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Endocrine Disrupting Chemicals: Human Evidence and Consequences

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Disclosures

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- Scientific Advisory Roles: Beautycounter, IS-Global, Footprint, Food Packaging Forum, Ahimsa

What are endocrine disrupting chemicals?

- Endocrine disrupting chemicals (EDCs) interfere with hormonal signaling systems
- We now know of >1,000 synthetic chemicals that can disrupt hormonal functions and thereby contribute to disease and disability
  - Mimic, block, or modulate the synthesis, release, transport, metabolism, binding, or elimination of natural hormones
  - Brain, pituitary, gonads, thyroid, and other components of the endocrine system

	Representative EDCs
Pharmaceuticals	Trenbolone acetate, ethinylestradiol, dexamethasone, levonorgestrel, rosiglitazone
Cosmetics, personal care products	DBP, benzophenones, parabens, triclosan, DEET
Pesticides, herbicides, fungicides	Chlorpyrifos, glyphosate, pyraclostrobin, DDT, atrazine
Industrial chemicals	BPA, PCBs, triphenyl phosphate, PBDEs
Metals	Lead, cadmium, mercury, arsenic
Synthetic and naturally occurring hormones	Progesterone, testosterone, cortisol, oestrone

Representative EDCs from diverse functional use categories. EDC=endocrine-disrupting chemical. DBP=dibutyl phthalate. DEET=N,N-diethyl-m-toluamide. DDT=dichlorodiphenyltrichloroethane. BPA=bisphenol A. PCB=polychlorinated biphenyl. PBDE=polybrominated diphenyl ether.

Table 1: **List of representative EDCs in use**

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement

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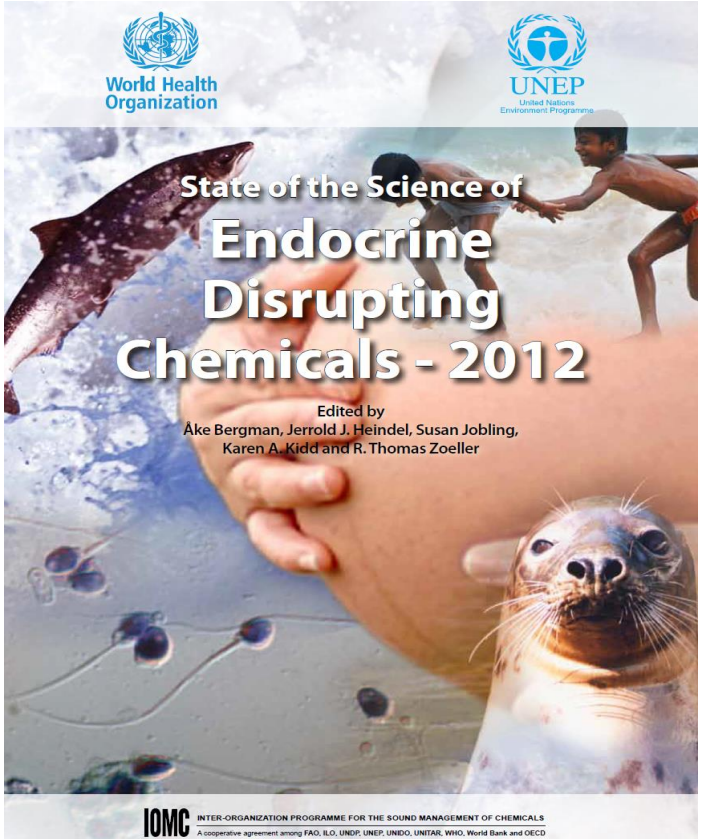
There is growing interest in the possible health threat posed by endocrine-disrupting chemicals (EDCs), which are substances in our environment, food, and consumer products that interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction. In this first Scientific Statement of The Endocrine Society, we present the evidence that endocrine disruptors have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology. Results from animal models, human clinical observations, and epidemiological studies converge to implicate EDCs as a significant concern to public health. The mechanisms of EDCs involve divergent pathways including (but not limited to) estrogenic, antiandrogenic, thyroid, peroxisome proliferator-activated receptor γ, retinoid, and actions through other nuclear receptors; steroidogenic enzymes; neurotransmitter receptors and systems; and many other pathways that are highly conserved in wildlife and humans, and which can be modeled in laboratory *in vitro* and *in vivo* models. Furthermore, EDCs represent a broad class of molecules such as organochlorinated pesticides and industrial chemicals, plastics and plasticizers, fuels, and many other chemicals that are present in the environment or are in widespread use. We make a number of recommendations to increase understanding of effects of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness. (***Endocrine Reviews* 30: 293–342, 2009**)



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Response to WHO/UNEP Report

WHO/UNEP report (2012) “welcomed” by all participant countries at 2015 Strategic Alliance for International Chemicals Management

EDC-2: The Endocrine Society’s Second Scientific Statement on Endocrine-Disrupting Chemicals

