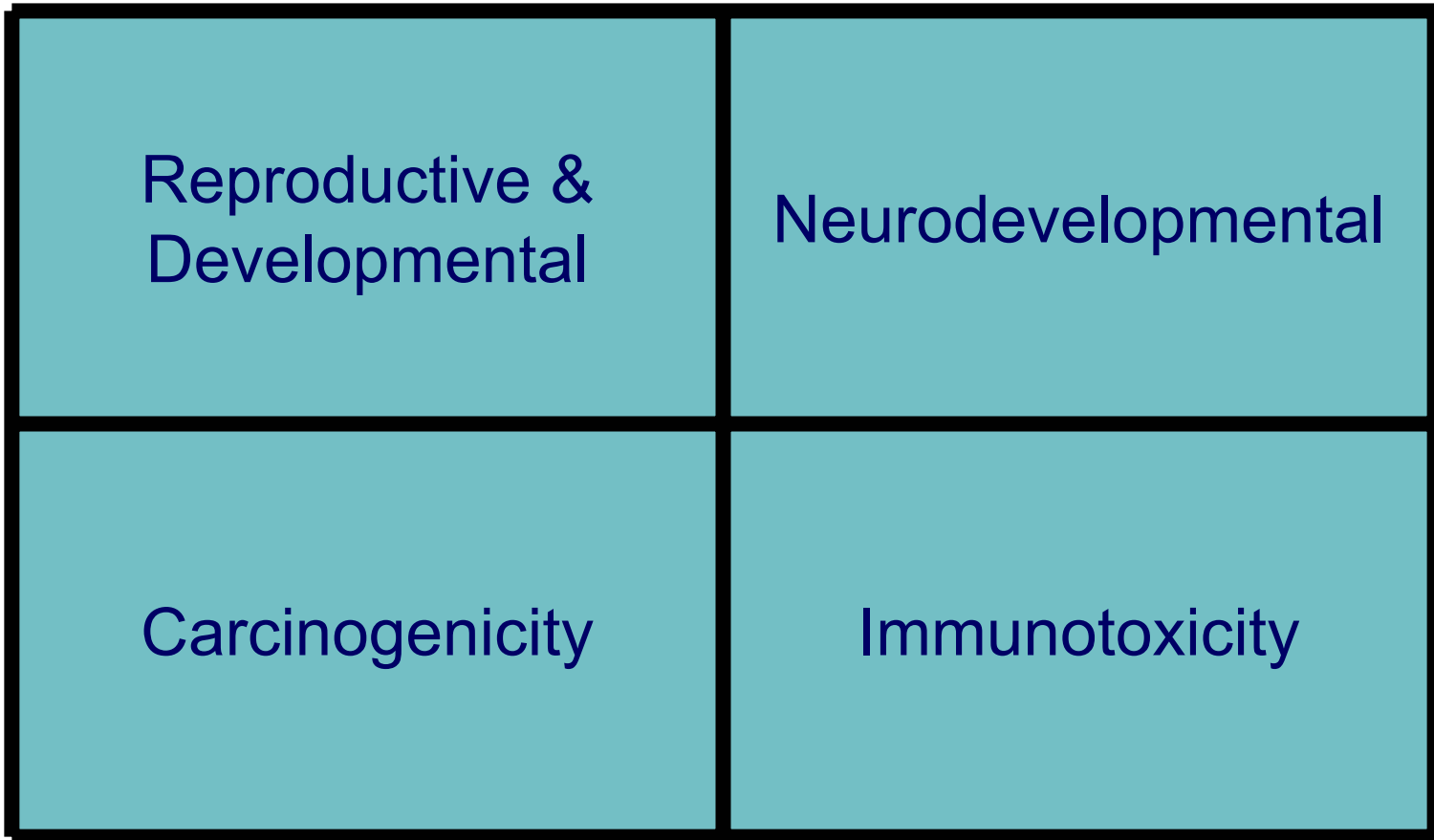
- C**ommunity
- H**obbies/**H**ome
- O**ccupational
- P**ersonal
- D**iet – 85% of exposure
- D**rugs



