ENDOCRINE DISRUPTORS and OBESITY
...in a Post–Truth World

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Oxford Dictionaries has seen a spike in frequency this year in the context of the EU referendum in the United Kingdom and the Presidential Election in the United States.
“Statement from the work session on chemically-induced alterations in sexual development: the wildlife/human connection”

First use of “endocrine disruptors”:
“The scope and potential hazard to wildlife and humans are great because of the probability of repeated and/or constant exposure to numerous synthetic chemicals that are known to be endocrine disruptors.”

“Many compounds introduced into the environment by human activity are capable of disrupting endocrine system of animals, including fish, wildlife, and humans.”

Colborn, Theo; Dumanoski, Dianne; Myers, John P. (1996)

The first major public exploration of endocrine disruption—how chemicals interfere with hormone action

The big kick-starter for public funding on EDCs research

“TEDX List of Potential Endocrine Disruptors” – 1 326 EDCs

http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/overview
Endocrine Disrupting Chemicals (EDCs)

An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

(WHO, 2002; EC, 2015)

The DEFINITION OF AN EDC IS CRITICAL, because it will dictate the evidence required to identify a chemical as an EDC and will inform the subsequent steps of assessing the risk of EDC exposures.
Position Statement from the Endocrine Society

EDC: an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action

(Endocrine Society, 2015)

In what classes of chemicals can we find EDCs?

**Household product ingredient**
Present in appliances, vehicles, building materials, electronics, crafts, textiles, furniture, and household cleaning products*.

**Personal care product/Cosmetic ingredient**
Cosmetics, shampoos, lotions, soaps, deodorants, fragrances, and shaving products.

**Food additives**
Antioxidants, dyes, compounds used in food processing and as components in food packaging.

**Flame retardants**
Mandatory prevention of fires in appliances* and fire extinguishers (firefighting in forest fires).
Pesticide ingredients
Insecticides/acaricides (miticides), herbicides, fungicides, rodenticides, and other biocides

Antimicrobials
Chemicals that prevent the growth of and/or destroy microorganisms.

Biogenic compounds
Naturally occurring or biologically derived chemicals such as phytoestrogens, flavonoids, monophenols, mycochemicals and phenolic acids.

Industrial additives
Preservatives, antioxidants, and surfactants used in such things as glue, plastic, rubber, paint, and wood products.

Solvents
Chemicals used to dissolve other chemicals.
**Metal/Metallurgy**  
Elements or chemicals used in the extraction, processing, or manufacturing of a metal or metal-containing product, including welding.

**Byproduct/Intermediate/Reactant**  
Chemicals used in the synthesis of other compounds and/or unwanted byproducts such as impurities and contaminants, including combustion byproducts.

**Medical/Veterinary/Research**  
Chemicals used in hospitals, medical supplies, and equipment, in laboratories or as reagents, and pharmaceuticals.

**Metabolite/Degradate**  
Breakdown products of other chemicals.
WHAT WE KNOW

the overarching conclusions of EDC research
Exposure to EDCs can have biologically adverse effects at doses well beneath those typically considered in toxicological experiments.

Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, [...] and John Peterson Myers


Exposures during fetal life can set in motion consequences that play out over the lifetime of the individual, and which often are not clearly evident at birth

“There are now robust data supporting the Developmental Origins of Health and Disease (DOHaD) paradigm”:

“Nutrition, Environmental Pollutants, and Stress”

(“in integrated form and considering all all windows of sensitivity to environmental stressors across the life span, including preconception, pregnancy, early childhood and others to be determined”)

Exposures to EDCs are ubiquitous:

- **Pervasive distribution of persistent** compounds (e.g., polychlorinated biphenyls – PCBs; pesticides that volatilize and are distributed by atmospheric currents - *Grasshopper effect*)

Incorporation into consumer products used worldwide in homes, offices, hospitals, etc.

- **EDCs** are key components of industrialized agriculture and thus are found abundantly in the human food supply.
People are exposed to mixtures of EDCs continuously, never one chemical at a time.

“Cumulative low-dose insult can [...] be more toxic than a single high-dose exposure [...] this tends to contradict elements of classical toxicology.”