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The Endocrine Society’s first Scientific Statement in 2009 provided a wake-up call to the scientific community about how environmental endocrine-disrupting chemicals (EDCs) affect health and disease. Five years later, a substantially larger body of literature has solidified our understanding of plausible mechanisms underlying EDC actions and how exposures in animals and humans—especially during development—may lay the foundations for disease later in life. At this point in history, we have much stronger knowledge about how EDCs alter gene-environment interactions via physiological, cellular, molecular, and epigenetic changes, thereby producing effects in exposed individuals as well as their descendants. Causal links between exposure and manifestation of disease are substantiated by experimental animal models and are consistent with correlative epidemiological data in humans. There are several caveats because differences in how experimental animal work is conducted can lead to difficulties in drawing broad conclusions, and we must continue to be cautious about inferring causality in humans. In this second Scientific Statement, we reviewed the literature on a subset of topics for which the translational evidence is strongest: 1) obesity and diabetes; 2) female reproduction; 3) male reproduction; 4) hormone-sensitive cancers in females; 5) prostate; 6) thyroid; and 7) neurodevelopment and neuroendocrine systems. Our inclusion criteria for studies were those conducted predominantly in the past 5 years deemed to be of high quality based on appropriate negative and positive control groups or populations, adequate sample size and experimental design, and mammalian animal studies with exposure levels in a range that was relevant to humans. We also focused on studies using the developmental origins of health and disease model. No report was excluded based on a positive or negative effect of the EDC exposure. The bulk of the results across the board strengthen the evidence for endocrine health-related actions of EDCs. Based on this much more complete understanding of the endocrine principles by which EDCs act, including nonmonotonic dose-responses, low-dose effects, and developmental vulnerability, these findings can be much better translated to human health. Armed with this information, researchers, physicians, and other healthcare providers can guide regulators and policymakers as they make responsible decisions. (*Endocrine Reviews* 36: 0000–0000, 2015)

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Mainstream recognition

POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Food Additives and Child Health

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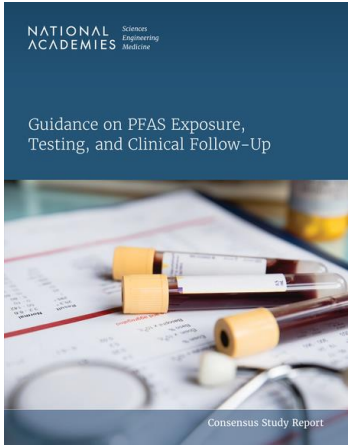
COUNCIL ON ENVIRONMENTAL HEALTH



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ETIOLOGY AND PATHOPHYSIOLOGY

OBESITY Reviews WILEY

Endocrine-disrupting chemicals and obesity risk: A review of recommendations for obesity prevention policies

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Summary
Emerging evidence indicates that industrially produced endocrine-disrupting chemicals (EDCs) may be as obesogenic as poor dietary patterns and should be considered in obesity prevention policies. The authors conducted two reviews: (a) a systematic search of four electronic databases for papers published since January 2010 to identify the policy recommendations contained in scientific reviews of EDC exposure and obesity risk and (b) a narrative review of obesity policy documents published since January 2012 to identify the recommendations of national and international agencies. A search of four electronic databases found 63 scientific reviews with policy recommendations, of which 26 suggested individual responsibility to avoid exposure, 11 suggested medical interventions to counter the effects of exposure, and 42 suggested regulatory control of hazardous chemicals. Of sixty policy documents examined, six mentioned pollutants as a possible risk factor for obesity, and only one made explicit reference to strategies for reducing exposure to EDCs. The UN Sustainable Development Goals include targets to prevent ill health from hazardous chemicals (Targets 3.9 and 12.4) and to remove unsafe industrial chemicals from the environment (Targets 6.3, 11.6, 12.4, and 14.1). The authors suggest these should be explicitly linked to World Health Assembly targets to halt the rise in obesity.

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Endocrine disruption and the developing brain

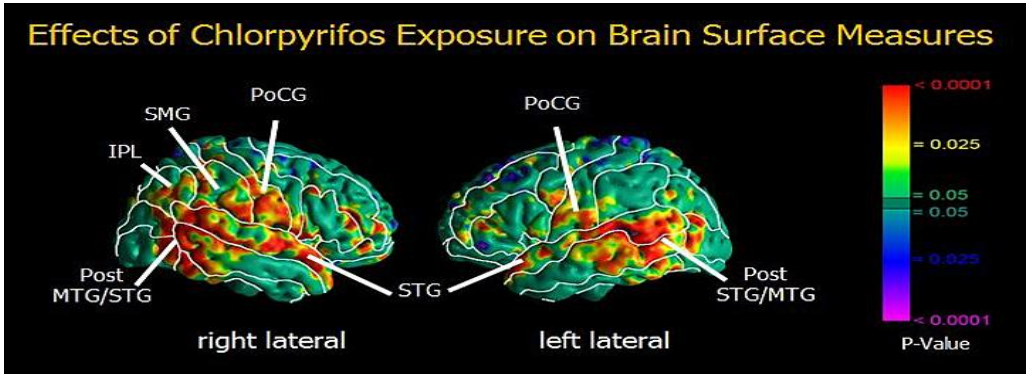
- Thyroid hormone has long been known to be critical to early brain development
    - Predictable outcomes of its disruption include global IQ deficits, as well as neurodevelopmental disabilities such as autism spectrum disorder (ASD), and attention-deficit hyperactivity disorder (ADHD).
- Interference with sex steroid and other hormonal modes of action may also adversely impair early brain development.

Organophosphorus pesticides

- Consistent dose/response relationships of organophosphate pesticide exposures in pregnancy with intellectual quotient across three carefully conducted longitudinal birth cohorts

Bouchard et al EHP 2011; Engel et al EHP 2011; Chen et al 2015

- Prenatal OP exposure has been associated with magnetic resonance imaging findings in children including frontal and parietal cortical thinning



Rauh et al PNAS 2012

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Brominated flame retardants

- Polybrominated diphenyl ethers (PBDE) required for flammability standard from 1970s until 2013 (California law TB-117)
  - Not required in EU, banned there in 2008
- Four well-designed longitudinal birth cohorts have examined PBDE effects on child neurodevelopment
  - Three (all US) identified consistent, exposure-response relationships with IQ, with carefully collected data on many potential confounders.