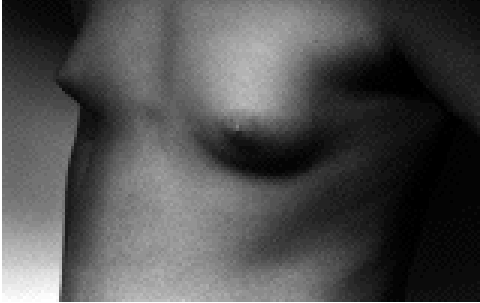
Pathways of human exposure not adequately studied for all substances



Range of Health Effects

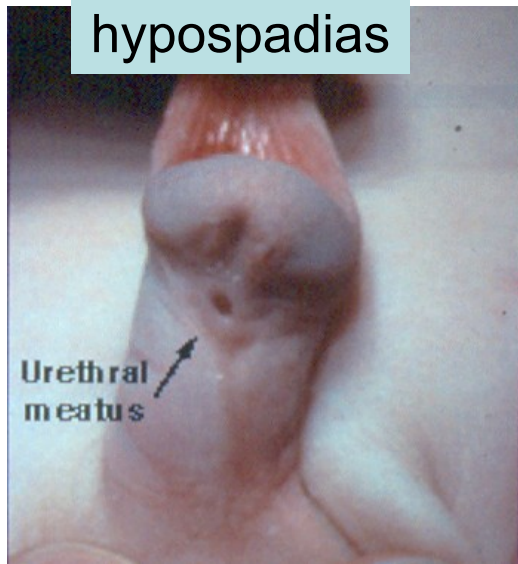


precocious thelarche



Source: Colon et al. 2000. Environ Health Perspect. 108:895-900.

hypospadias



Source: Hatch. 1996. <http://www.meddean.luc.edu/lumen/MedEd/urology/abnpdv.htm>

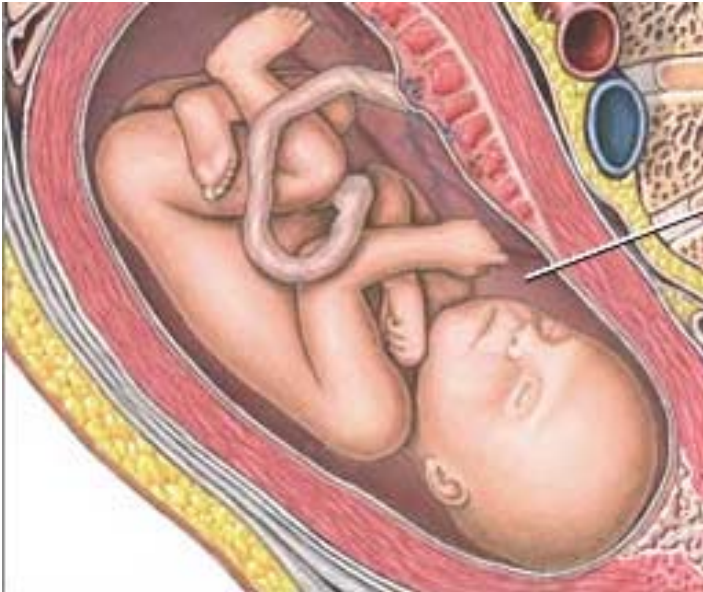
Worldwide Trends

- ↑ incidence of hypospadias, cryptorchidism
- ↓ sperm count?
- ↓ age at menarche
- ↑ infertility

