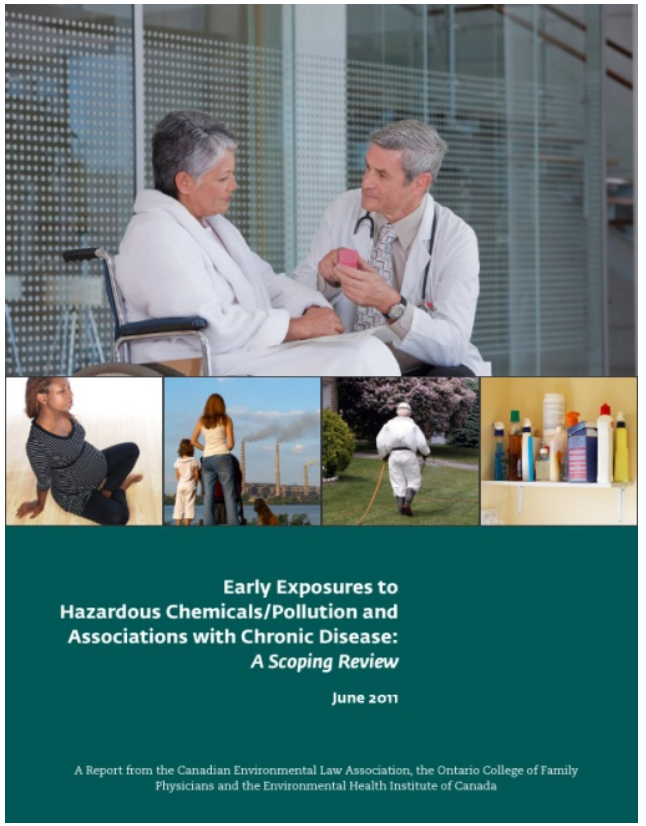
Troubling Science, High Stakes Risks:
Early Environmental Exposures and Chronic Disease - Obesity and Diabetes



Presentation to:

New Brunswick Environmental Network

New Maryland Centre, Fredericton, NB

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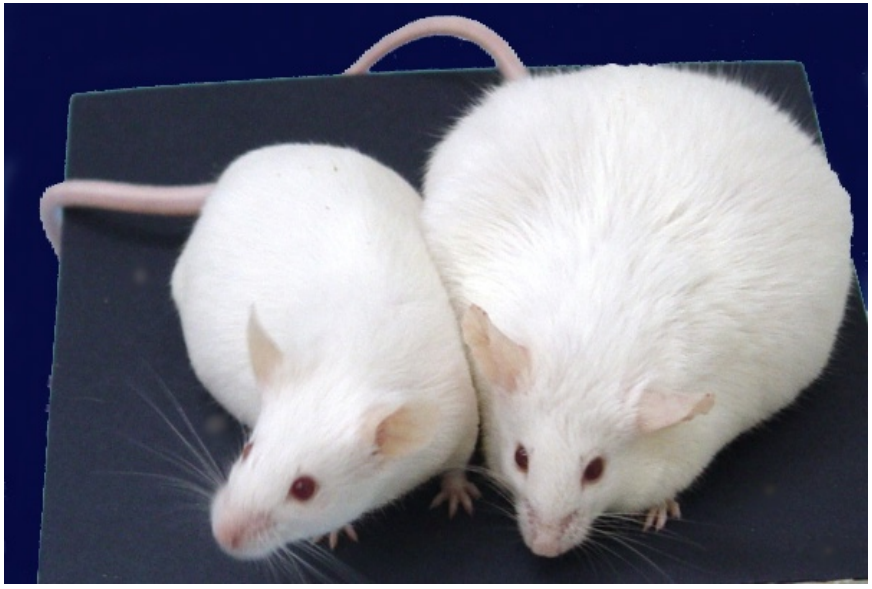
Canadian Environmental Law Association

Canadian Environmental Law Association

EQUITY. JUSTICE. HEALTH.

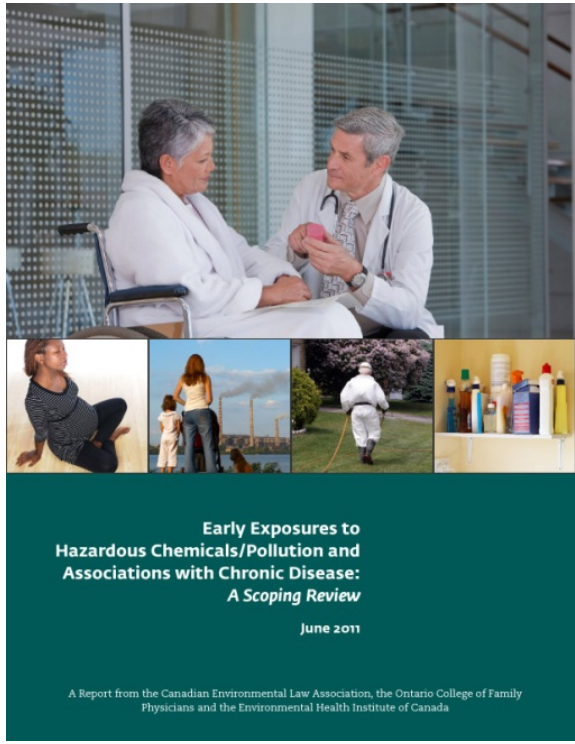
Outline

1. **Context and Trends**
2. DOHaD Concept
3. Endocrine Disruption
4. Multiple Risk Factors



Context – Chronic Disease In An Aging Population

- High prevalence and/or rising incidence:
  - *Cardiovascular disease*
  - *Dementia*
  - *Obesity and diabetes*
  - *Cancer*
- Projections: millions affected; billions in costs
- Disproportionately worse health and shorter lifespan among those living in poverty



Diabetes and Obesity – Greater Risk of Death and Disease

Adults with Type 2 Diabetes have greater risk of:

- mortality (2x)
- hypertension, heart attack or stroke (3x)
- heart failure (4x)
- chronic kidney disease (6x)
- lower limb amputations (19x)

Adult obesity brings greater risk of:

- mortality (2.5X)
- cardiovascular disease (4X)
- Type 2 Diabetes (5X)
- hypertension, gall bladder disease, some cancers

Definitions

Obesity and Overweight

- Obesity: Body Mass Index above 30 kg/m^2
- Overweight: BMI between 25 and 30
- Calculation from height and weight; different calculation for children
- http://www.cdc.gov/healthyweight/assessing/bmi/index.html (useful calculator)

Diabetes (Type 2 – 90% of cases)

- Chronic condition; body does not produce enough and/or does not properly use its own insulin (intolerance/resistance).
- Result: chronic hyperglycemia (high blood sugar), in turn adversely affecting how the body metabolizes carbohydrates, fats, and proteins.
- Insulin: hormone produced in the pancreas that enables cells to absorb glucose and transform it into energy. Also involved in blood vessel elasticity, cognition, and whole-body homeostasis.

Metabolic Syndrome ("pre-diabetes")

- 3 out of 5 of: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol levels, elevated blood pressure, and elevated fasting glucose levels

Obesity and Type 2 Diabetes – High Prevalence and Rising Incidence

Type 2 Diabetes

- Projected for 2012 - ~2.8 million Canadians
- Annual increase of ~6% and overall increase of ~25% since 2007.
- Biggest ↑ is in young adults.
- **Higher prevalence among the poor** (low income 4x > highest income; First Nations 3 to 5X > gen'l pop'n)

Obesity

- Similar increase; approx. 25% of pop'n esp. among children, and much higher in First Nations
- If include both overweight and obesity – over 50% of the population

Metabolic Syndrome/"pre-diabetes"

- Approx. 25% of pop'n

Changes in Built Environment and Food System

Land use planning and the built environment:

- car-dependence, resulting air pollution and climate change, sedentary lifestyles

Food and the food system:

- Mechanized, centralized and fossil fuel-dependent food production system: major contributor to air pollution, climate change, and glut of inexpensive unhealthy food
- Changes in balance of fats in animals and in baked goods
- Loss of micronutrients
- Diet shift to excessive fat, salt, sugar as fructose, refined carbs, lack of whole grains, inadequate fruits and vegetables
- Chemicals in containers and packaging