Chen et al EHP 2014; Eskenazi et al EHP 2013; Herbstman et al EHP 2010

  - Fourth (from Spain), suffered from modest sample size, with few detectable PBDE levels, though this study showed substantial directionality towards cognitive and motor dysfunction at age 4.
    - IQ was not measured
    - Exposure levels in the US are much higher than in the EU.

Gascon et al Environment International 2011

Environmental chemicals and endocrine mechanisms for adiposity and insulin resistance

Table 1 | Environmental chemicals associated with obesogenic properties

Chemical	Source/commercial use	Potential mechanism
Cigarette smoke	First-hand and second-hand smoke	Prenatal nicotine exposure alters neurological development and exposures ↑ rates of preterm and low-weight births[41,46,47]
Air pollution Polycyclic aromatic hydrocarbons	Incomplete combustion of fossil fuels	↑ Accumulation of visceral fat[55] Inflammation[56]
Tributyltin	Fungicide in paints and components of polyvinyl chlorides	Activation of peroxisome proliferator-activated receptor γ[37,58,59] and increased fat cell differentiation[60–63]
Bisphenol A	Plastics and epoxy resins	Estrogenic[82,83] Inhibition of proliferation of neural progenitor cells[86]
Flame retardants	Chemicals applied to furniture and electronics	↑ Rate of adipogenesis[105] ↑ Glucose intolerance[106]
Polychlorinated biphenyls	Coolants, plasticizers and flame retardants	Altered thyroid function[96,101] Altered metabolism[112] Bioaccumulation in fat cells[109]
Phthalates	Plasticizers, adhesives and personal care products	↑ Rate of adipocyte differentiation[117,120–122]
Perfluorooctanoic acid Perfluorooctanoate sulphonate	Components of lubricants, nonstick coatings and stain-resistant compounds	↑ Serum levels of insulin[126] ↑ Serum levels of leptin[126]

Bisphenols

- Used in polycarbonate plastics and epoxy resins (aluminum cans, thermal paper receipts)

- Bisphenol A disrupts multiple metabolic mechanisms, at levels commonly seen in humans
  - Increases fat cell size, disrupts adiponectin function and low-grade synthetic estrogen

- As concern has increased, ~40 chemically similar replacements now in use: bisphenol S (BPS), BPF, BPAF, BPZ, BPP…
  - BPS: similar estrogenicity, embryotoxicity (potentially others)

Masuno et al. *J Lipid Res.* 2002;43(5):676-684; Sakurai K et al. *Br J Pharmacol.* 2004;141(2):209-214;

Phthalates

Low-molecular weight (LMW) phthalates used in shampoos, cosmetics, lotions and other personal care products to preserve scent

- Anti-androgenic properties (reduced transcription of the androgen receptor)

High molecular weight (HMW) phthalates used to produce vinyl plastic for flooring, clear food wrap and intravenous tubing.

- Mono-(2-ethylhexyl) phthalate (MEHP), a metabolite of one HMW phthalate used in food packaging, di-2-ethylhexylphthalate (DEHP), increases expression of receptors which play key roles in lipid and carbohydrate metabolism

Bornehag and Nanberg 2010; Colon et al. 2000; Engel et al. 2010; Miodovnik et al. 2011; Sathyanarayana 2008; Swan 2008; Swan et al. 2005; Desvergne et al. 2009, Grun and Blumberg 2007, Philips et al Repro Tox 2019

Phthalates and bisphenols in Generation R First: fetal and postnatal growth

- Pregnancy-averaged phthalic acid (PA, end metabolite of all phthalates; -0.08 SD: 95% CI -0.14, -0.02) and LMW (-0.09 SD: 95% CI -0.16, -0.02): lower fetal weight through 40 weeks postpartum.
- Pregnancy-averaged MEOHP (DEHP metabolite): increased risk of preterm birth (OR 1.43; 95% CI: 1.03-1.97)
- Prenatal phthalate exposures: largely null for body mass outcomes at ages 6 and 10.
- Pregnancy averaged total bisphenol: lower BMI (0.10, 95% CI: -0.17, -0.03) at 10, associations stronger in girls, significant after multiple testing correction.
- First trimester BPS: decreased bone mineral density (6.13 mg/cm^2; 95% CI: -10.02, -2.23) and content (0.12 g, 95% CI: -0.20, -0.04) at age 10 (no sex specific differences, endured multiple testing). (van Zwol-Janssens et al Env Res 2020)

Phthalates and preterm birth: NIH ECHO Program

- 5006 mother–child dyads from 13 cohorts in the ECHO Program
- Phthalic acid, diisodecyl phthalate (DiDP), di-n-octyl phthalate (DnOP), and diisononyl phthalate (DiNP) were most strongly associated with gestational age, birth length, and birthweight, especially compared with DEHP or other metabolite groupings.
- Although DEHP was associated with preterm birth (odds ratio 1·45 [95% CI 1·05–2·01]), the risks per $\log_{10}$ increase were higher for phthalic acid (2·71 [1·91–3·83]), DiNP (2·25 [1·67–3·00]), DiDP (1·69 [1·25–2·28]), and DnOP (2·90 [1·96–4·23]).
- We estimated 56 595 (sensitivity analyses 24 003–120 116) phthalate-attributable preterm birth cases in 2018 with associated costs of US$3·84 billion (sensitivity analysis 1·63– 8·14 billion).