The Updated Tables, February 2015 presents data for a total of 265 chemicals.
Risk assessment as practiced by public health agencies

Use tools that are incomplete, out-of-date and delegitimized by incorrect assumptions

Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, [...], and John Peterson Myers


Incomplete

for EDCs because *at best* they consider **only chemical effects on the estrogen and androgen system.**

All **other EDC mechanisms are ignored**, including thyroid, which is evaluated solely by hormone levels in the blood.

Out-of-date

they use assays that date, in the most extreme case, back to the 1930s, and **fail to incorporate our current understanding** of the complexity of these systems.
Delegitimized

at least two assumptions core to regulatory testing have been extensively distorted:

(1) Standard protocols test the **effects of high doses** and assume those tests can be used to **estimate the adverse effects of lower doses** (Nonmonotonicity in EDC dose-response curves)

(2) All tests are done one chemical at a time (e.g., pesticides: only the ‘active’ ingredient not the complex mixture is tested- the mixture is designed to enhance the effectiveness of the active ingredient.)

This testing also assumes that **high-dose short-term exposures are generalizable to low-dose, life-long exposures** despite empirical evidence in humans that this assumption is not true.
In 2012 a report jointly presented by the World Health Organization (WHO) and the United Nations Environment Program (UNEP) concluded

**EDCs are a Global Public Health Threat**

Additionally, it stated that

1. **Disease risks** due to EDCs may still be **significantly underestimated**, and

2. **Significant opportunities** for **disease prevention** by reducing exposures may be **within reach**.
Obesity is a growing problem in developed countries but also in the developing world.

Growing scientific evidence indicates that the “traditional” explanation for the Obesity epidemic - the imbalance of caloric consumption and exercise does not fully explain the obesity epidemic.

“Because of the established health risks and substantial increases in prevalence, obesity has become a major global health challenge. Not only is obesity increasing, but no national success stories have been reported in the past 33 years.”

DNA mutations also cannot explain the global obesity trends

Changes in genes rarely occur over such short periods of time as the one during which obesity has become a problem (approximately 30 years)

The obesity epidemic is global

Even if the mutation was to occur there would be no scope for it to be passed on globally

A study using data collected over nearly four decades by the U.S. National Health and Nutrition Examination Survey (NHANES) observed that:

For a given amount of caloric intake, macronutrient intake, or leisure-time physical activity, the predicted BMI was significantly higher in 2006 than in 1998.

And concluded “Factors other than diet and physical activity may be contributing to the increase in BMI over time.”

Over the past decade, many research studies have evaluated the hypothesis that environmental contaminants could contribute to obesity, and evidence is rapidly accumulating in support of this hypothesis.

**the Obesogen Hypothesis**

(Gore et al. 2015; Grun and Blumberg, 2006; Grun and Blumberg 2009)

Perturbations in metabolic signaling, resulting from exposure to dietary and environmental chemicals, may further exacerbate the effects of imbalances in diet and exercise, resulting in an increased susceptibility to obesity and obesity-related disorders.

In general refers to those xenobiotics that trough an inappropriate activation of nuclear receptors induce adipocyte differentiation (TBT, BPA, Phthalates, PFOA,...).
Chemical Toxins: A Hypothesis to Explain The Global Obesity Epidemic

...beware of spurious correlations...

Baillie-Hamilton 2002
Potential Mechanism

Endocrine disruptors and obesity

Jerrod J. Heindel, Retha Newbold and Thaddus T. Schug

Figure 1 | Potential mechanism by which environmental chemicals cause obesity in animals and in humans. Several EDCs and obesogens such as organotins and the fungicide triclorfum are known to activate PPAR-γ, which leads to weight gain in vivo and reprogramming of mesenchymal stem cell fate to favor formation of adipogenic cells at the expense of the osteogenic fate. Triclosan also functions via PPAR-γ to induce adipogenesis in mesenchymal stem cells and preadipocytes in vitro through a PPAR-γ-dependent mechanism and promotes increased white adipose tissue depot size and altered stem cell programming in vivo. Abbreviations: EDC, endocrine-disrupting chemical; PPAR-γ, peroxisome proliferator-activated receptor γ.