All of which tends to be inequitably felt/distributed

Chemical Production and Pollution since WWII

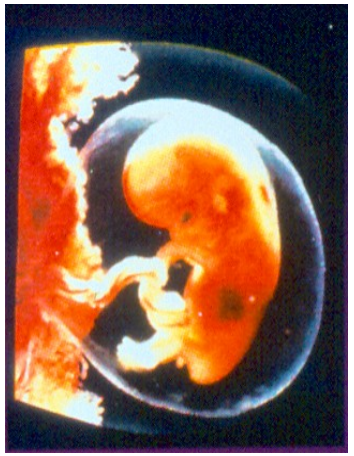
Over 80,000 chemicals in US commerce

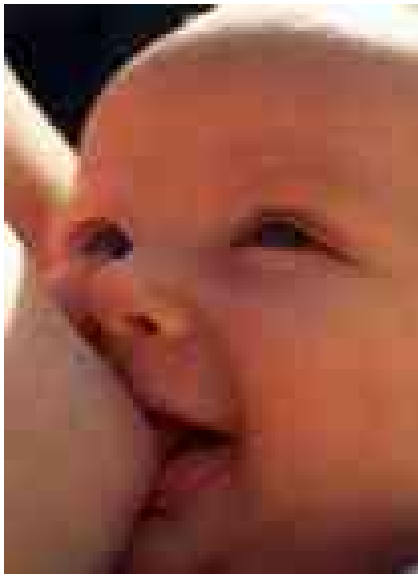
Huge increases in air and water pollution albeit reductions in recent decades

Big increase in exposures from products

Biomonitoring results confirm widespread low-level exposure

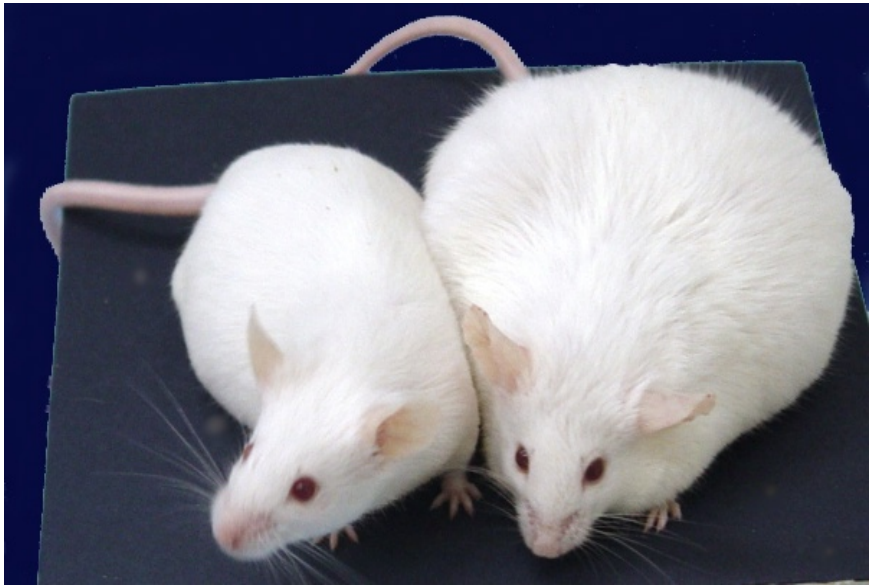
- All carry low levels of many different chemicals
- Highest levels in children
- Breast-fed babies at “top of food chain.”
- (Results should not deter breastfeeding)
- Poverty increases exposure risk





Outline

1. Context and Trends
2. **DOHaD Concept**
3. Endocrine Disruption
4. Multiple Risk Factors



The Developmental Origins of Health and Disease (DOHaD)

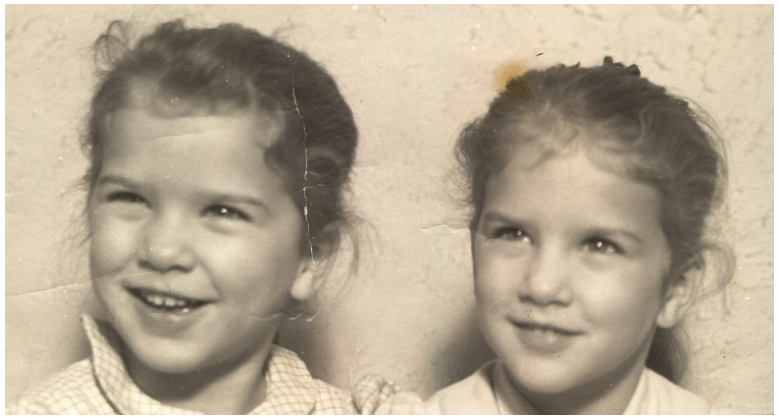
- Early life – sets trajectory for lifelong health
- Strong evidence
- Fetal under-nutrition and major risk factors for latent:
  - cardiovascular disease
  - diabetes
  - metabolic syndrome

Concept is expanding rapidly to include early environmental exposures

Tulip bulb puree was one response to the Dutch famine of 1944

DOHaD Mechanisms: Epigenetics

- Gene-environment interactions - *heritable changes* caused by the activation and deactivation of genes with no change in the underlying DNA sequence.
- Cellular differentiation during development relies strongly on epigenetic vs genetic inheritance.



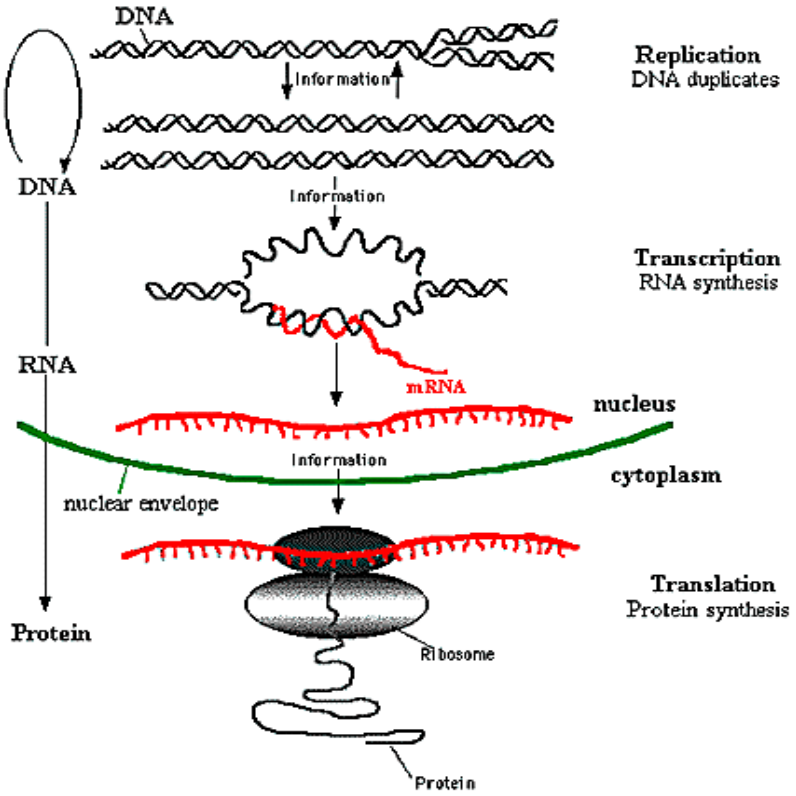


Image source: http://www.accessexcellence.org/RC/VL/GG/central.php

Epigenetic changes resulting from fetal under-nutrition

DOHaD evidence indicates:

- Loss of structural or functional capacity in cells of kidney, heart, pancreas, skeletal muscles
- Permanent alteration of developmental pattern of cellular proliferation and differentiation. Vulnerability can also be passed on to future generations.
- **E.g., for diabetes risk**: epigenetic changes permanently alter the expression of genes governing:
  - development and functioning of the pancreas
  - metabolic processes involved in glucose regulation and insulin secretion
  - Both contribute to increased latent risk of T2D
  - Can start with obesity and metabolic syndrome