Trasande et al Lancet Planet Health
. 2024 Feb;8(2):e74-e85. doi: 10.1016/S2542-5196(23)00270-X.

Phthalates and bisphenols in Generation R First: fat mass, insulin resistance and BP

- First trimester PA: 0.13 (95% CI: 0.04, 0.21) SD deviation score increase in pericardial fat index (stronger among boys, significant after multiple comparison). (Sol et al Int J Obesity 2020)
- Second trimester maternal urine total bisphenol and BPA: higher systolic BP (0.13; 95% CI 0.03, 0.23 and 0.14; 95% CI 0.04; 0.23) among boys.
- Third trimester PA: 0.20 (95% CI 0.07, 0.34) SD higher triglycerides among boys at age 10. (Sol et al Env Int 2020)
- Some opposite (beneficial) sexually-dimorphic effects:
- Second trimester maternal HMW and DEHP: (0.19; 95% CI 0.31-0.07 and 0.18; 95% CI 0.31-0.06) lower glucose concentration among boys.
- Third trimester BPF: lower non-fasting insulin and glucose concentrations (-0.22; 95% CI -0.35, -0.09 and 0.19; 95% CI 0.32; 0.05) among boys. (Sol et al Env Int 2020)

Phthalates → cardiovascular mortality

- Low T either predictor of or marker of cardiovascular mortality in adult men

- High molecular weight phthalates were associated with lower total, free, and bioavailable testosterone among men age ≥60.
  - Attina et al Lancet Diab Endo 2016; Hauser et al JCEM 2015

Cardiovascular mortality was significantly increased in relation to a prominent DEHP metabolite, mono-(2-ethyl-5-oxohexyl)phthalate.

- Extrapolating to the population of 55-64 year old Americans, 50,200 attributable deaths and $23.4 billion in lost economic productivity.

Trasande et al Env Pollution 2021

Bisphenols → cardiovascular mortality

BPA associated with:

- Reduced carotid intima-media thickness of 12-30 and >70 year olds

  Lin et al Atherosclerosis 2015, Lind et al Atherosclerosis 2011)

- Severity of coronary artery disease in angiography

  Melzer et al PLOS One 2012

- Reduced heart rate variability in adults

  Bae et al Hypertension 2012

- All-cause mortality, and cardiovascular disease mortality

  Bao et al JAMA Network Open 2020

Table 3. Adjusted associations between exposure to BPA and BPS and the risk of type 2 diabetes in the D.E.S.I.R. cohort (single-pollutant models).

	At baseline		At year 3		Average exposure at baseline-year 3	
Bisphenol exposure/detections	*n/N*[a]	aHR (95% CI)[b]	*n/N*[a]	aHR (95% CI)[c]	*n/N*[a]	aHR (95% CI)[d]
BPA exposure		*N* = 726		*N* = 623		*N* = 623
BPA-G concentration (ng/mL)						
<0.71	62/233	1	11/94	1	10/75	1
0.71–1.75	48/182	0.80 (0.53, 1.21)	28/162	1.42 (0.66, 3.07)	33/176	2.56 (1.16, 5.65)
1.75–3.78	39/158	1.01 (0.65, 1.55)	44/190	2.40 (1.16, 4.98)	36/198	2.35 (1.07, 5.15)
≥3.78	38/153	0.85 (0.54, 1.35)	25/177	0.99 (0.44, 2.21)	29/174	1.56 (0.68, 3.55)
BPS detection		*N* = 644		*N* = 579		*N* = 529
BPS-G concentration ≥LOD						
No	139/546	1	92/522	1	61/389	1
Yes	32/98	1.68 (1.09, 2.58)	15/57	1.92 (1.02, 3.62)	38/140	2.81 (1.74, 4.53)

Note: Groups of BPA exposure were defined on the pooled baseline and year 3 BPA-G concentrations in subcohort members. aHR, adjusted hazard ratio; BMI, body mass index; BPA-G, BPA-glucuronide; BPS-G, BPS-glucuronide; CI, confidence interval; D.E.S.I.R., Data from an Epidemiological Study on the Insulin Resistance Syndrome; LOD, limit of detection (0.3 ng/mL).

[a]*n/N* indicates the numbers of type 2 diabetes cases relative to the total number of participants in each exposure category.

[b]aHRs quantify the association between exposure to BPA/BPS and incidence of diabetes between baseline and year 9. Cox models with age as the timescale and stratified on smoking status were adjusted for sex and the following variables from baseline: urinary creatinine level, education level, employment, marital status, physical activity, caloric intake, family history of diabetes, hypertension, and BMI.

[c]aHRs quantify the association between exposure to BPA/BPS and incidence of diabetes between year 3 and year 9. Cox models with age as the timescale and stratified on smoking status were adjusted for sex and the following variables from year 3: urinary creatinine level, education level, employment, marital status, physical activity, caloric intake, family history of diabetes, hypertension, and BMI.

[d]aHRs quantify the association between exposure to BPA/BPS and incidence of diabetes between year 3 and year 9. Cox models with age as the timescale and stratified on smoking status were adjusted for sex, average urinary creatinine level, and the following variables from year 3: education level, employment, marital status, physical activity, caloric intake, family history of diabetes, hypertension, and BMI.

Ranciere et al EHP 2019

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Per- and polyfluoroalkyl substances (PFAS)

Synthetic organic fluorinated compounds with high stability and thermal resistance

Detectable in blood of >98% of the US population.