Figure 2 | Potential mechanisms of obesogen action that alter metabolic set-points and increase the risk of obesity. If these programming events occur early in embryonic development, they can lead to persistent changes in hormone signalling. Numerous obesogens have been shown to act through activation of fat-regulating nuclear receptors or other receptors that regulate key metabolic signalling processes. Other obesogens act via unidentified pathways such as those that result in various epigenetic changes, and which can have transgenerational effects on a variety of health endpoints, including obesity in offspring.

Obesogens promote weight gain by:

- Acting directly on fat cells (to increase their number or the storage of fat)
- Acting indirectly by altering mechanism through which the body regulates appetite and satiety
- Altering basal metabolic rate
- Altering energy balance to favor the storage of calories

Obesogens can act as direct ligands for nuclear hormone receptors, or affect components in metabolic signaling pathways under hormonal control e.g., tributyltin (TBT) and triphenyltin (TPT) stimulate adipogenesis in vitro and in vivo (nanomolar affinity ligands for the RXR-PPAR heterodimer)

TBT and TPT stimulate 3T3-L1 preadipocytes to differentiate into adipocytes in a PPAR-dependent manner
Environmental Chemicals associated with obesogenic properties

### Endocrine disruptors and obesity

**Jerrold J. Heindel, Ratha Newbold and Thaddeus T. Schug**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Source/commercial use</th>
<th>Potential mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoke</td>
<td>First-hand and second-hand smoke</td>
<td>Prenatal nicotine exposure alters neurological development and exposures ↑ rates of preterm and low-weight births⁴¹,⁴⁶,⁴⁷</td>
</tr>
<tr>
<td>Air pollution</td>
<td>Incomplete combustion of fossil fuels</td>
<td>↑ Accumulation of visceral fat⁵⁵</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td></td>
<td>Inflammation⁶⁶</td>
</tr>
<tr>
<td>Tributyltin</td>
<td>Fungicide in paints and components of polyvinyl chlorides</td>
<td>Activation of peroxisome proliferator-activated receptor γ³⁷,⁵⁸,⁵⁹ and increased fat cell differentiation⁵⁵-⁵⁸</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Plastics and epoxy resins</td>
<td>Estrogenic⁶²,⁹³</td>
</tr>
<tr>
<td>Flame retardants</td>
<td>Chemicals applied to furniture and electronics</td>
<td>↑ Rate of adipogenesis¹²⁹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Glucose intolerance¹⁰⁶</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>Coolants, plasticizers and flame retardants</td>
<td>Altered thyroid function²⁶,¹⁰²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Altered metabolism¹¹²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioaccumulation in fat cells¹⁰⁹</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Plasticizers, adhesives and personal care products</td>
<td>↑ Rate of adipocyte differentiation¹¹⁷,¹²⁰-¹²²</td>
</tr>
<tr>
<td>Perfluorooctanoic acid</td>
<td>Components of lubricants, nonstick coatings and stain-resistant compounds</td>
<td>↑ Serum levels of insulin¹²⁶</td>
</tr>
<tr>
<td>Perfluorooctanoate sulphonate</td>
<td></td>
<td>↑ Serum levels of leptin¹²⁶</td>
</tr>
</tbody>
</table>
Experimental animals exposed to environmental contaminants such as bisphenol A (BPA), dichlorodiphenyltrichloroethane (DDT), phthalates, perfluorooctanoic acid (PFOA), dioxins, and tributyltin (TBT) during pregnancy are more likely to give birth to offspring that display increased fat accumulation leading to obesity (Angle et al. 2013; Grun et al. 2006; Hao et al. 2013; Hines et al. 2009; Manikkam et al. 2013; Skinner et al. 2013; Somm et al. 2009; van Esterik et al. 2015)
The **exposure levels** used in many of these studies were **similar to those measured in human populations**.

La Merrill et al. (2014) showed that **exposure to DDT during pregnancy** can **reduce basal metabolism in the offspring**, a fact that could explain **why these offspring gain extra weight for a given energy intake**.

**Exposure to BPA** has been reported to **lead to increased food intake** due to changes in the brain resulting in **stimulated appetite** (Mackay et al. 2013).

La Merrill M, Cirillo PM, Terry MB, Krigbaum NY, Flom JD, Cohn BA. 2013. Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: a longitudinal birth cohort study. Environmental Health Perspectives 121(5):594–599

Human studies have supported the hypothesis that the obesogenic effects noted in experimental animals are also relevant for humans.

