# MIREC

Maternal-Infant Research on Environmental Chemicals

Northern Ontario Health Conference

**Paul Fredette, MD CCFP**

# Awareness of Environmental Exposures & Impacts Is Growing

- Air pollution
- Water contamination
- Harmful substances in physical structures and workplaces
- Food contamination
- Personal care products


Woodruff TJ, et al. *Fertil Steril*. 2008.
www.arhp.org/core

# Awareness of Reproductive Effects Is Growing

*"…exposures of males and females to foreign substances prior to conception can affect both their ability to conceive and the health of their offspring."*

Davis DL, et al.
*JAMA.* 1998

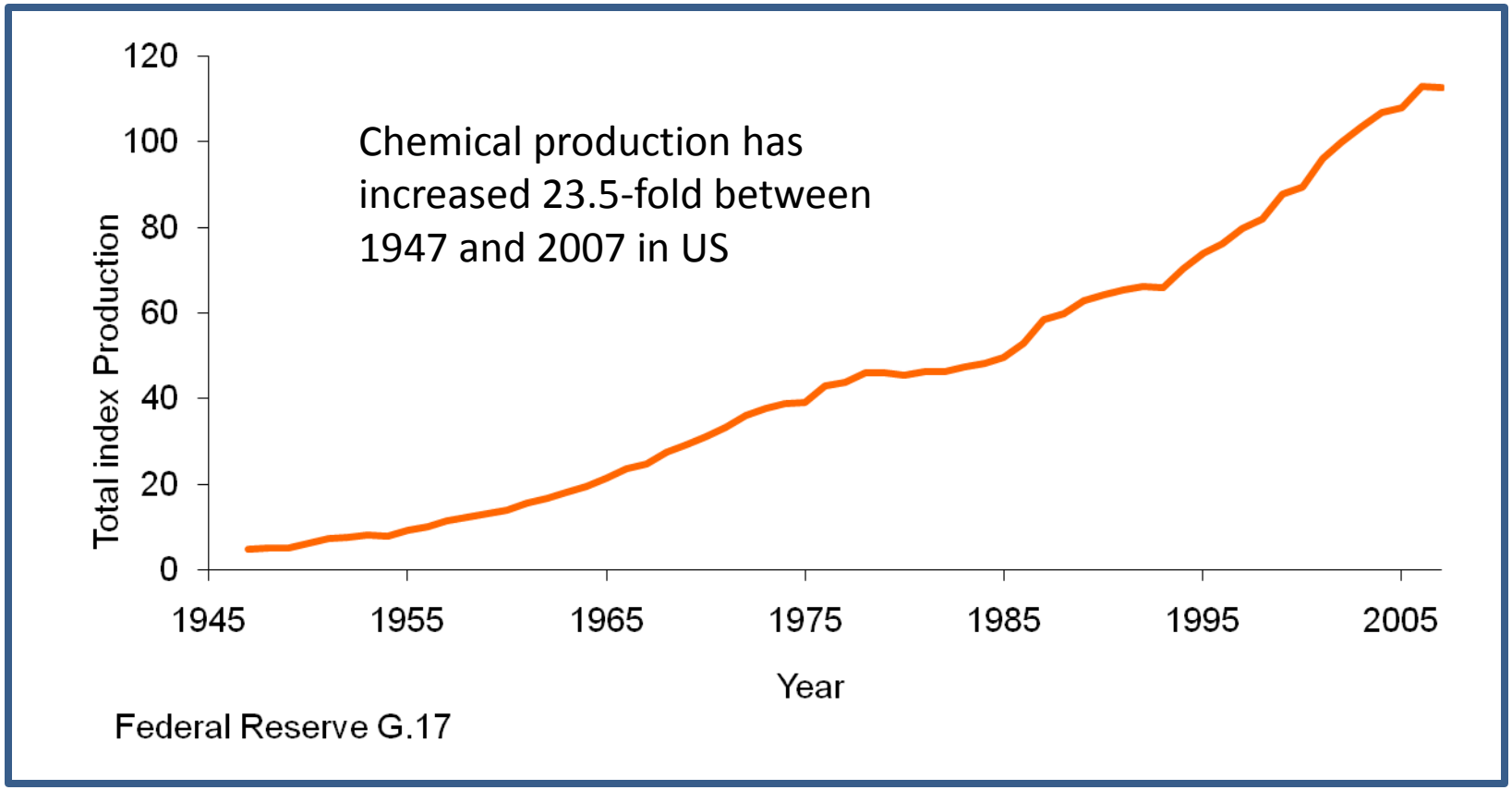
# Environmental Reproductive Health

- Interdisciplinary study of :
  - exposures to environmental contaminants (ECs),
  - during critical periods in development, and
  - their potential effects on all aspects of future reproductive health throughout the life course including:
    - conception,
    - fertility,
    - pregnancy,
    - child and adolescent development, and
    - adult health.

Woodruff TJ, et al. *Fertil Steril*. 2008.

# Environmental Contaminants (ECs)

- Since World War II, there has been a dramatic increase in human exposures to both natural and synthetic chemicals.




Woodruff TJ, et al. Fertil Steril. 2008.
Addapted from Woodruff TJ, www.ourstolenfuture.org

# Environmental Contaminants (ECs)

- In US, as of 2006…


about 1/10 have had some testing for potential health effects

However, not necessarily for reproductive/ environmental effects

Woodruff TJ, et al. Fertil Steril. 2008.

# Common Environmental Contaminants

- **Pesticides and Herbicides**
  atrazin & chlorpyrifos
- **VOCs – Volatile Organic Compounds**
  benzene, toluene, & chloroform
- **Heavy Metals**
  lead, mercury, cadmium, manganese, & arsenic
- **Air Contaminants**
  carbon monoxide, ozone, particulate

Woodruff TJ, et al. Fertil Steril. 2008.