Food packaging is a major route of exposure (nonstick cooking, microwaveable popcorn bags)

Meta-analysis of 24 studies: −10·5 g (95% CI: −16·7, −4·4) birth weight per ng/ml increase in maternal or cord blood PFAS

Steenland et al Epidemiology 2018

PFAS and adult weight gain/diabetes

Diabetes Prevention Program lifestyle intervention trial:

- Total PFAS were associated with increased weight gain exclusively among the control group.

Cardenas et al 2018

Follow-up of the successful POUNDS LOST trial:

- Perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFNA), were associated with reductions in resting metabolic rate.

Liu et al 2018

PIVUS (Sweden), Nurses (US), DPPOS (US):

- PFAS associated with incident diabetes

Cardenas et al 2019, Sun et al 2018, Lind et al 2014

Endocrine disruption and fertility

- Fertility is a condition of a couple, where reproductive health of both sexes plays a role

Louis et al 2013

- Fetal exposure to phthalates with reduced infant anogenital distance (AGD)

Swan et al EHP 2005, Bornehag et al EHP 2014

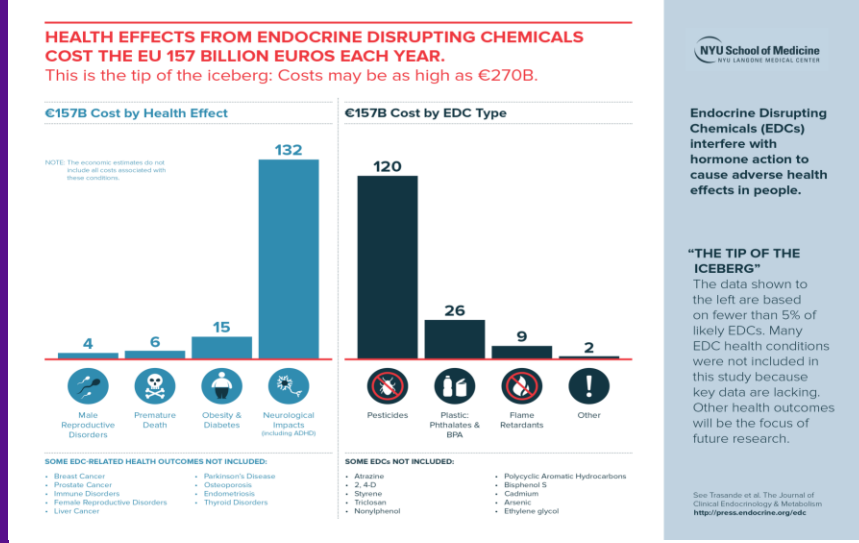
- Shortened adult AGD is associated with reduced semen quality and testosterone level

- Multiple studies have identified reduced male fertility and poor semen quality with multiple EDCs, including phthalates, bisphenol A, and polyfluorinated chemicals

Juul et al Nat Rev Endo 2014

What is the burden of disease burden and are the health costs due to EDCs?

- Expert panels identified conditions where the evidence is strongest for causation
  - Developed ranges for fractions of disease burden that can be attributed for EDCs
  - Adapted GRADE Working Group and WHO criteria for evaluating epidemiologic evidence
  - Adapted Danish EPA criteria for evaluating toxicology evidence
  - Adapted IPCC approach to integrate epidemiology and toxicology evidence and estimate probability of causation



Fewer than 5% of EDCs

Subset of diseases due to EDCs selected

Subset of costs due to conditions examined

Severe underestimate of total costs

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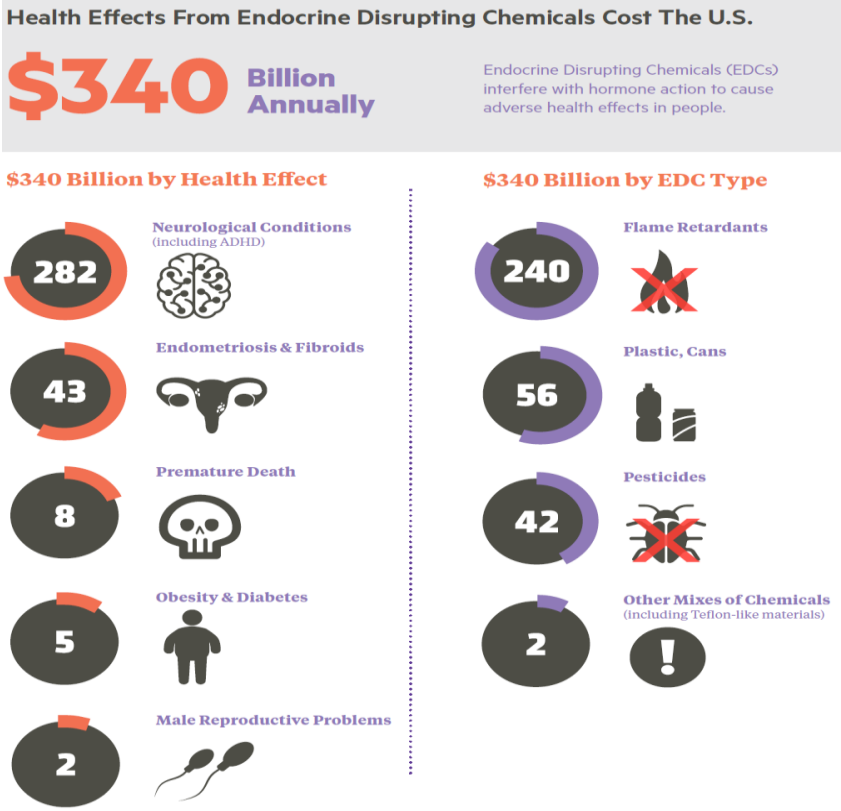
Policies predict exposure.