Exposure of pregnant women to environmental contaminants is associated with increased weight gain of their babies:

Prenatal exposure to dichlorodiphenyldichloroethylene (DDE) is associated with rapid weight gain in children (Izsatt et al. 2015; Valvi et al. 2014)

Higher levels of DDE in the blood of pregnant mothers is associated with obesity in the adult offspring (Karmaus et al. 2009).

Similar associations have been seen with other pollutants such as hexachlorobenzene (HCB) (Smink et al. 2008; Valvi et al. 2014) as well as mixtures of organochlorines (Agay-Shay et al. 2015).

EDCs exposures (DDE, BPA, Phthalates) in the EU contribute substantially to obesity and diabetes, with a moderate probability of over €18 billion costs/year.

Most cost estimates do not account for emerging evidence for other endocrine disrupting chemicals (EDC) linked to obesity.

Environmental contributions to the burden of disease may be easily underestimated due to uncertainties in the evidence.

Environmental prevention programmes

- 46%, p<0.001

Clinical intervention programmes

- 16%, p<0.001;

Nonclinical, person-directed interventions

- 13%, p<0.001;

Potential Impact on Future Generations

A disquieting finding in mice showed that Tri-Butyl-Tin (TBT) obesogenic effect appears not only in the first generation but is passed on to further generations (Chamorro-Garcia et al. 2013).

This Transgenerational Effect, has been shown to be due to epigenetic mechanisms.

Epigenetic events do not involve alterations in the genetic code, but rather mitotically stable changes in the regulation of gene expression (Skinner et al. 2013).

TBT activates PPARγ, the master regulator of adipogenesis and increases its functioning in future generations.

Such effects are more pronounced when the experimental animals are maintained on a high-fat diet (Chamorro-Garcia et al. 2013).


Fig. 5. EDCs many promote epigenetic alterations that influence somatic cells and so the disease status of the individual exposed (F0 generation). In pregnant females, EDC exposure could also cause epigenetic modifications in the next two generations (F1 and F2) through the fetus and its germ line. The effect of such multigenerational exposure in subsequent generations (F3 and beyond) would be considered a transgenerational phenotype.
Policy responses lag significantly...

In the US the recently passed Lautenberg Chemical Safety Act does little to advance regulations of EDCs, consigning the next several generations of America’s children to more EDC exposures.

In the European Union there has been several “incidents” regarding environmental contaminants (e.g., the glyphosate scandal) and the Directive regarding EDCs is one year late.

In both cases particular interests have been linked to the slowness and incompleteness of the process.
An Action Plan for the future

• Increase research initiatives and funding to further explore mechanisms associated with chemical obesogen-induced metabolic disruptions, to examine mixtures, and to use exposure levels relevant to those encountered by human populations.

• Ensure that knowledge of obesogenic environmental chemicals is incorporated into regulatory and policy making.

• Demand that new chemicals that are to be released onto the market are tested in an appropriate fashion regarding their effects on metabolism.

• Demand that all chemicals included in consumer products are disclosed in order to increase public awareness of their use and to provide individuals with the information they need to avoid exposures.
• **Find** additional ways to **increase public awareness** about factors **beyond caloric balance** that are involved in obesity development, **including** the role of some environmental contaminants.

• **Increase awareness** about the potential of these exposures to **generate effects in future generations**. This action item should also include **education on how to avoid exposure to these contaminants**.

• **Inform physicians** and **other health care professionals** regarding the effects of environmental contaminants on metabolism to **increase the awareness** of this problem, and **how they could guide their patients**, as well as the **general population**, to **limit their exposure to these contaminants**.

“... so that obesity does not become the normal outlook in the future”.

Uppsala Consensus Statement on Environmental Contaminants and the Global Obesity Epidemic
While researchers leapt in, the evidence had to build before it reached mass critical enough to attract the attention of practicing physicians... but it is happening!!

Hopefully, the growing public awareness of EDC risks, engagement by scientific and medical societies and market opportunities for chemists to make money by avoiding these hazards will over time reduce the burden of EDC related diseases.
ACKNOWLEDGMENTS

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CURSO DE FORMAÇÃO CONTÍNUA

DISRUPÇÃO ENDÓCRINA:
IMPACTOS NO AMBIENTE
E NA SAÚDE

/12/13/14/15/16
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