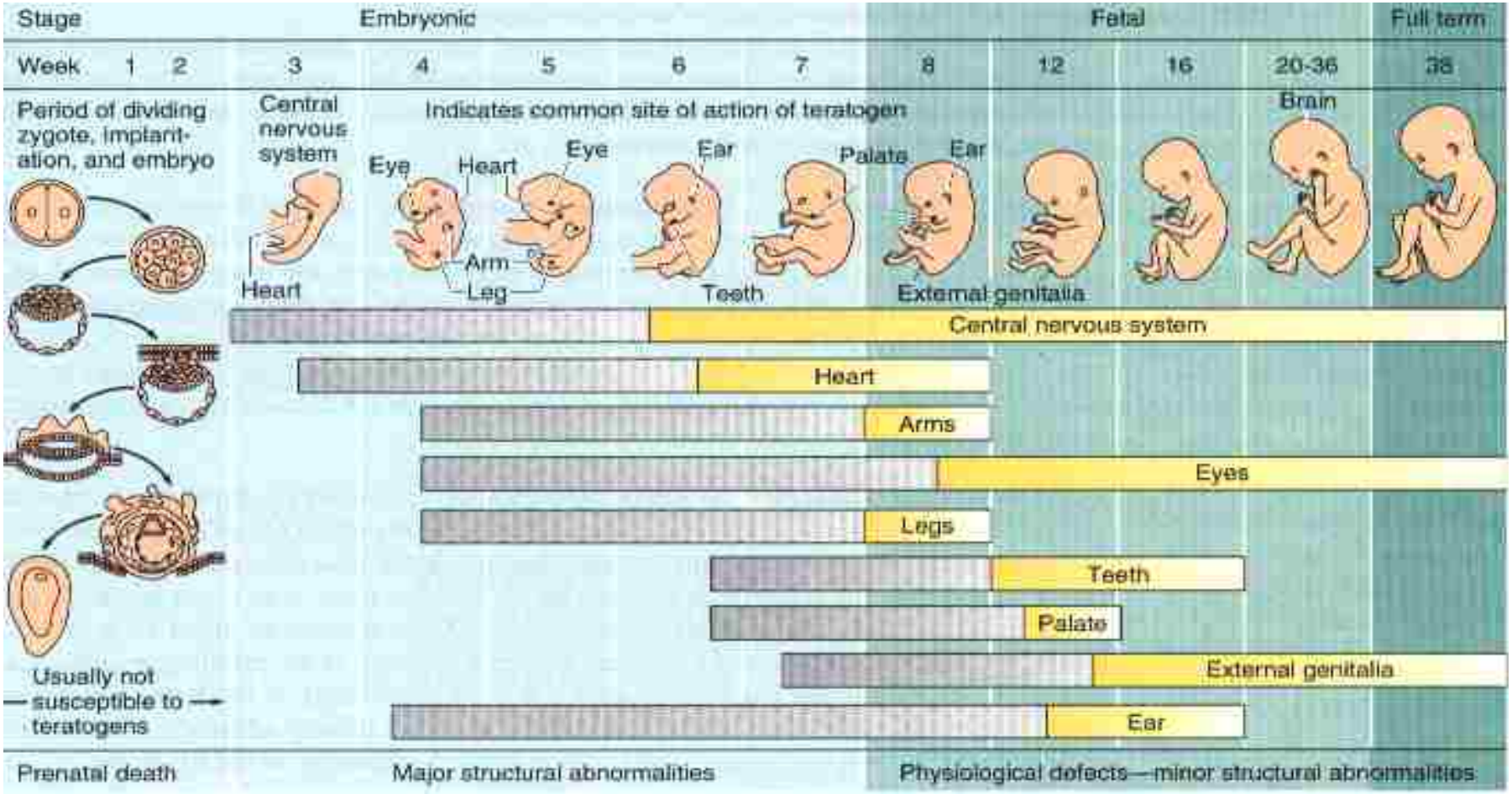
Dutch Famine Studies – Importance of Timing

First Trimester → → → → → →	Second Trimester → → → → → →	Third Trimester → → → → → →
• Glucose intolerance • Cardiovascular disease • Hypertension • Dyslipidemia • Obesity • Affective Disorders	• Glucose intolerance • Pulmonary disease • Renal disease	• Glucose intolerance

Timing of in utero nutritional deprivation is associated with different later-life disease outcomes

Roseboom et al, 2001, 2006 in Boekelheide et al 2012 Predicting Later-Life Outcomes of Early-Life Exposures. *Env. Health Perspect*. 120(10):1353-61

Prenatal Windows of Vulnerability



- Developing body systems and organs are highly susceptible to harm
- First trimester: structural abnormalities/birth defects
- Second and third trimesters: physiological defects (e.g. brain function/later behaviour) and minor structural abnormalities

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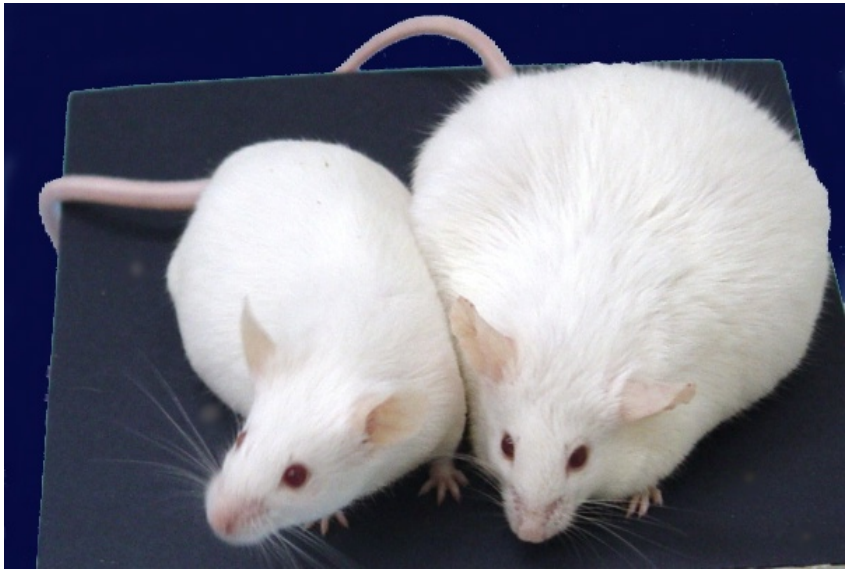
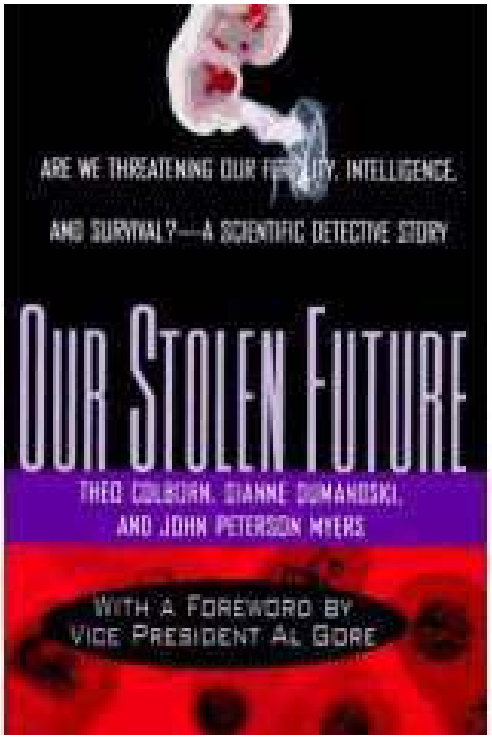
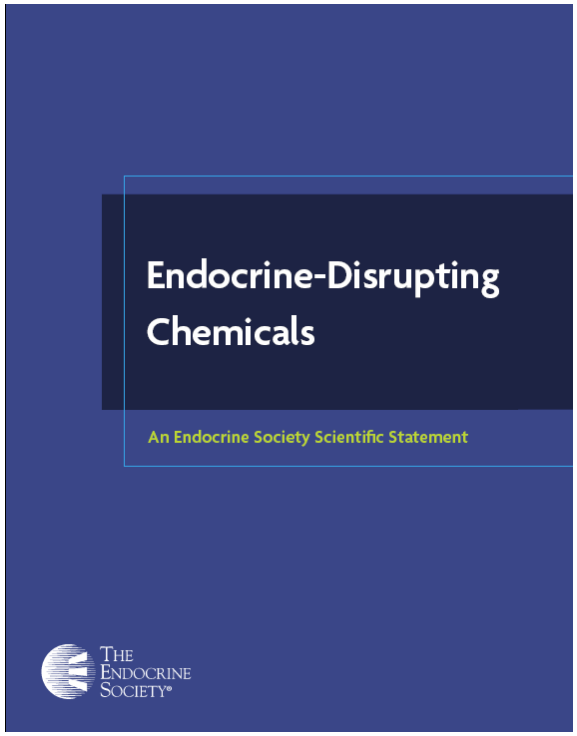


Science of Endocrine Disruption

- 1991 - Dr. Theo Colborn and 21 scientists coined the term “endocrine disruption”
- 1996 - *Our Stolen Future* – multi-disciplinary observations ; science of endocrine disruption
- 2009 - Endocrine Society Scientific Statement
- 2012 – ED Chemicals and Public Health: End. Soc. Statement of Principles