Exposure contributes to disease.

Disease affects us all.

- Costs in US higher than EU
  - Largely due to PBDE legacy
- Lower costs due to pesticides in US
  - Thanks to the Food Quality Protection Act!



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PFAS disease burden and costs

PFAS-attributable disease costs in the US: $5.52-62.6 billion/year across 13 conditions

- LBW due to prenatal exposure
- childhood obesity due to prenatal exposure
- kidney cancer due to lifetime exposure
- testicular cancer due to lifetime exposure
- hypothyroidism in females due to lifetime exposure
- adult obesity due to exposure over the lifespan
- T2D in females due to exposure over the lifespan
- GDM due to exposure measured in pregnancy
- endometriosis due to exposure over the lifespan
- PCOS due to exposure over the lifespan
- couple infertility due to lifetime exposure in females
- female breast cancer due to lifetime exposure, and
- pneumonia in children due to prenatal exposure

Obsekov et al Exposure and Health 2022

Data from 70 countries suggest exposure to PFAS contributed to approximately 461,635 (95% CI: 57,418-854,645) cases per year of LBW during the past two decades, predominantly from Asian regions.

Fan et al ES&T 2022

How much of the disease burden due to EDCs is related to plastic?

- 97.5% for bisphenol A (96.25-98.75% for sensitivity analysis)
- 98% (96%-99%) for di-2-ethylhexylphthalate
- 100% (71%-100%) for butyl phthalates and benzyl phthalates,
- 98% (97%-99%) for PBDE-47
- 93% (16%-96%) for PFAS

Chemicals Used in Plastic Materials: An Estimate of the Attributable Disease Burden and Costs in the United States

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Abstract

Context: Chemicals used in plastics have been described to contribute to disease and disability, but attributable fractions have not been quantified to assess specific contributions. Without this information, interventions proposed as part of the Global Plastics Treaty cannot be evaluated for potential benefits.

Objective: To accurately inform the tradeoffs involved in the ongoing reliance on plastic production as a source of economic productivity in the United States, we calculated the attributable disease burden and cost due to chemicals used in plastic materials in 2018.

Methods: We first analyzed the existing literature to identify plastic-related fractions (PRF) of disease and disability for specific polybrominated diphenylethers (PBDE), phthalates, bisphenols, and polyfluoroalkyl substances and perfluoroalkyl substances (PFAS). We then updated previously published disease burden and cost estimates for these chemicals in the United States to 2018. By uniting these data, we computed estimates of attributable disease burden and costs due to plastics in the United States.

Results: We identified PRFs of 97.5% for bisphenol A (96.25-98.75% for sensitivity analysis), 98% (96%-99%) for di-2-ethylhexylphthalate, 100% (71%-100%) for butyl phthalates and benzyl phthalates, 98% (97%-99%) for PBDE-47, and 93% (16%-96%) for PFAS. In total, we estimate $249 billion (sensitivity analysis: $226 billion-$289 billion) in plastic-attributable disease burden in 2018. The majority of these costs arose as a result of PBDE exposure, though $66.7 billion ($64.7 billion-67.3 billion) was due to phthalate exposure and $22.4 billion was due to PFAS exposure (sensitivity analysis: $3.85-$60.1 billion).

Conclusion: Plastics contribute substantially to disease and associated social costs in the United States, accounting for 1.22% of the gross domestic product. The costs of plastic pollution will continue to accumulate as long as exposures continue at current levels. Actions through the Global Plastics Treaty and other policy initiatives will reduce these costs in proportion to the actual reductions in chemical exposures achieved.

- In total, we estimate $249 billion (sensitivity analysis: $226 billion-$289 billion) in plastic-attributable disease burden in 2018.
- The majority of these costs arose as a result of PBDE exposure, though $66.7 billion ($64.7 billion-67.3 billion) was due to phthalate exposure and $22.4 billion was due to PFAS exposure (sensitivity analysis: $3.85-$60.1 billion).

Trasande et al J Endo Soc 2024

HASSENFELD CHILDREN'S HOSPITAL AT NYU LANGONE

Disparities in high-income countries

- EDC exposure levels and associated burden of disease and costs higher in non-Hispanic Blacks ($56.8 billion; 16.5% of total costs) and Mexican Americans ($50.1 billion; 14.6%) compared with their proportion of the total population (12.6% and 13.5%, respectively).

- Associated costs among non-Hispanic whites comprised 52.3% of total costs ($179.8 billion) although they comprise 66.1% of the US population.

What can we do limit EDC exposures?

- **Fortunately, there are safe and simple steps families can take at home to limit these exposures.**

- We can also advocate for proactive policies that limit exposures to common dietary contaminants.