# Common Environmental Contaminants

- **Persistent organic pollutants (POPs)**
  dioxins, polychlorinated biphenols (PCBs)
  dichlorodiphenyltrichloroethane (DDT)
  dichlorodiphenyldichloroethylene (DDE)
- **Plasticizers, Surfactants, and Flame Retardants**

- **EDCs – Endocrine Disrupting Compounds**
  exogenous substances that alters the functioning of the endocrine system
  causing adverse health effects in an intact organism or its progeny

Woodruff TJ, et al. Fertil Steril. 2008.

# Endocrine Disrupting Chemicals (EDCs)

- EDCs interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis and the regulation of developmental processes.

Woodruff TJ, et al. Fertil Steril. 2008.

# Endocrine Disrupting Chemicals (EDCs)

- EDCs encompass a variety of chemical classes, including natural and synthetic hormones, plant constituents, pesticides, compounds used in the plastics industry and in consumer products, and other industrial by-products and pollutants.

WHO. Global assessment of the state-of-the-science
Of endocrine disruptors, 2002

# Endocrine Disrupting Chemicals (EDCs)

- Some of the common EDCs include
  - Bisphenol A (BPA),
  - Phthalates,
  - Perfluorinated compounds (e.g., PFOS, PFOA)
  - Brominated flame retardants
  - Polybrominated diphenyl ethers (PBDEs)
  - Polychlorinated biphenyls (PCBs)
  - Organochlorine metabolites (e.g., DDE, aldrin, mirex)
  - and other pesticides (e.g., vinclozolin, atrazine).

Woodruff TJ, et al. Fertil Steril. 2008.

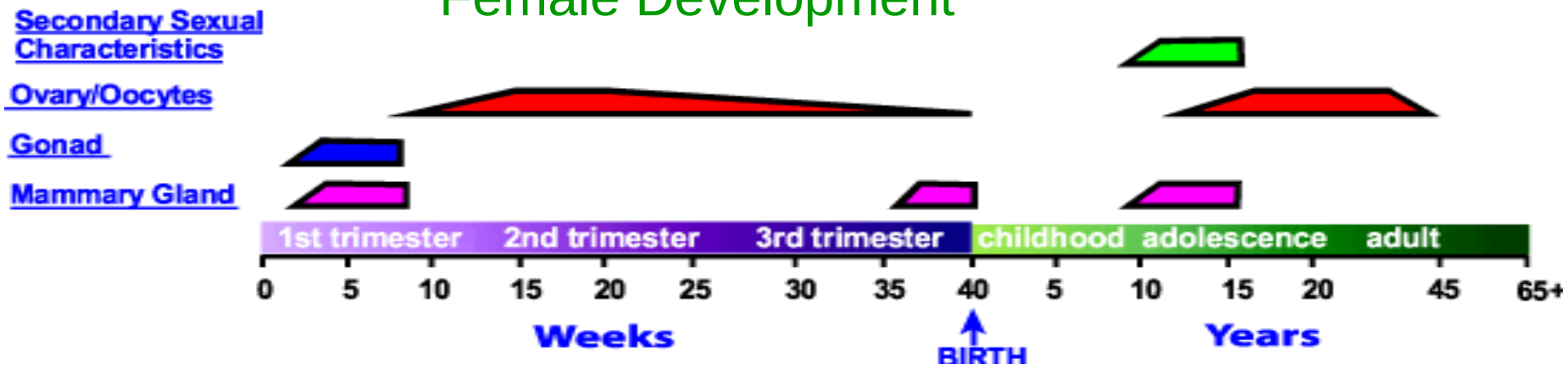
# Endocrine Disrupting Chemicals (EDCs)

- EDCs are often pervasive and widely dispersed in the environment.
- Some are persistent, can be transported long distances across national boundaries, and have been found in virtually all regions of the world.
- Others are rapidly degraded in the environment or human body or may be present for only short periods of time but at critical periods of development.

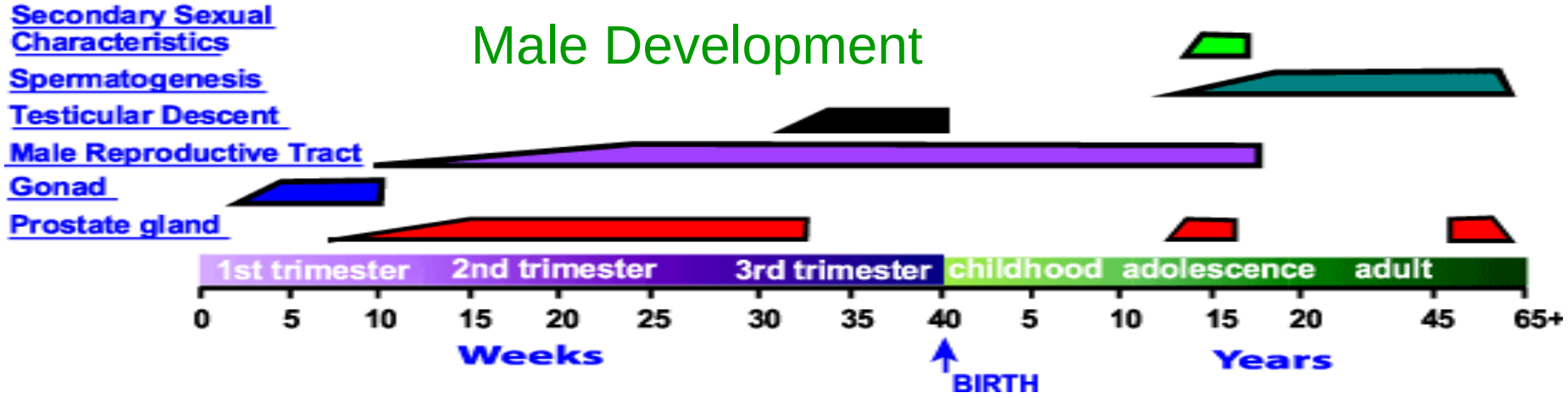
WHO. Global assessment of the state-of-the-science
Of endocrine disruptors, 2002

# Critical Windows of Sensitivity to EDCs

## Female Development




## Male Development




http://www.emcom.ca/EM/windowsfr.shtml

# Human health effects of some Endocrine Disrupting Chemicals

## EDCs

# PCBs

Found in Coolants and Lubricants in Electrical Equipment before 1977

Health Effects:

- Altered Neurodevelopment as a result of in utero exposure
- Endometriosis
- Reduced Fertility
- Decreased Semen Quality
- Miscarriage
- Altered pubertal development
- Reproductive tract malformations

Woodruff TJ, et al. *Fertil Steril*. 2008.