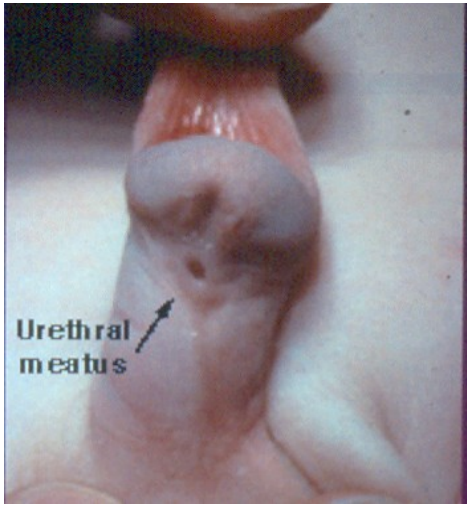


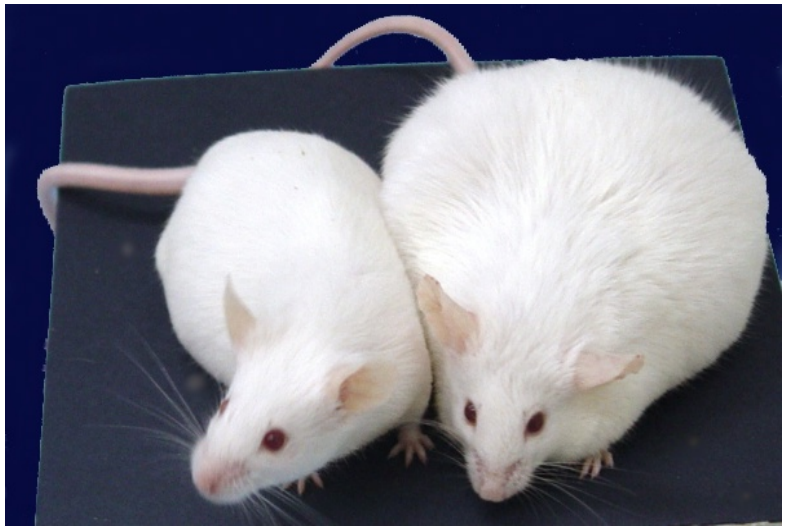
“The rise in the incidence in obesity matches the rise in the use and distribution of Industrial chemicals that may be playing a role in generation of obesity, suggesting that endocrine disrupting chemicals may be linked to this epidemic.”

Endocrine Society Scientific Statement, 2009

Key Observations: Characteristics of Endocrine-Disrupting Chemicals

- Low dose, often non-linear, effects
- Persistent and latent effects, timing matters
- Wide range of effects
- Ubiquitous exposure





Endocrine-Disrupting Chemicals

HERBICIDES: 2,4,-D, 2,4,5,-T, Alachlor, Amitrole, Atrazine, Linuron, Metribuzin, Nitrofen, Trifluralin

FUNGICIDES: Benomyl, Ethylene thiourea, Fenarimol, Hexachlorobenzene, Mancozeb Maneb, Metiram –complex, Tri-butyl-tin, Vinclozolin, Zineb

METALS: Cadmium, Lead, Manganese, Methyl mercury

INSECTICIDES: Aldicarb, beta-HCH, Carbaryl, Chlordane, Chlordecone, DBCP, Dicofol, Dieldrin, DDT and metabolites, Endosulfan, Heptachlor/H-epoxide, Lindane (gamma-HCH) , Malathion, Methomyl, Methoxychlor, Oxychlordane, Parathion, Synthetic pyrethroids, Transnonachlor, Toxaphene

INDUSTRIAL CHEMICALS: Bisphenol –A, Polycarbonates, Butylhydroxyanisole (BHA), Chloro-& Bromo-diphenyl, Dioxins, Furans, Nonylphenol, Octylphenol, PBDEs, PCBs, Pentachlorophenol, Penta-to Nonylphenols, Perchlorate, PFOA, p-tert-Pentylphenol, Phthalates, Styrene

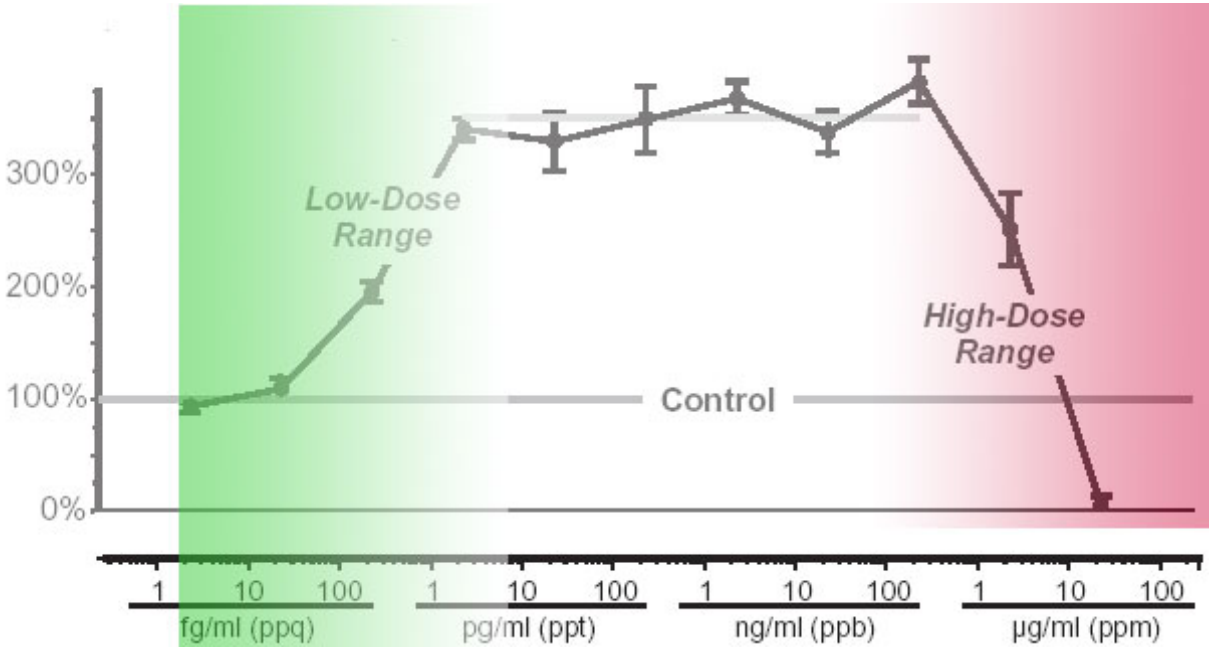
Testosterone synthesis inhibitor, Estrogen receptor agonist, Thyroid hormone disruptor, Androgen receptor antagonist (source: Birnbaum, 2010)

EDCs: Scientific Evidence Creates Fundamental Challenge to Regulatory Approaches

Assumptions: Chemicals have toxicity thresholds; Linear dose-response

Yet: U-shaped dose-response curves very common

Effects at low dose cannot be predicted by observations at higher dose



Obesogens

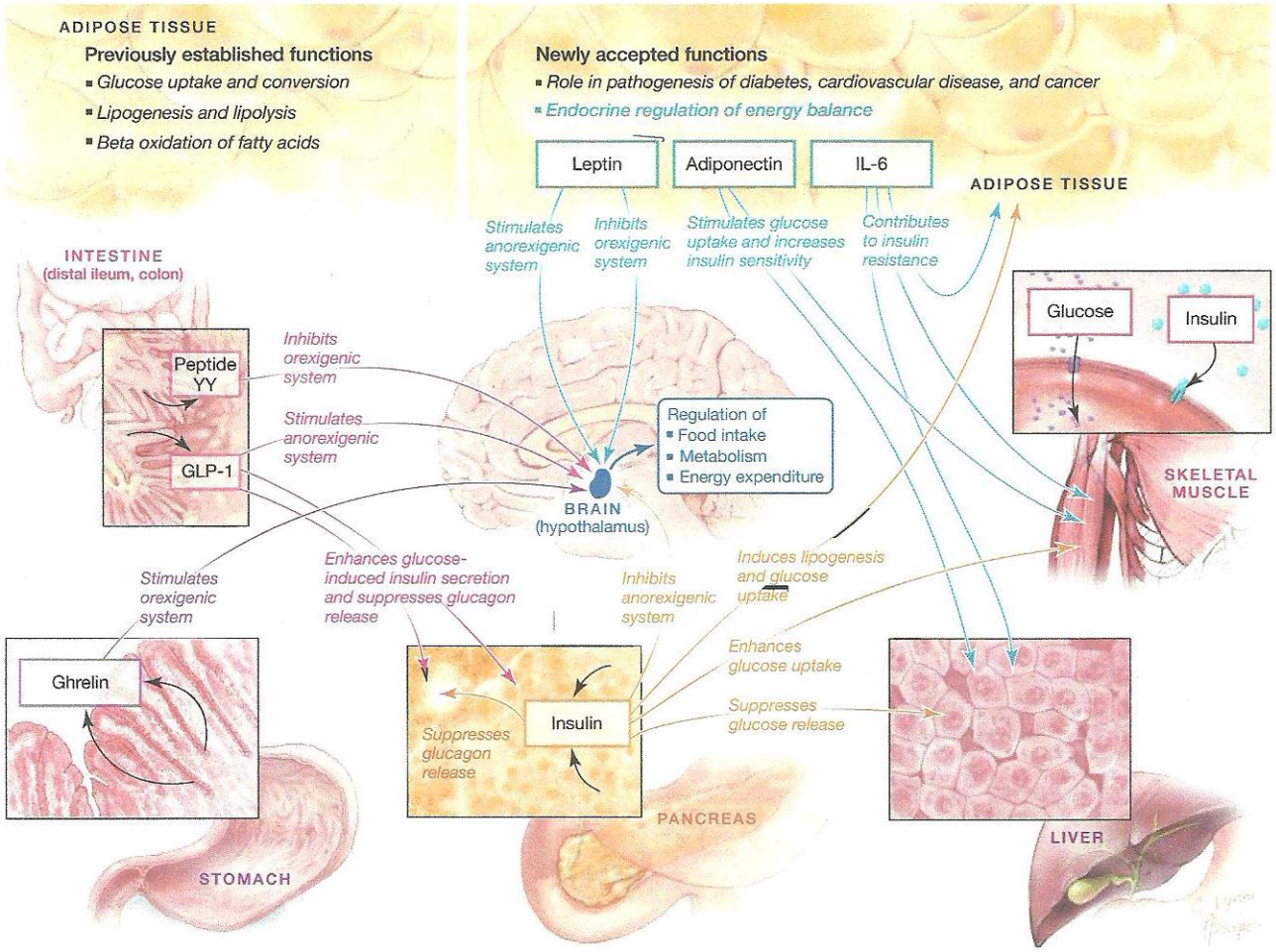
Chemicals that Promote Obesity by:

- Increasing the # of fat cells (and fat storage into existing fat cells).
- Changing the amount of calories burned at rest.
- Altering energy balance to favour storage of calories.
- Altering the mechanisms through which the body regulates appetite and satiety.