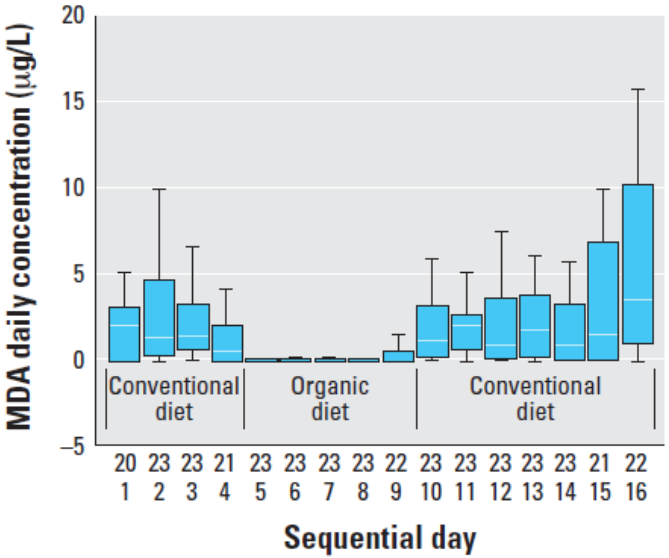


Figure 1. Box plots of DVWA of MDA concentrations in 23 children 3–11 years of age for 15 consecutive days in which conventional and organic diets were consumed. The top row of numbers on the *x*-axis represents numbers of children.

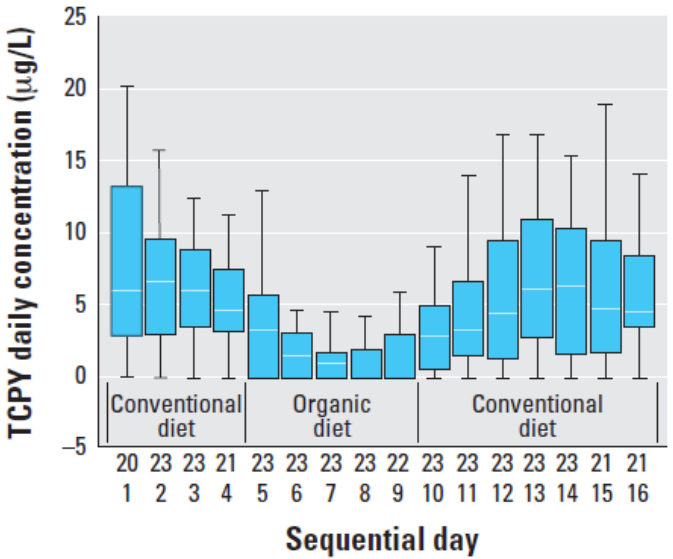


Figure 2. Box plots of DVWA of TCPY concentrations in 23 children 3–11 years of age for 15 consecutive days in which conventional and organic diets were consumed. The top row of numbers on the *x*-axis represents numbers of children.

Lu et al EHP 2006

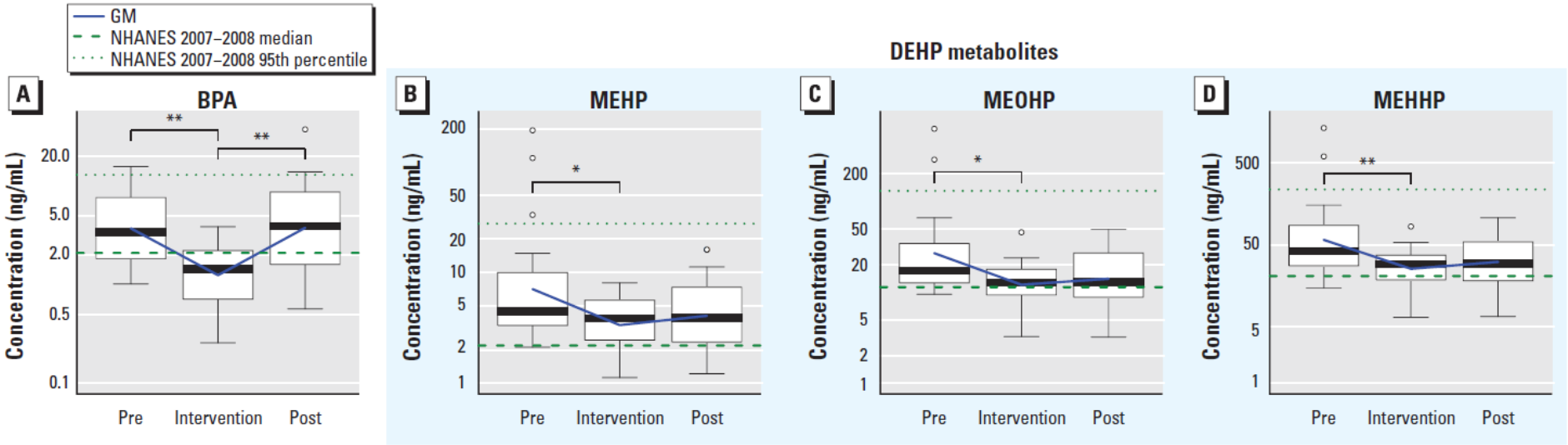
Pesticide exposures are preventable in high SES populations…

Organic diet intervention in Mexican-American children

- 3-6 years of age, California urban and agricultural communities
- Adjusted geometric mean concentrations were significantly lower for total dialkylphosphates (DAPs) and dimethyl DAPs (DMs; metabolites of OP insecticides) and 2,4-D (2,4-dichlorophenoxyacetic acid, a herbicide), with reductions of 40%, 49%, and 25%, respectively ($p < 0.01$).