Epidemiologic Findings

- ↓ menstrual cycle length
- Conception problems
- ↓ duration lactation

Prenatal window of vulnerability



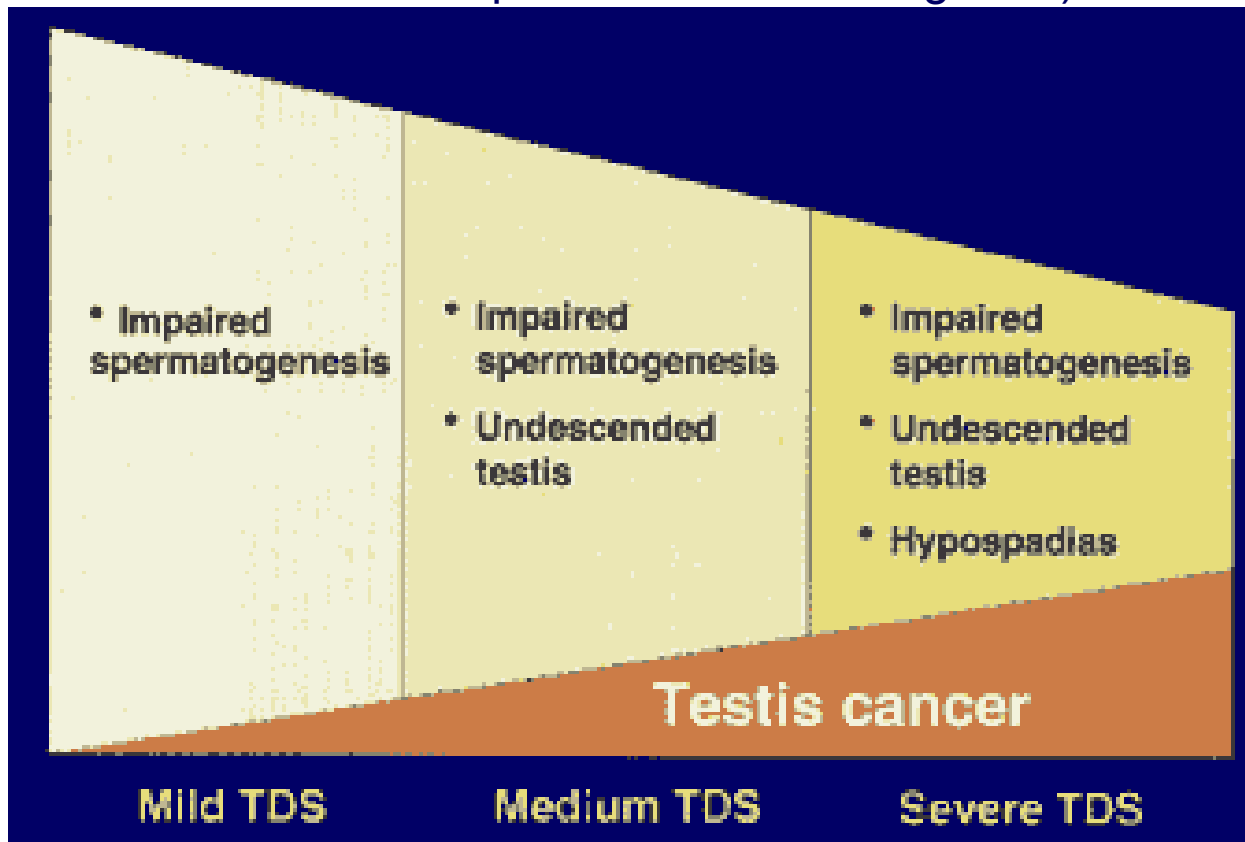
- Increasing trends in human breast, testicular prostate cancers
- Not linked to serum levels of EDs at time of dx
- Linked to immune changes, endocrine alteration?
- Prenatal exposure window?
 - DES-exposed
 - Testicular cancer risk linked with maternal serum organochlorine levels (Hardell et al. 2003. EHP)

Source: University of Pennsylvania Health System
http://www.pennmedicine.org/newsletters/preg_parenting/preg_printfriendly/week22.html

Testicular Dysgenesis Syndrome

hypospadias, undescended testis, poor semen quality and testicular cancer as symptoms of an underlying syndrome – ED while in the womb

(Skakkebaek et al. 2001. Hum. Reprod. 16: 972-78. Figure 4)



- Lk Michigan Fish Eaters Study
- Cohort of children exposed to PCBs from mother's fish consumption before and during pregnancy
- Lower birth weight, head circumference at birth
- Delays in developmental milestones
- Age 11 higher exposure linked with lower average IQ, poorer word comprehension and reading mastery

"long-term impact on intellectual function".