# Phthalates: Potential developmental and reproductive effects

- Decreased Anogenital Distance (AGD) in males
  - Disbalance in testosterone production
  - leydig cells differentiation

- Decreased AGD in 106 boys (1, 2)
- Lower post-natal surge of reproductive hormones (3)

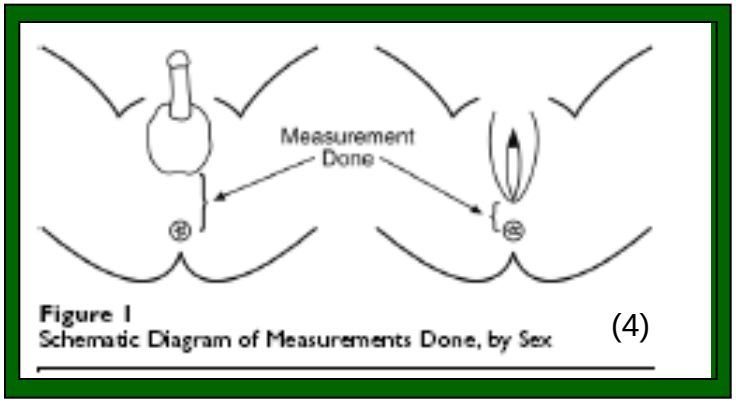



Figure 1
Schematic Diagram of Measurements Done, by Sex (4)

*(1) Swan et al, 2005, (2) Swan et al, 2008, Main et al, 2006, (3) Salazar-Martinez, 2004*