Bradman et al EHP 2015

…and low-resource communities as well



Rudel et al EHP 2011

Bisphenol and phthalate exposures are preventable (also in high SES populations)…

- Youth-led, community-based participatory research intervention
- 100 Latina girls using personal care products whose labels stated they did not contain these chemicals for 3 days
- Urinary concentrations of monoethyl phthalate decreased by 27.4% (95% CI: –39.3, –13.2) on average over the 3-day intervention

Harley et al EHP 2016

…and low-resource communities as well

- 15 PFAS, 8 PBDEs, and 19 organophosphorus esters (PBDE replacements) measured in dust from offices, common areas, and classrooms having undergone:
  - no intervention (conventional rooms in older buildings meeting strict fire codes)
  - full “healthier” materials interventions (rooms with “healthier” materials in buildings constructed more recently or gut-renovated), or
  - partial interventions (other rooms with at least “healthier” foam furniture but more potential building contamination).
- Rooms with full “healthier” materials interventions had 78% lower dust levels of PFAS than rooms with no intervention ($p<0.01$).
- Rooms with full “healthier” interventions also had 65% lower OPE levels in dust than rooms with no intervention ($p<0.01$) and 45% lower PBDEs than rooms with only partial interventions ($p<0.1$), adjusted for covariates related to insulation, electronics, and furniture.

Young et al Env Int 2020

Household environment matters too!

Safe and simple steps to limit exposure

- Avoid canned foods. Bisphenol A (BPA) doesn't discriminate by the type of can – soda, vegetables, tuna. Acidity is probably the biggest driver of absorption into food, but all types of canned food have detectable levels of BPA.
- Don't microwave plastic containers or put them in the dishwasher. Heat and harsh cleaning agents are effective at getting the chemicals out of plastic.
- Avoid plastic bottles with the numbers 3, 6 or 7.
- If plastic bottles were meant for single use, keep them that way. Besides, reusing them raises the chance of bacterial contamination.
- If plastic food containers are etched, it's time to throw them away. Etching increases the odds of leaching.
- Use stainless steel or cast iron cookware.
- Vacuum regularly with a HEPA filter and mop with a wet mop to prevent dust from accumulating.

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Change is needed

- Testing and identifying
- Evaluating exposures
- Limiting exposures through regulation
- An International Agency for Research on EDCs

Testing and identifying EDCs

- Currently available/validated tests do not cover all endocrine modes of action
- US regulations require testing for estrogen agonist activity only for pesticides and drinking water contaminants
    - Even for estrogen and androgen signaling, validated tests too insensitive, working best for endogenous hormones (e.g., uterotrophic assay)
- EU ECHA/EFSA guidance document: estrogenic, androgenic, thyroid and steroidogenic modalities
- Sensitive assays exist to test a broader number of nuclear receptors
- Assays to examine receptor expression, hormone transport, hormone synthesis, and epigenetic alterations, should soon be validated for inclusion in regulatory requirements.

Testing and identifying EDCs: a proposal

- Two-tiered pre-market testing system to prevent regrettable substitutes and new hazards

- Tier 1: High-throughput *in vitro* screening methods for agonist and antagonist activities of a broad range of receptors (not limited to nuclear types), as well as receptor-independent mechanisms
- Tier 2: More sensitive *in vivo* assays focusing on endpoints relevant to human diseases, and relevant critical windows
    - Non-mammalian vertebrate models have great potential

Evaluating exposures

- If persist with risk based approach, need broader and stronger human biomonitoring platform
- Particularly to address gaps in low- and middle-income countries
- Can also inform educational campaigns about safe and simple steps to limit exposure

- Disclosure of ingredients also crucial (right-to-know)

Shifting to a hazard-based paradigm

- For many EDCs, data are lacking to support using risk-based approaches, hampering other regulatory actions

- Lag from identifying new exposures to completing human studies of effects, especially for disease outcomes with longer latencies such as diabetes or cancers
- Non-monotonic exposure-response relationships exist for many synthetic chemicals including EDCs → inability to extrapolate to no adverse effect levels
- While some risk-based approaches try to account for age-related vulnerability, they falsely presume that the population sensitivity can be quantified *a priori*
- *Precedents in EU:* Carcinogens; Persistent, bioaccumulative and toxic; very bioaccumulative; EDCs (pesticides and biocides only)

An International Agency for Research on EDCs

- We suggest the establishment of a new international agency, or a broadening of the International Agency for Research on Cancer (IARC)'s scientific charge, to include endocrine disruption

- Established in 1965, IARC tasked with evaluating the evidence of carcinogenesis due to environmental hazards

- Monographs describe three streams of evidence (mechanistic, animal, and epidemiological studies)

- Autonomous body like IARC can bring together diverse experts for international collaborative reports on EDCs would foster global movement on regulations

- An International Agency for Research in Endocrine Disruption would further support post-2020 process of Strategic Alliance for International Chemicals Management

The role of health care providers

- The health care system itself has contributed to the EDC crisis and is part of the solution.
- Some polyvinylchloride and polycarbonate plastics are essential for the proper functioning of medical devices such as blood bags, nutrition pockets, tubing, umbilical venous catheters, hemodialysis equipment, newborn incubators, syringes and nebulizers.
- But many uses in patient care are optional!

The role of health care providers

Fortunately, health care facilities have begun to support sustainability initiatives that reduce the use of chemical hazards.

- Practice Greenhealth, a network of over 1,400 hospitals in the US, has implemented sustainability initiatives and climate-smart strategies in their facilities. The network also includes industry partners (manufacturers, suppliers, service providers, and other supply chain partners).
- Health Care without Harm supports hospital partners in recommending safer medical products and other materials that health care organizations and hospitals should adopt.

Summary

Endocrine disruption by synthetic chemicals is costly to human health and the environment

Urgent needs for:

- Establishment of global biomonitoring programs
- Mandatory provision of chemical composition for marketed substances
- Inclusion of economic costs associated with EDC-related morbidities
- Hazard-based approach to regulation of EDCs
- Establishment of International Agency for Research on EDCs

Thank you

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