"Diabetogens": Chemicals associated with altered insulin signaling

Fat/Adipose Tissue

- active endocrine tissue
- dynamically regulates energy expenditure, appetite, food intake and metabolism.
- Signif. involved in growth and development
- Endocrine signaling pathways permanently established during perinatal development.
- In line with DOHaD concept – obesogens act during same prenatal and perinatal periods via the same epigenetic mechanisms

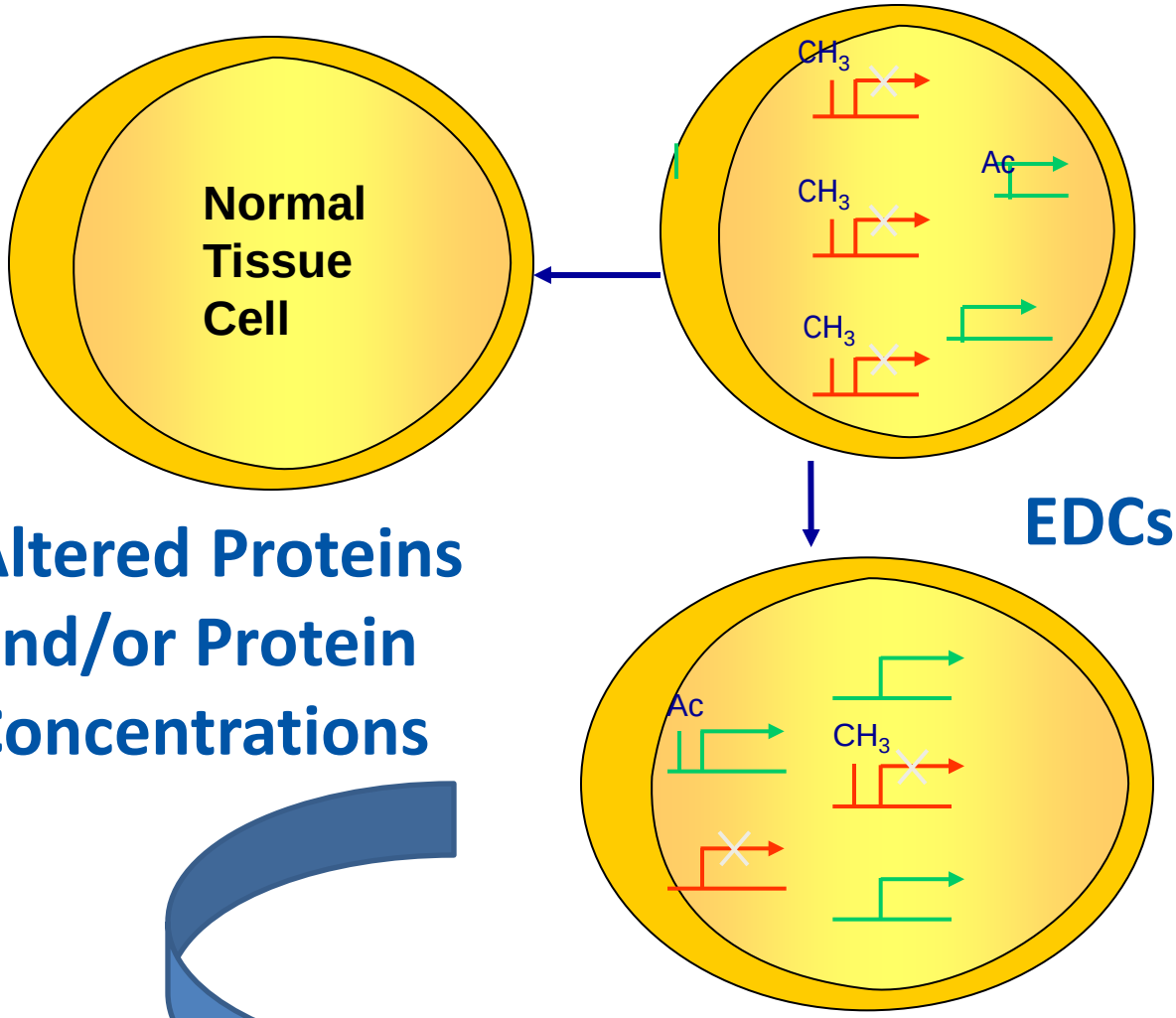


Neuroendocrine and Endocrine Pathways of Obesity. Once a cell thought to be a simple, passive storehouse for lipids, the adipocyte is now known to be marvelously complex. It senses the body's energy state and sends signals to many organs, coordinating their function. The solution for the obesity epidemic might lie in better understanding adipocyte biology.

JAMA, September 19, 2012 – Vol 308, No. 11

Epigenetic/Environmental Basis of Disease

Image source: Jerrold Heindel, US NIEHS



Normal Differentiating Cell (Development)

EDCs

Altered Proteins and/or Protein Concentrations

Altered Gene Expression (persists due to epigenetic marks)

Disease/Dysfunction

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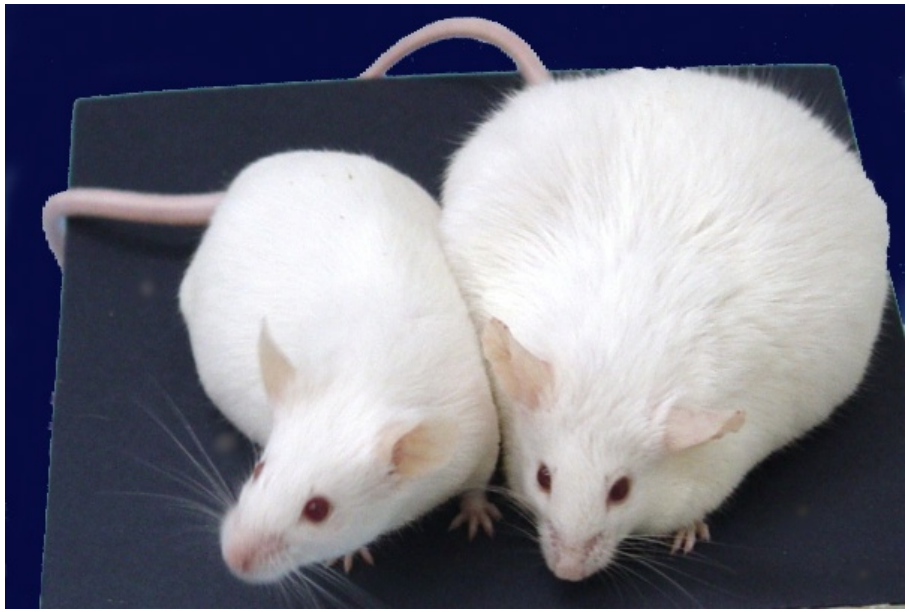
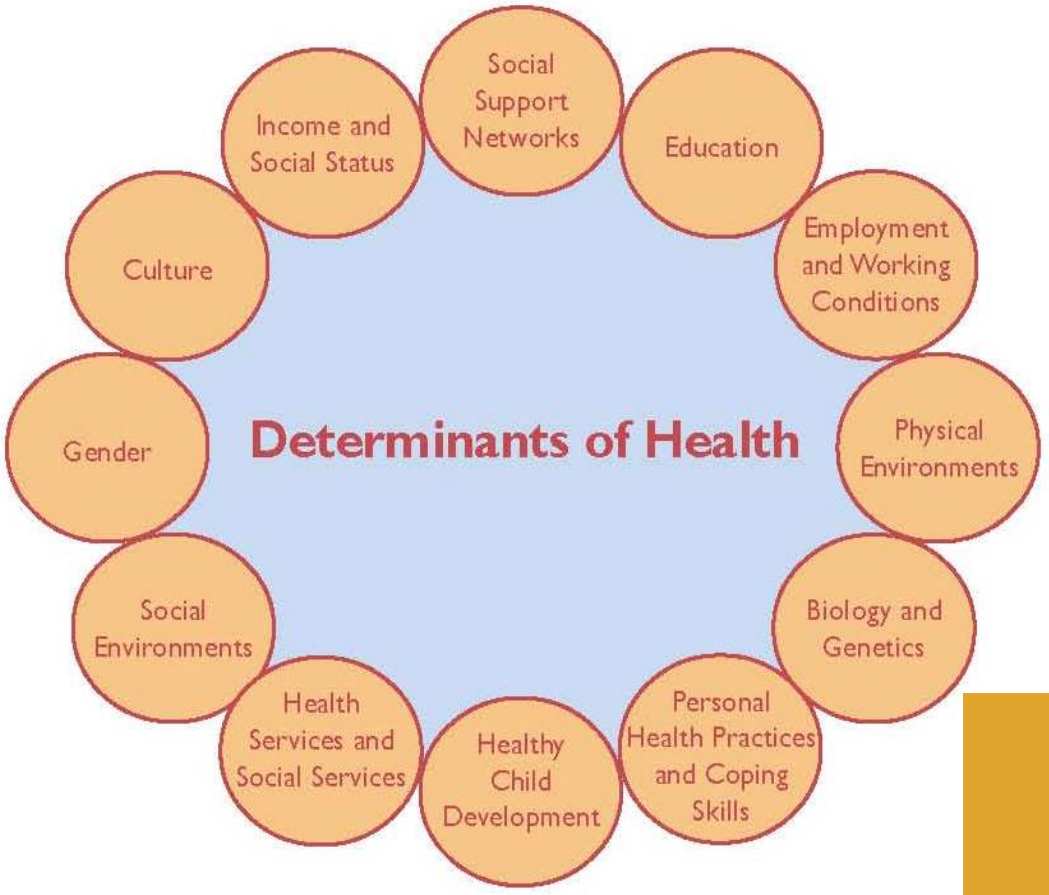