# Human Health Effects of Heavy Metals Exposures.

Lead

Mercury

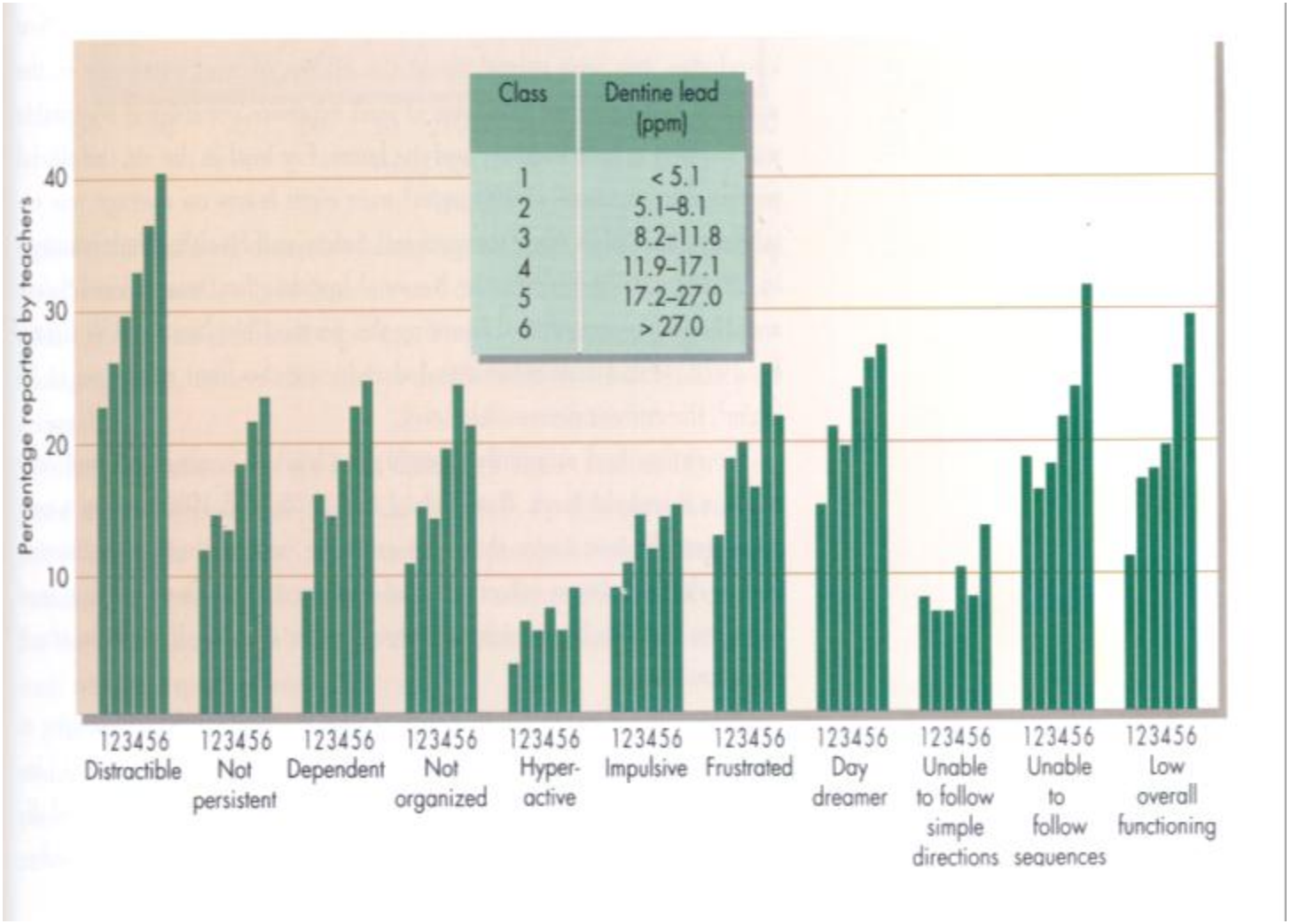
Cadmium

Arsenic

Manganese

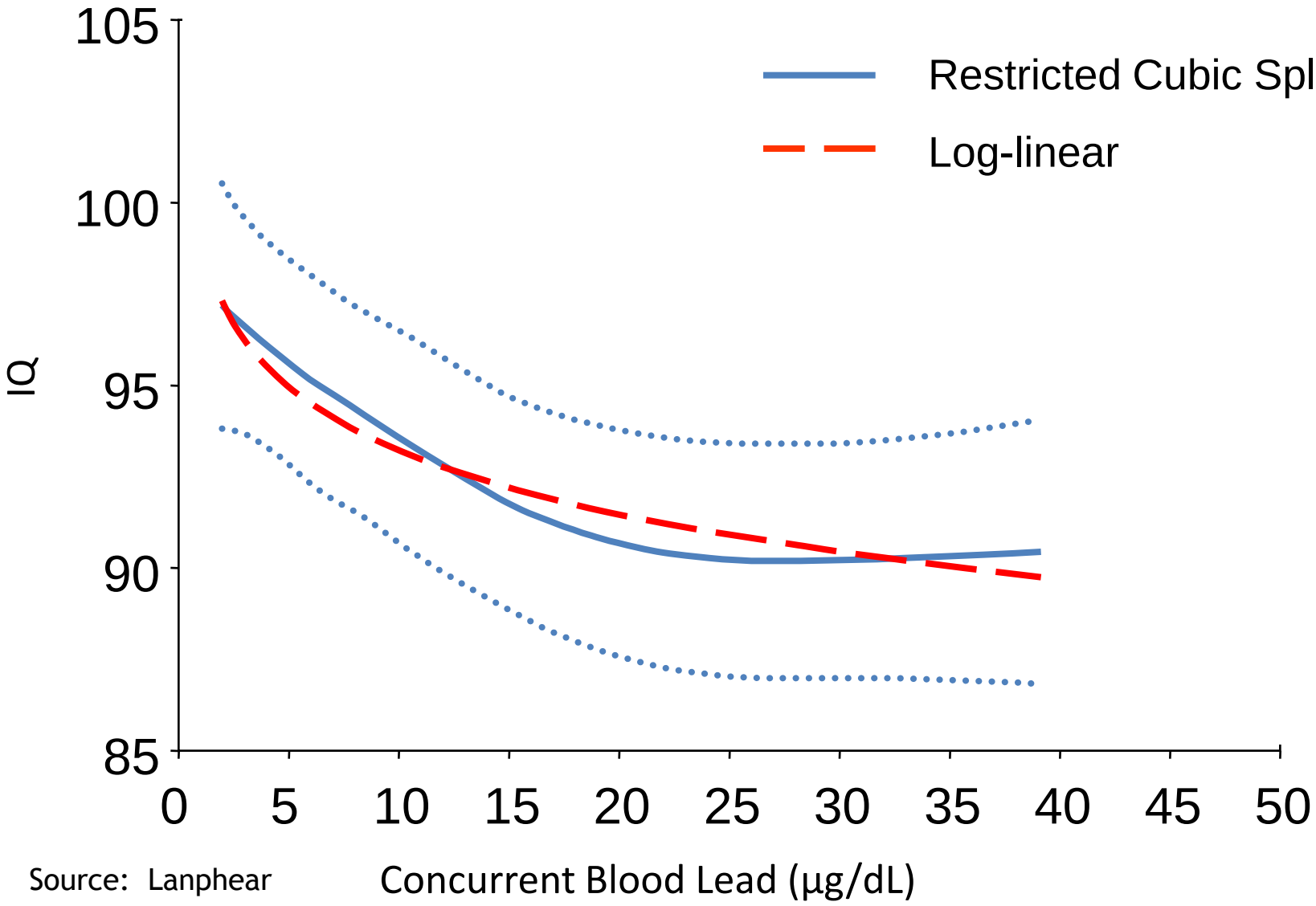
Many others…

# Lead-associated Behavioral and Emotional Problems in Children



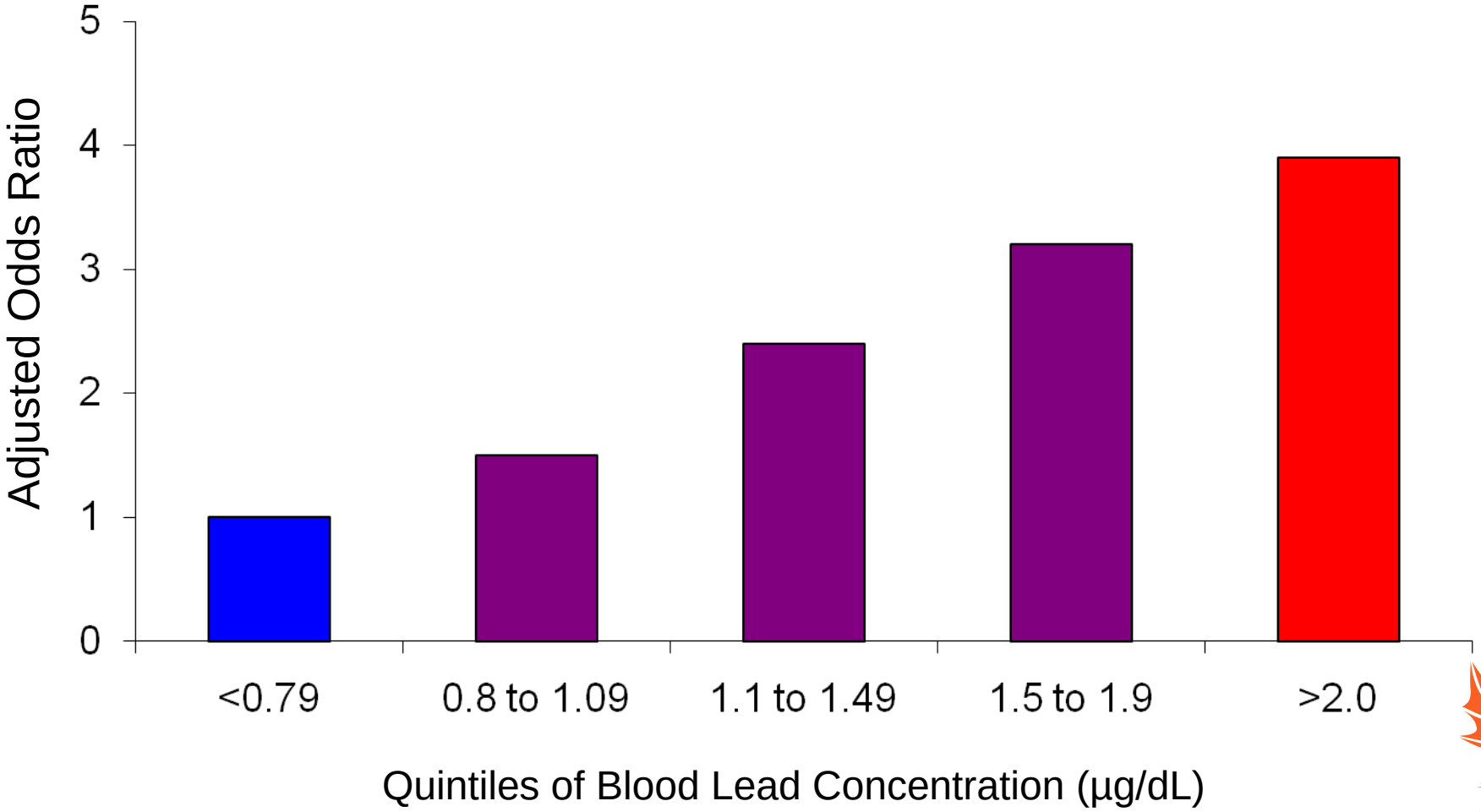

Needleman HL, et al. N Engl J Med 1979;300:689-95.

# Relationship of Concurrent Blood Lead Concentration with Children's Intellectual Function




Source: Lanphear

# Risk of ADHD by Blood Lead Levels in US Children, NHANES 1999-2002




Braun J, et al. EHP 2006;17:500-505. Adjusted for child's age, sex, race and ethnicity, preschool attendance, serum ferritin, prenatal tobacco exposure and health insurance status.

# LEAD: Burden of Disease

- Total Annual Cost in the US:
  Childhood Lead Poisoning – 43.4 billion USD.
  Childhood Asthma – 2.0 billion USD.

- Though current exposure levels are expected to have decrease in Canada in the last 25 years, lead toxicity remains a problem as Lead bioaccumulates in adult bones and becomes mobilized during pregnancy and lactation.

- Lead freely crosses the placental barrier and bone lead contributes a substantial fraction of the lead in cord blood.

- Maternal blood lead and mercury are strong and significant predictors of infant blood levels at birth.

# Sources of Exposure

| Chemical Group | Biomarkers | Uses and Sources of Exposure |
|---|---|---|
| Metals/metalloids | Lead | Gasoline, paint, dust, drinking contaminated water |
| | Mercury | Batteries, fluorescent light bulbs, fish consumption, dental amalgams |
| | Cadmium | Pigments, municipal waste incineration, cigarette smoke |
| | Arsenic | Pressure-treated wood, drinking contaminated water |
| | Manganese | Burning of fossil fuels |
| Plasticizers | Bisphenol A (BPA) | Polycarbonate food containers, refillable water bottles, metal food and beverage cans, dental sealants |
| | Phthalate metabolites | Polyvinyl chloride flooring, toys, detergents, personal care products, food packaging, dust |

# Sources of Exposure

| Chemical Group | Biomarkers | Uses and Sources of Exposure |