Jacobson JL and Jacobson SW. Intellectual Impairment in children exposed to polychlorinated biphenyls in utero. *NEJM* 1996;335:783-789.

McCarthy Memory Scale scores

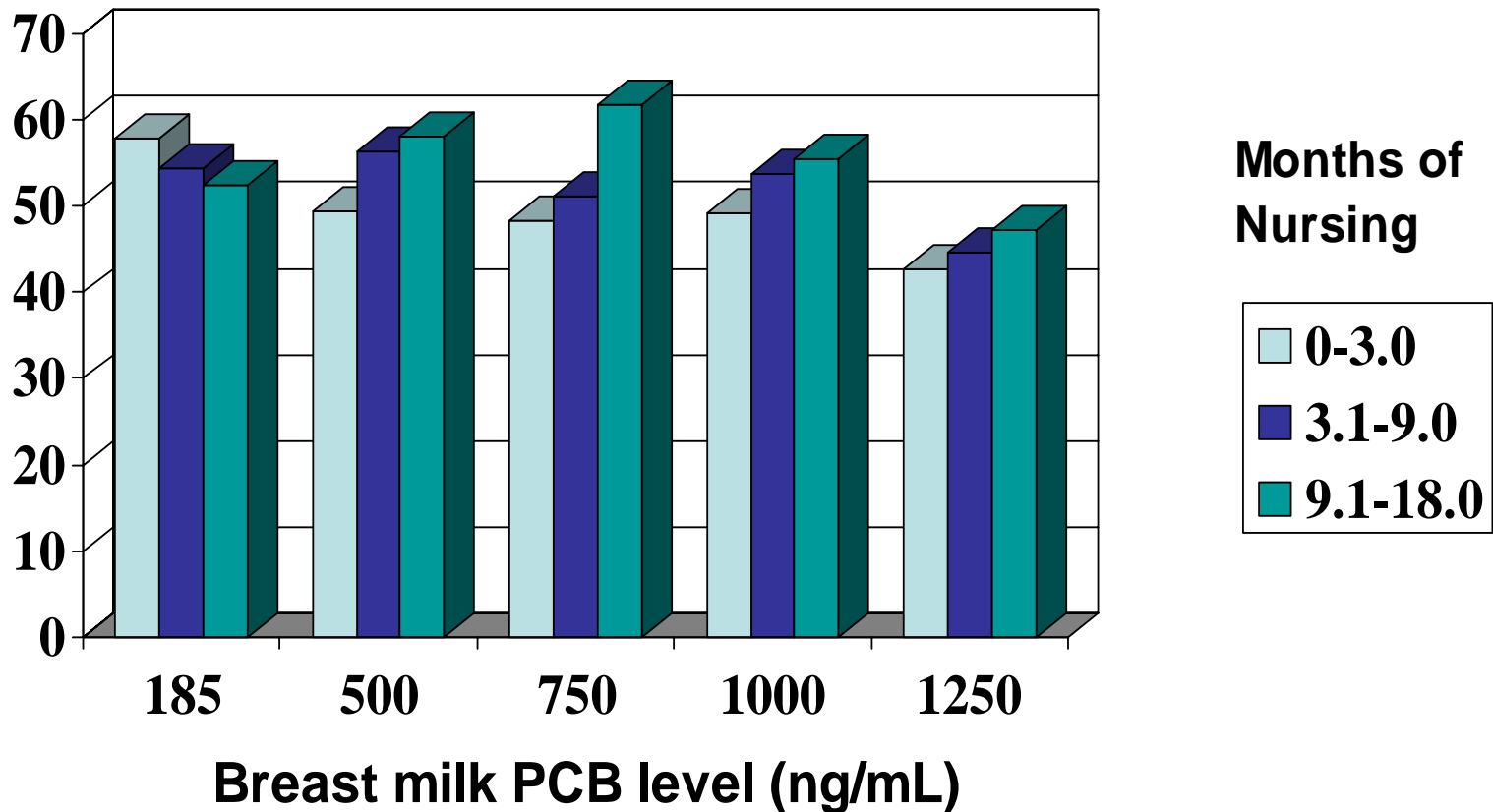
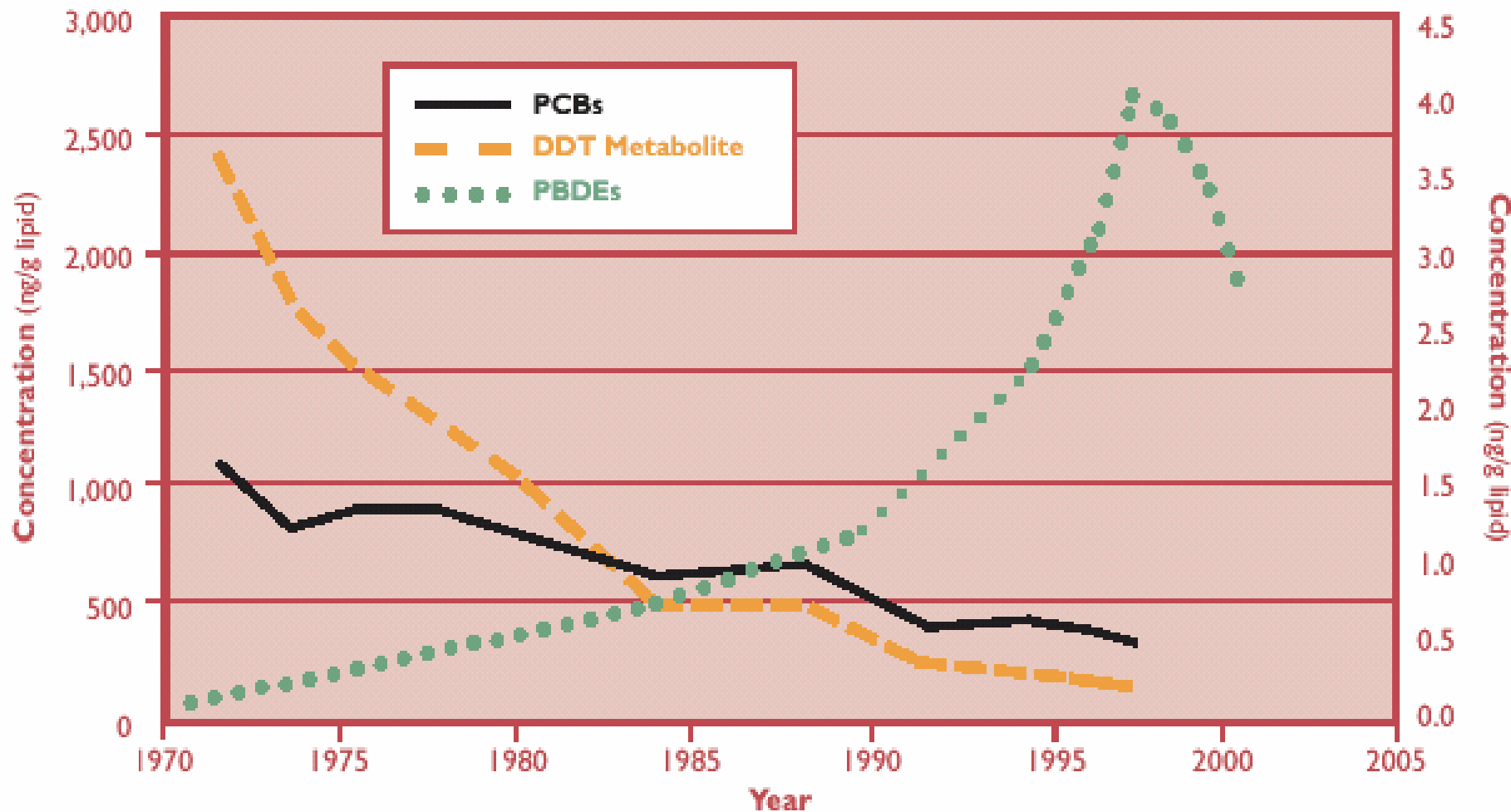
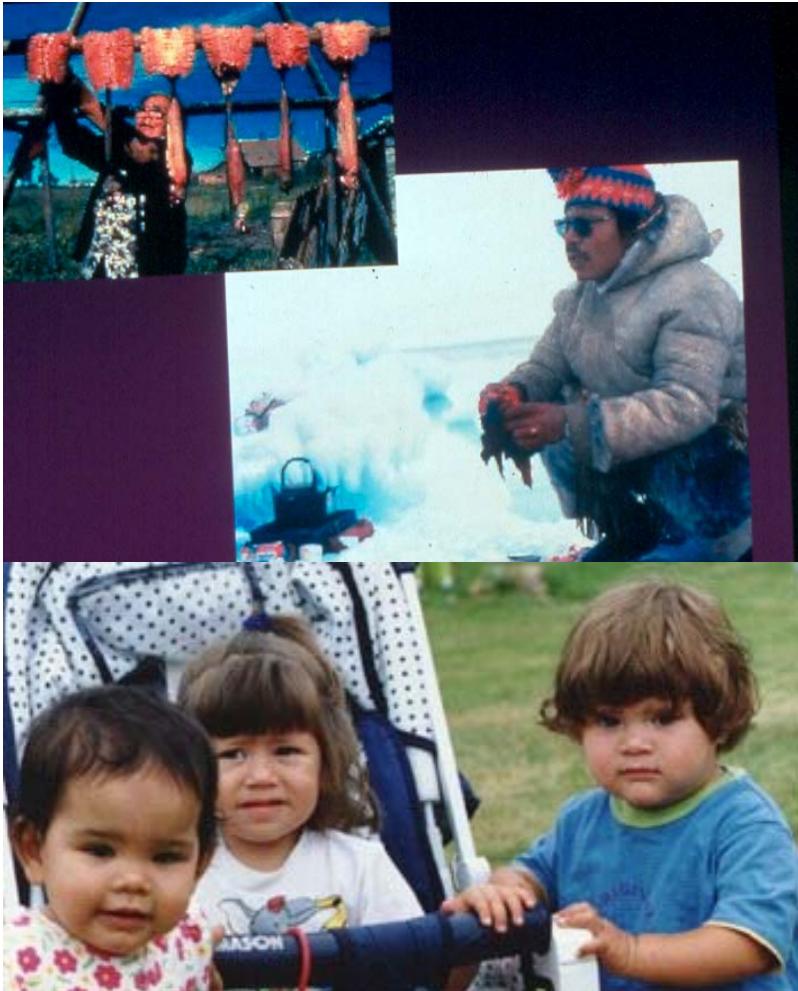


Figure 11: Trends in Chemicals in Breast Milk, Sweden



Source: Adapted from NRDC (www.nrdc.org/breastmilk/chems.asp) and Hooper and She, 2003.



- Long-range transport
- Biomagnification
- Bioaccumulation
- Traditional diet high on food chain (e.g. marine mammals)
- ↑POPs in breastmilk
- ↓birth wt; ↓immune response; ↑ear infections

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Widespread human exposure (largely food?)

- Food (infant formula; canned foods – soups and pastas)
- Food preparation (heating fluids in plastic baby bottles)

Low level BPA exposure in animals linked to:

- endocrine disruption, neurobehavioural and reproductive effects, prostate, mammary gland effects, earlier sexual maturation in females

Pregnant women may have a ↓ capacity to metabolize BPA.

- Fetal, newborn BPA detoxification system not fully developed
- **Therefore, fetus and newborn exposed to higher levels of biologically active BPA**

More Emerging Concerns

- Links to obesity and diabetes
- New mechanisms of effect?
- “Cocktail” effects
- Significant research gaps
- Hugely complex science
- Challenges to policy responses

Loren Vanderlinden
Toronto Public Health
Ivander@toronto.ca