The Multiple Determinants of Health

Figure 1: Determinants of Health



Source: World Health Organization, undated.

- Any health outcome, esp. chronic disease, results from multiple determinants
- Well understood risk factors for most chronic disease
  - Behavioural/"lifestyle" the "Big 3" – diet, exercise, smoking
  - Biomedical factors or intermediate conditions
  - **But, not the full story**

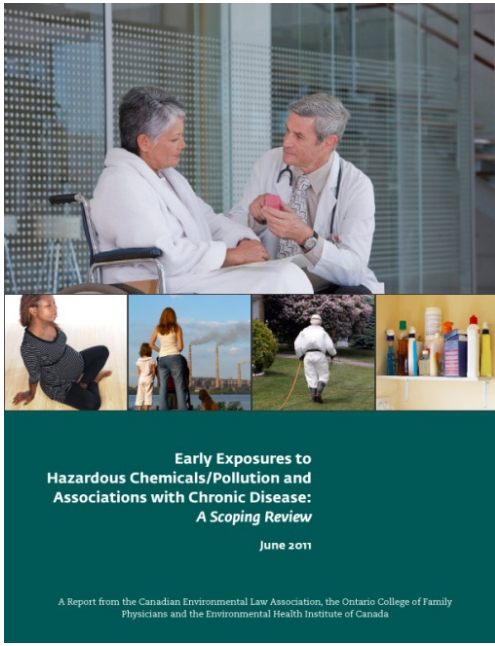
"poverty is the greatest predictor of health"

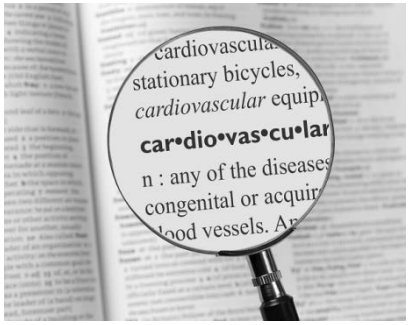
CMA President, 2009

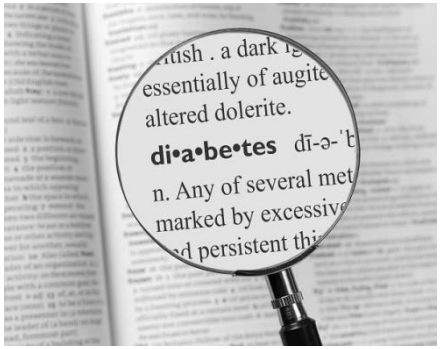
Common Risk Factors Across Multiple Chronic Diseases

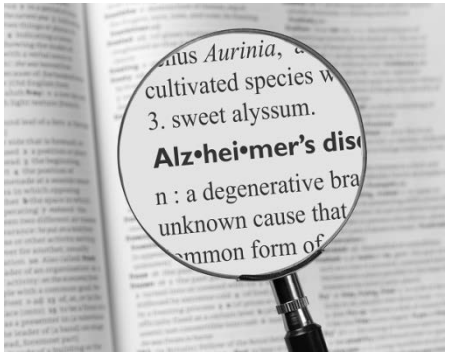
Continuum of common and overlapping risk factors for:

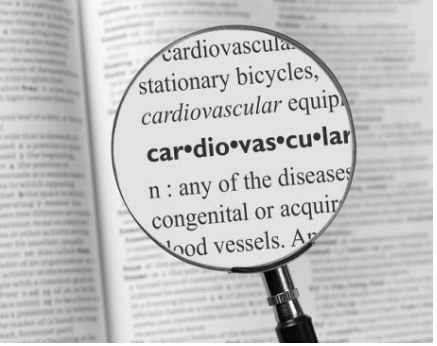
- Obesity
- Metabolic Syndrome
- Type 2 Diabetes
- Cardiovascular Disease
- Vascular Dementia
- Alzheimer's Disease (Type 3 or "diabetes of the brain")



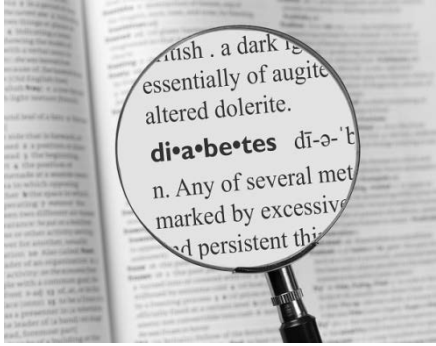








Risk Factors



Non-modifiable RF:

- gender, age, genetic predisposition (affecting blood lipids, blood pressure, obesity, insulin resistance and T2D risk)

"Modifiable" RF - considered to account for most of CVD risk:

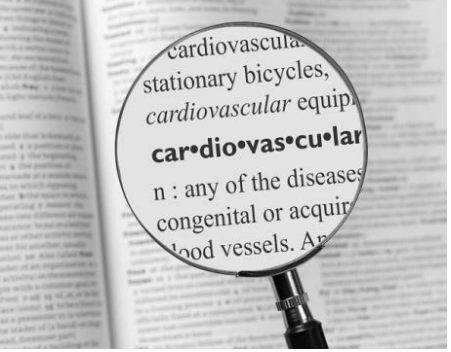
- Diet, smoking, physical inactivity, abnormal lipids, hypertension, abdominal obesity, type 2 diabetes, stress, etc.

Closer look at psychosocial stress finds stronger influence

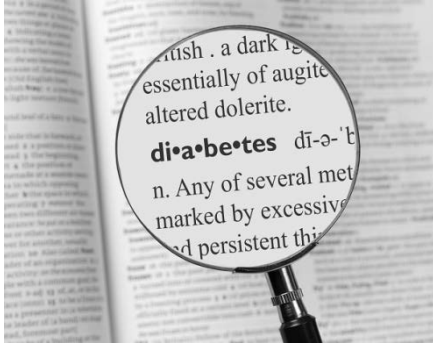
> "greater stress and corresponding greater risk of CVD when life circumstances were perceived to be beyond personal control"

Findings support SDOH analysis that "modifiable" RF are inseparable from living conditions; also apparent in higher prevalence of CVD among those in poverty

- Fetal Nutrition (DOHaD concept)
- **Environmental Exposures**

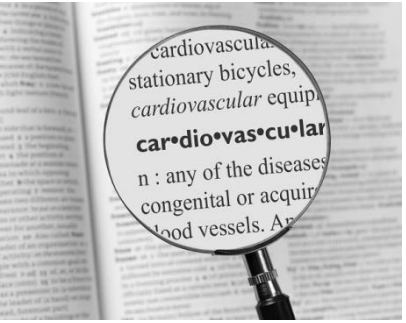


Environmental Exposures

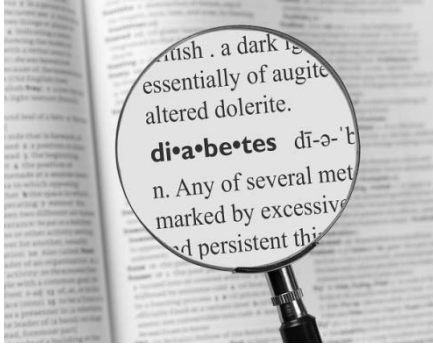


Evidence from adults:

- **Air pollution:** systemic inflammation and oxidative stress – risk factors for elevated blood pressure, insulin resistance, and abnormal blood lipids. (*Causal relationship between air poll'n and CVD*)
- **Lead:** hypertension (*Strong evidence of association*)
- **Bisphenol A:** altered insulin signaling (*animal data and limited epidemiological/human population studies*)
- **Phthalates:** links to measures of obesity and insulin resistance (*limited epi. evidence*)
- **Organophosphate pesticides:** links to altered insulin signaling (*limited epi., some animal data*)
- **POPs** (organochlorine pesticides, dioxins, PCBs): altered insulin signaling, elevated rates of T2D (*epi. and animal data*)



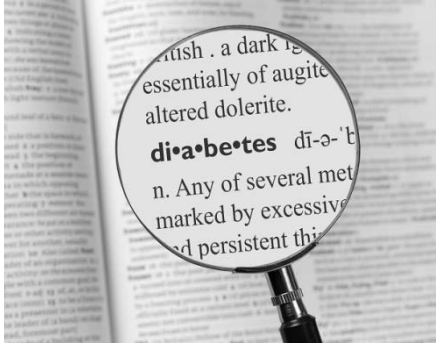
Early Life Exposures: Endocrine Disruption



Evidence from Bisphenol A, phthalates, tributyltin, (and PCBs):

- Prenatal and perinatal BPA exposure associated with permanent alteration of insulin metabolism.
  - Thus, potential risk factor for obesity, metabolic syndrome and sequelae (CVD, some cancers, Type 2 Diabetes and Alzheimer's disease)
- Pre- and perinatal exp. to BPA, phthalates (and adult exp. to PCBs) assoc'd with lower testosterone in adult males
  - Risk factor for metabolic syndrome, CVD, and T2D
- Single prenatal exposure to tributyltin (mice) – premature accumulation of fat, and greater size of fat tissues relative to body mass (epigenetic mechanism here is clearly established)

Diabetes and Early Env'l Exposures



- Epi. evidence prompted much animal research
  - seeing disruption of metabolic homeostasis through endocrine pathways with greater risk when exposure occurs in utero or perinatally
- Progression of DOHaD research – greater understanding of epigenetic mechanisms underlying obesity, metabolic syndrome, etc .
- Fetal under-nutrition and over-nutrition both relevant – former resulting in later life obesity, etc. whereas latter resulting in neuroendocrine responses that program fat cell development and appetite regulation
  - Implications of latter: childhood and adolescent obesity and thus ability to lead to intergenerational obesity

Chemicals Suspected as Obesogens/Diabetogens

- Diethylstilbesterol (DES)
- Bisphenol A (BPA)
- Phthalates
- Tributyltin
- Persistent Organic Pollutants (POPs) including polybrominated diphenyl ethers (PBDEs), organochlorine pesticides, PCBs, dioxins, polyfluoroalkyl compounds

Above are: pharmaceuticals, consumer products, or banned but still circulating substances (often contaminating food)

High-fructose diet assoc'd with:

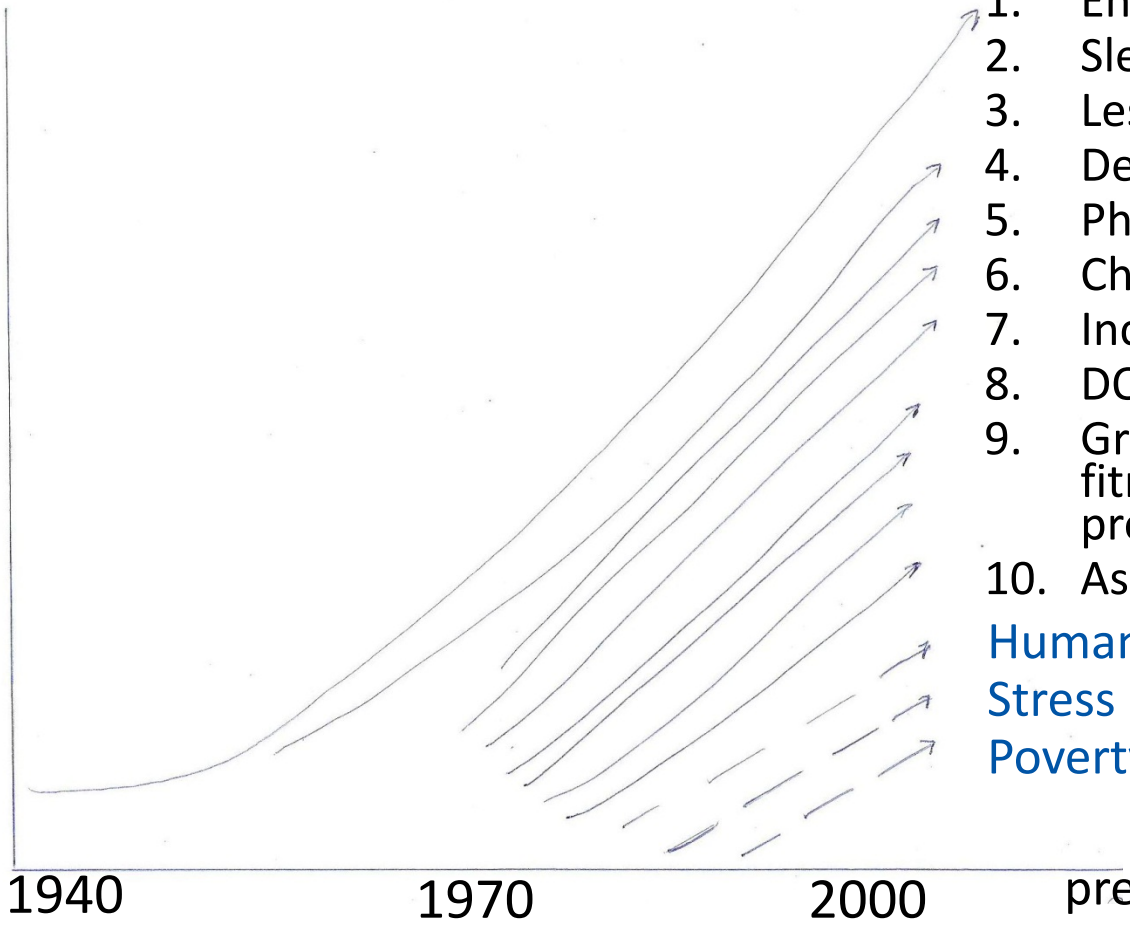
- higher blood pressure and fasting glucose
- insulin resistance and inflammatory factors that contribute to heart and vascular disease.
- Lower levels of cardiovascular protectors such as such as HDL cholesterol and adiponectin (hormone involved in metabolism including glucose regulation)

Risk Factors for Obesity

- Diet and exercise – often the primary focus
  - Sedentary lifestyles
  - changes in built env't, food system and food composition
- Many other RF are equally plausible, causal factors.
- That is, for link to diet and exercise there is an incomplete but reasonably compelling body of evidence.
- A similar body of evidence exists for at least 10 additional risk factors. Similar evidence in terms of data for:
  - Statistical trends over time
  - Human studies, both cross-sectional and longitudinal, including clinical and epidemiological
  - Animal evidence, e.g., to indicate mechanism of action
  - Epidemiological studies supported by animal experimental data.
  - Epigenetic research about DOHaD
  - Etc.

Multiple interactions across all

Risk Factors Contributing to Pop'n-Wide Increase in Obesity



1. Endocrine-disrupting substances
2. Sleep debt
3. Less variability in ambient temp.
4. Decreased smoking
5. Pharmaceutical iatrogenesis
6. Changes in distrib'n of ethnicity and age
7. Increasing gravida age
8. DOHaD intergenerational effects
9. Greater BMI assoc'd with greater repro. fitness yielding selection for obesity-pre-disposing phenotpye
10. Assortative mating effects

Human AD-36
Stress
Poverty

First 10 risk factors: as with excess food and limited exercise, evidence for link to obesity is incomplete but equally plausible (Keith, 2006)

Human Adenovirus 36 correlates with rise in obesity; more limited evidence base

Can we know what proportion of the obesity epidemic is caused by chemicals?