|---|---|---|
| Surfactants | Perfluorinated compounds (e.g., PFOS, PFOA) | Non-stick cookware, stain repellent furnishings, fast-food packaging |
| Pesticides | Organophosphate metabolites | Insecticides, food contaminant |
| Flame Retardants | Polybrominated diphenyl ethers (PBDEs) | Electronic equipment, furniture, construction materials, textiles, foods, house dust |
| Persistent Organic Pollutants (POPs) | Polychlorinated biphenyls (PCBs) | Industrial equipment, food |
| | Organochlorine metabolites (e.g., DDE, aldrin, mirex) | Insecticides, food contaminant |
| Tobacco Smoke | Cotinine | Active and passive exposure to tobacco smoke |

# Epidemiological evidence for causal relationships between reproductive and child health outcomes and environmental chemical contaminants.


"There is a great need for population-based, multidisciplinary and collaborative research on the many relationships supported by inadequate evidence, as these represent major knowledge gaps".

Wigle DT, **Arbuckle TE**, Turner MC, Bérubé A, Yang Q, Liu S, Krewski D. J Toxicol Environ Health B Crit Rev. 2008 May;11(5-6):373-517. Review.

# MIREC

Maternal-Infant Research on Environmental Chemicals

# Funding Agencies

Health Canada
Santé Canada


# Investigators

| **Principal Investigators:** | |
|---|---|
| Tye Arbuckle, PhD | Senior Epidemiologist & Research Scientist, Health Canada |
| William D. Fraser, M.D | Professor and Chair Obstetrics and Gynecology Université de Montréal & CHU Ste-Justine |

**Co-investigators:**

Jean-Philippe Weber, Melissa Legrand, Premkumari Kumarathasan, Renaud Vincent, Zhong-Cheng Luo, Adrienne Ettinger, Robert Platt, Grant Mitchell, Kevin Cockell, Maya Villeneuve, Sheryl Tittlemier, Pierre Julien, Denise Avard, Nick Hidiroglou, Hope Weiler, Alain LeBlanc, **Site Investigators:** Peter von Dadelszen (Vancouver), Michael Helewa (Winnipeg), Mathiew Sermer (Toronto), Warren G. Foster (Hamilton), Gregory Ross and Paul Fredette (Sudbury), Graeme Smith (Kingston), Mark Walker (Ottawa), Roberta Shear (Montreal), and Linda Dodds (Halifax).