Probably not

What we do know:

- Endocrine disrupting chemicals operate by diverse mechanisms
- Increasing but incomplete body of knowledge showing associations
- Across all – greater effects seen from early life exposure
- Likewise for some drugs and foods → alterations in dev't, physiology, metabolism, and behaviour that favours the storage of excess calories as fat
- **Metabolic changes from obesogens are superimposed on current trends in other obesity risk factors**

Public Health Definition of Risk Factor

an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, ***on the basis of epidemiologic evidence****, is known to be associated with health-related condition(s) considered important to prevent (*emphasis added*).*

*(*Govt of Canada*, Chronic Disease Risk Factor Atlas*)

- Doesn't sufficiently recognize primary influence of SDOH
- Epidemiological evidence for environmental problems – very difficult; once obtained, can be far too late to achieve prevention or even clean-up in some cases

School of Sober Reflections…

‘‘We should keep in mind that a positive finding in an epidemiology or clinical study is, in reality, a failure of preventive medicine policy.’’

Dr. George Lucier, September 2007 to Domestic Policy Subcommittee Oversight and Government Reform Committee “Will NIEHS’ new direction protect public health?”

Paradigm Shift in Toxicology: demanded by endocrine disruption science

BPA: illustrative example of endocrine disruption

- New mechanisms of action.
- Timing of exposure is crucial.
- Measuring different endpoints.
- Development looks normal but functional changes (at gene and cell level) persist… after exposure gone… and lead to increased sensitivity to disease later in life
- Intergenerational effects
- Effects at very low doses, and likely no safe level of exposure.
- “Quasi-persistence”

Politics

Minority Gov't, 2008:

Baby bottle ban:

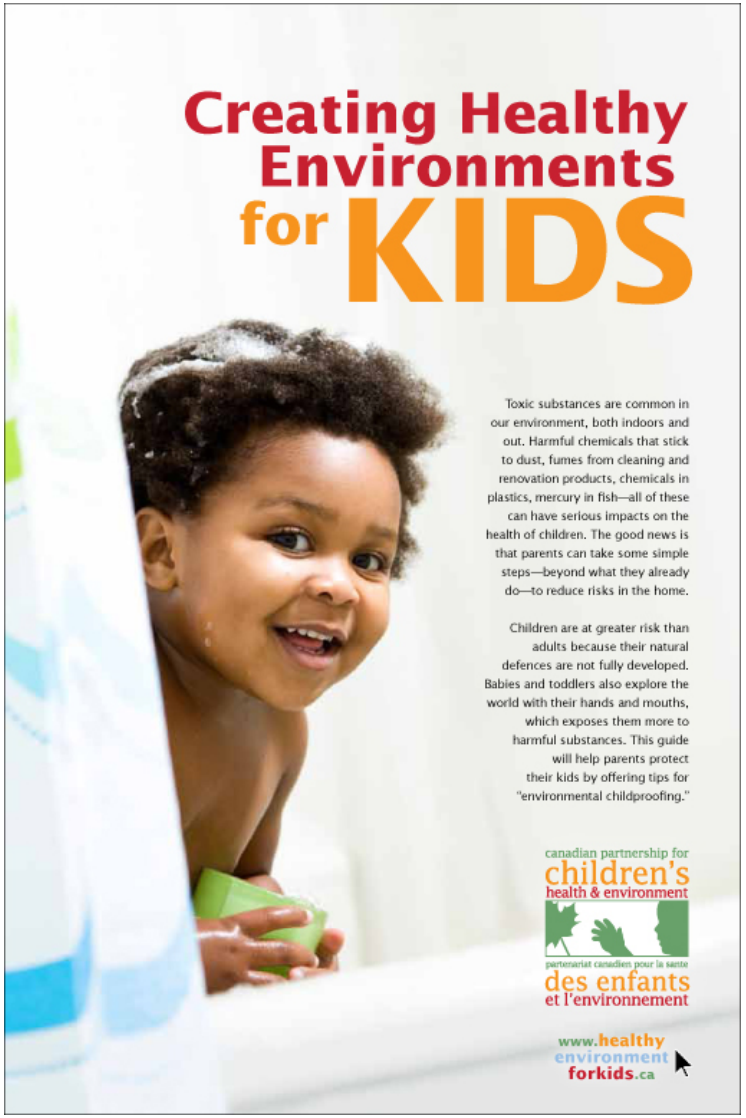
- Easy move; achieved political brownie points
- Trivial effect on industrial status quo
- Avoids addressing most relevant prenatal exposures

Majority Government, 2012:

- Massive environmental deregulation to facilitate pipelines and Asia-Pacific oil exports
- Massive cuts to publicly funded research on environmental contaminants

Halifax Herald, April 19, 2012

Creating Healthy Home Environments for Kids - Top 5 tips



Strong evidence:

- Greater exposure and greater vulnerability
- Top five areas – distilling complexity and giving people actionable steps that address important areas of exposure.

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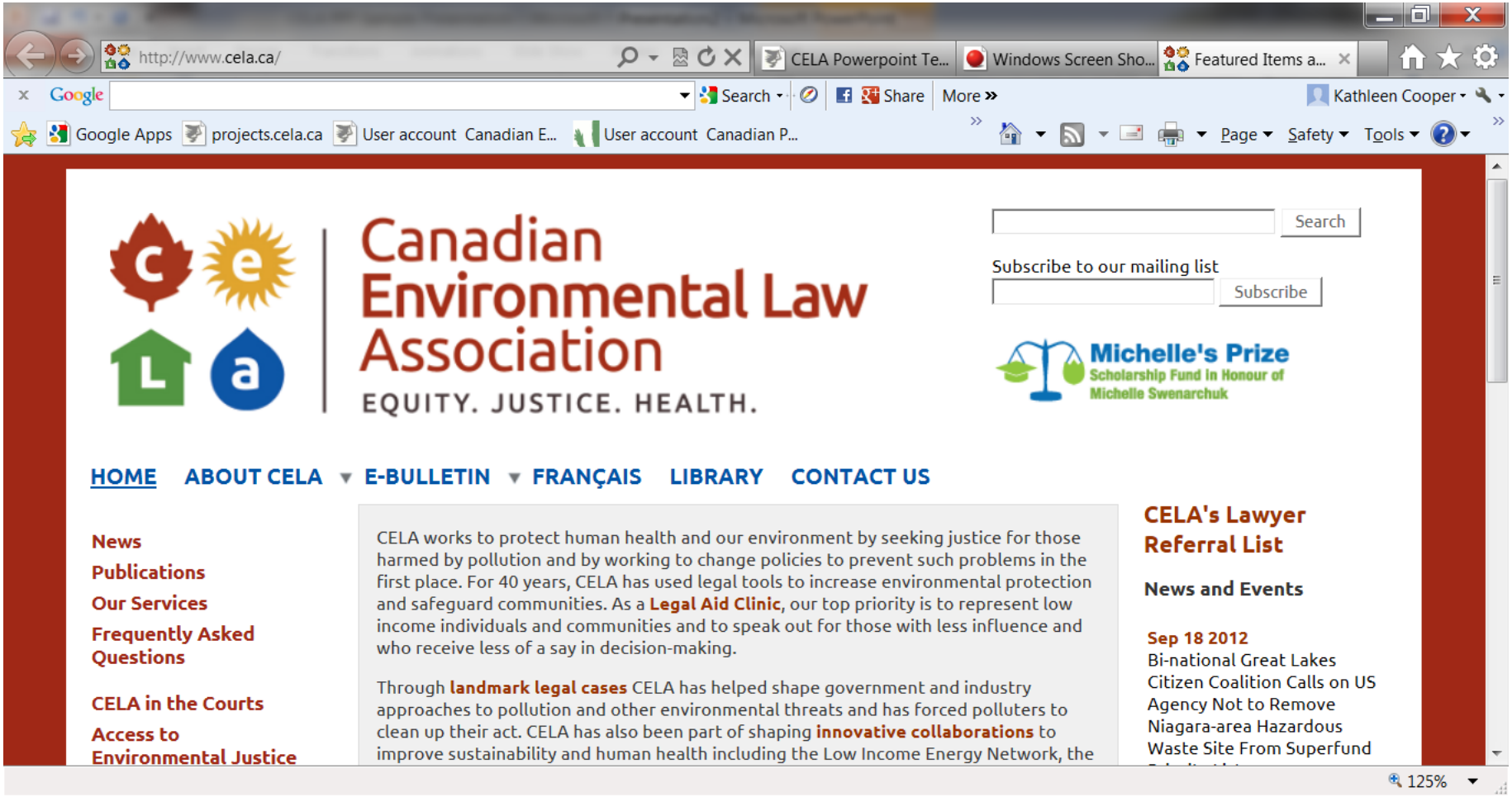
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CELA works to protect human health and our environment by seeking justice for those harmed by pollution and by working to change policies to prevent such problems in the first place. For 40 years, CELA has used legal tools to increase environmental protection and safeguard communities. As a Legal Aid Clinic, our top priority is to represent low income individuals and communities and to speak out for those with less influence and who receive less of a say in decision-making.
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