# Study coordinating centre

CHU Sainte-Justine
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*Pour l'amour des enfants*

Université de Montréal

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# Objectives

- To obtain national-level data on maternal and neonatal exposure to priority environmental contaminants
- To obtain Canadian data on smoking behaviour and exposure to tobacco smoke (active and passive) in pregnancy
- To determine if heavy metal exposure is related to elevated maternal blood pressure, hypertension, altered sex ratio and fetal growth restriction

# Objectives

- To obtain contemporary levels of priority environmental chemicals, selected nutrients and relevant immunoprotective endpoints in mature human milk
- To obtain contemporary levels of maternal hair-mercury
- To characterize dietary exposure of breastfed infants and allow for time-trend analyses of those analytes which were included in previous human milk surveys

# Study Design

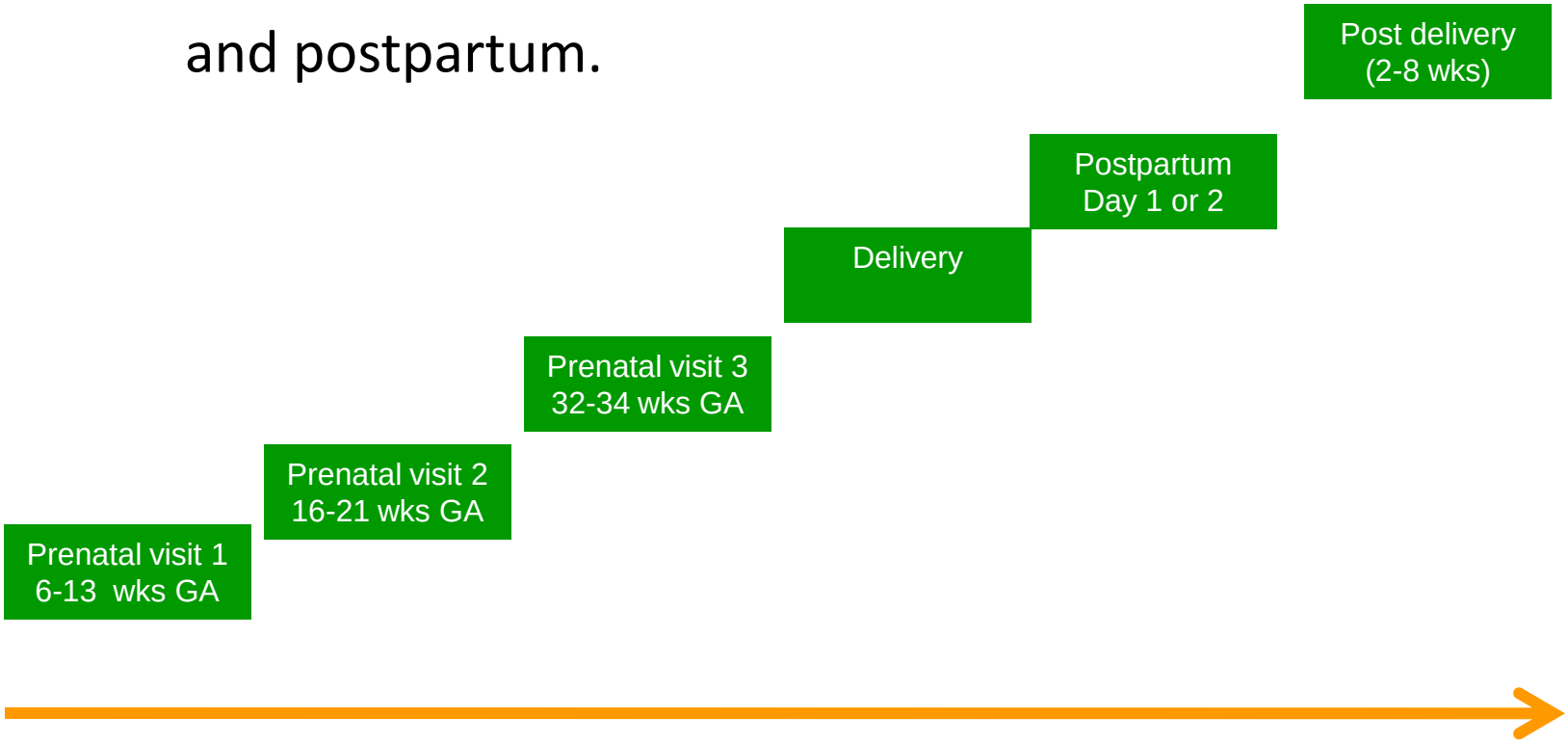
# Study population
# Eligibility criteria

- Inclusion Criteria

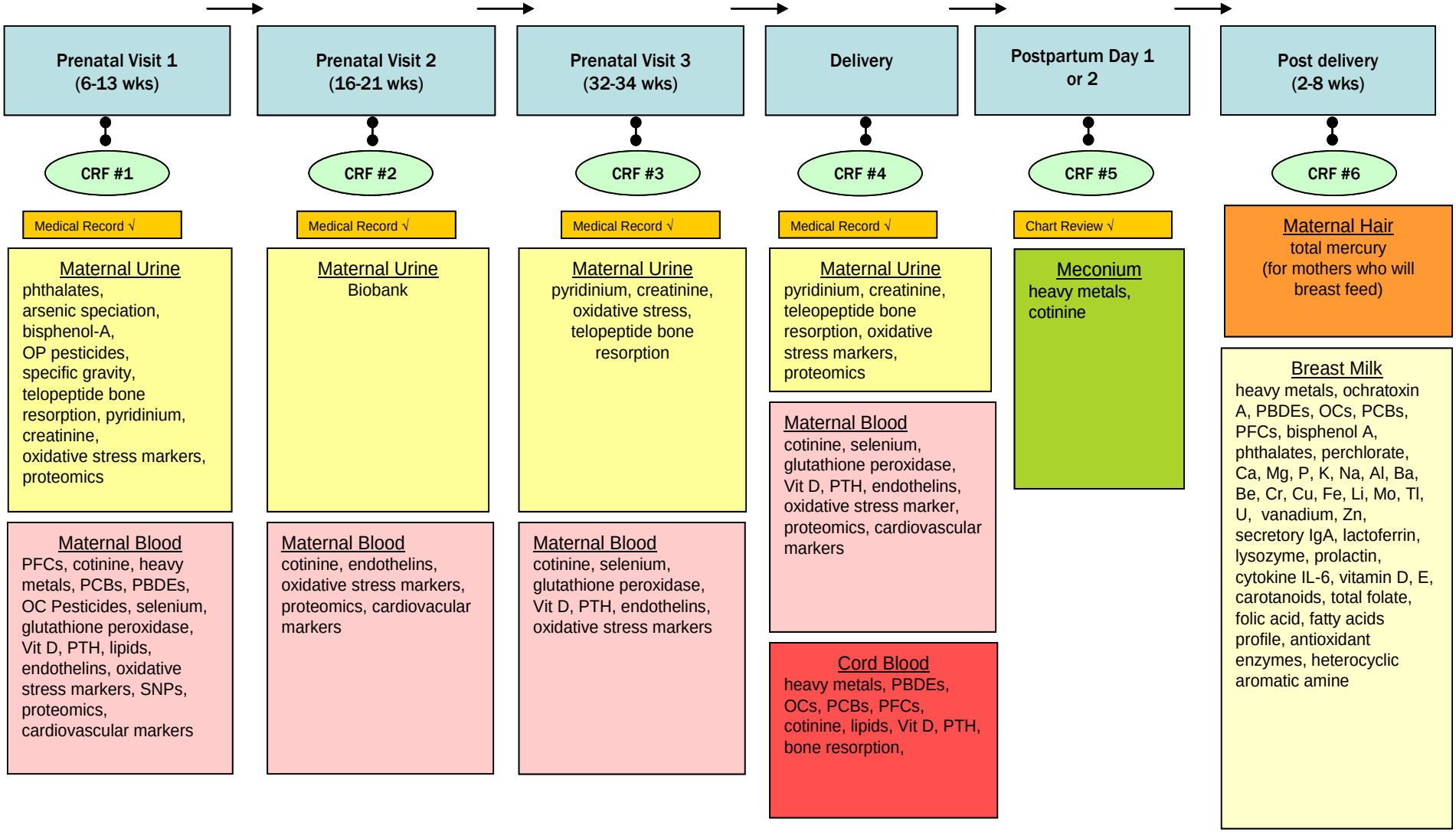
1. The woman is pregnant between $6^{0/7}$ and $13^{6/7}$ completed weeks
2. Age $\geq$ 18 years
3. Speaks a language known by the medical staff (French or English)
4. Plans to deliver in a study participating hospital
5. The woman is able to understand and sign a consent form

# Study Design

- 2,000 pregnant women recruited during 1st trimester
- 6 points of contacts which span each trimester of pregnancy, delivery, and postpartum.



# Data Collection



# Nutritional Data Collected

- **First Trimester**
  - Supplements (product names)
    - Prenatal vitamins
    - Folic acid supplements
    - Other supplements
  - Beverages (milk, water, juice, tea, coffee, alcohol)
  - Species of fish
- **Second Trimester** (take home questionnaire)
  - Within past 24 hours

    Name of product, amount taken, frequency
  - During last 30 days

    Name of product, amount taken, frequency

# Nutritional Data Collected

- **Second Trimester (continued)**
  - Food Frequency Questionnaire
    - During the past month
    - Frequency
    - Serving size
    - Primarily focusing on calcium and iron sources
- **Third Trimester**
  - Beverages (milk, water, juice, tea, coffee, alcohol
  - Species of fish
- **Lactational questionnaire**
  - Fish species
  - Beverages
  - Nutrient supplements while breastfeeding

# Other Data Collected

- 1st and 3rd Trimesters
  - Smoking (active and passive)
  - Socio-demographics
  - Obstetrical history
  - Employment
  - Environmental exposures (work, home)
  - Physical activity
  - Sunlight exposure
  - Anthropometry
  - Blood pressure
- Pregnancy outcomes

# Additional and Future Research

- **Biobank** of maternal and infant biospecimens (blood, urine, meconium, cord blood, maternal hair, breast milk)
- At the conclusion of the study, there will be approximately 65% of the aliquots in the MIREC biobank.
- Long-term storage of these valuable samples in the biobank will be used for future research on environmental chemicals and maternal and infant health.

# Additional and Future Research

## MIREC-ID:
## Effects of ECs on Infant Development

- Health Canada is now providing funding to follow the infants from 0 to 6 months of age.
- Growth, Sexual & Sensory Development.
- Correlations will be made with in utero exposures to the variables quantified in MIREC.

Co-PIs: Gina Muckle, Tye Arbuckle, William Fraser, Bruce Lanphear, Jean Seguin

# MIREC-ID

| Tests performed on the infant | Birth | Six months |
|---|---|---|
| Sexual development | | |
| Genital clinical exam | √ | |
| Pigmentation of the areolar and scrotum skin | √ | √ |
| Steroid hormones | Biobank | |
| Growth | | |
| Weight | √ | √ |
| Head, chest and abdominal circumference | √ | √ |
| Height | √ | √ |
| Back and arm skinfold thickness | √ | √ |

# MIREC-ID

| Tests performed on the infant | Birth | Six months |
|---|---|---|
| Neurobehavioral/Sensory development | | |
| Hearing screening (tympanometry, otoacoustic emission) | | √ |
| Electrophysiological testing: brainstem auditory evoked potentials 2 (BAEP) | | √ |
| Eye examination | | √ |
| Teller Acuity Cards: TAC | | √ |
| Visual reinforcement audiometry (VRA) | | √ |
| Electrophysiological testing: visual evoked potentials (VEP) | | √ |

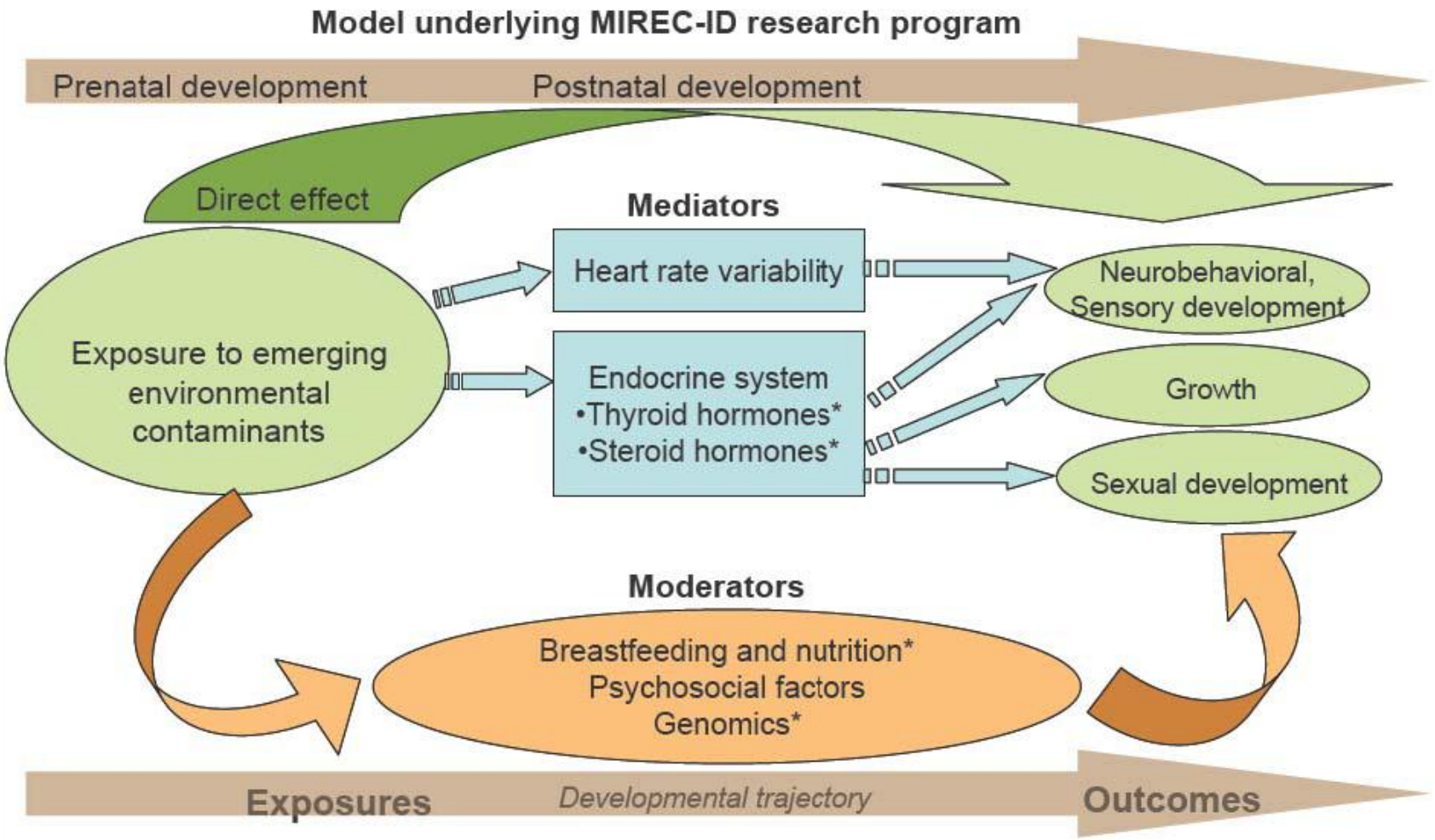
# MIREC-ID

| Tests performed on the infant | Birth | Six months |
|---|---|---|
| Mechanisms of action, mediators and moderators | | |
| Heart rate variability (HRV) and vagal tone | | √ |
| TSH, total T4, free T4, total T3, iodine, TTR | Biobank | |
| Other parameters: | Biobank | |
| long chain polyunsaturated fatty acids (LCPUFAs) | | |
| Trans fatty acids (TFA) | | |
| iron, zinc, copper, selenium, iodine | | |
| vitamin A, C, E and folate | | |
| Genomics | | |

# MIREC-ID

| Maternal Variables | Delivery | Six months |
|---|---|---|
| Mechanisms of action, mediators and moderators | | |
| Breastfeeding | √ | √ |
| Postnatal Smoking | √ | √ |
| Alcohol use | √ | √ |
| BMI | | √ |
| Questionnaire (psycho-social factors and maternal stress) | | √ |
| TSH, total T4, free T4, total T3, iodine, TBG, TPO-Ab | Biobank | |

# MIREC-ID


Model underlying MIREC-ID research program
Prenatal development
Postnatal development
Direct effect
Mediators
Heart rate variability
Endocrine system
•Thyroid hormones*
•Steroid hormones*
Exposure to emerging environmental contaminants
Neurobehavioral, Sensory development
Growth
Sexual development
Moderators
Breastfeeding and nutrition*
Psychosocial factors
Genomics*
Exposures
Developmental trajectory
Outcomes

# Additional and Future Research

MIREC-???

# Acknowledgments


- Participants – Northern Health Research Conference
- All Investigators - Dr. William Fraser
- Health Canada
- Ontario Ministry of the Environment
- Canadian Institutes of Health Research
- Medicor – Nurses & Research Assistants
- Study Coordinating Centre – Sainte Justine Hospital
- Sudbury Regional Hospital
- NOSM – Dr. Greg Ross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Ontario

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

# Thank you!

For more information visit:

www.mirec-canada.ca