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Food Additives and Child Health:

A Review of the Technical Report and Policy Statement from the American Academy of Pediatrics

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Introduction to American Academy of Pediatrics (AAP)

The AAP is an organization of 67,000 pediatricians committed to the optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.

The Council on Environmental Health (COEH) is the home for Academy members interested in and concerned about children's environmental health and toxic exposures.

Introduction to AAP's Council on Environmental Health (COEH)

Our key activities include:

- Advising the AAP Board of Directors on issues pertaining to environmental health and toxic exposure. Council-authored policy statements address issues such as air pollution, lead screening, pesticides, radiation disasters, and secondhand smoke.
- Supporting legislative initiatives designed to protect the health of the fetus, infant, and child from debilitating or hazardous environmental agents.
- Developing educational initiatives related to children's environmental health.
- Publishing the Academy landmark Pediatric Environmental Health manual, currently in its third edition.

Introduction to AAP Statements


TECHNICAL REPORT

American Academy of Pediatrics

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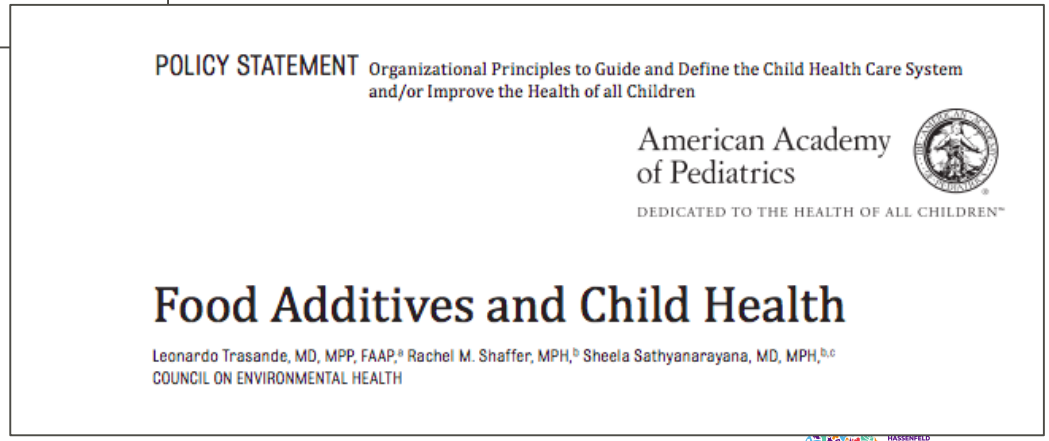
Food Additives and Child Health

Leonardo Trasande, MD, MPP, FAAP,[a] Rachel M. Shaffer, MPH,[b] Sheela Sathyanarayana, MD, MPH,[b,c]
COUNCIL ON ENVIRONMENTAL HEALTH


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

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Food Additives and Child Health

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Technical Report

Goal: Review evidence of harm to child health from food additives

- Epidemiological & toxicological data
- Exposure data & trends

Categories of food additives:

- Indirect: food contact materials, used in packaging or processing
  - Adhesives, coatings, plastics, paperboard
- Direct: deliberately added to food
  - Colorings, flavorings

Chemical environmental agents and the endocrine system

Endocrine disruptors (EDs) are chemicals that have the capacity to interfere with hormonal signaling systems

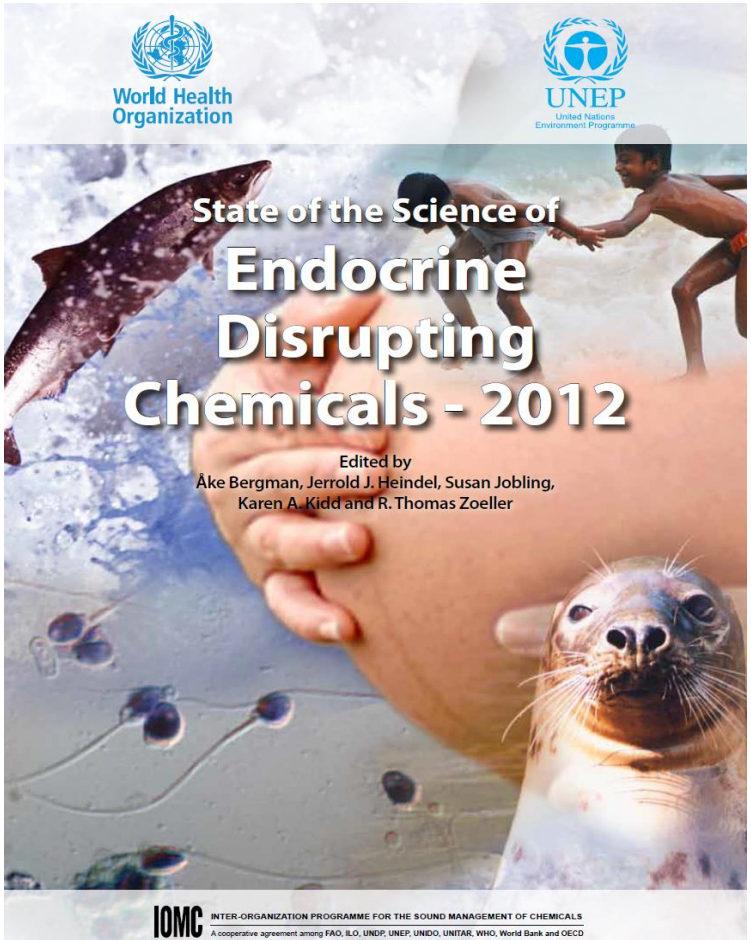
- May mimic, block, or modulate the synthesis, release, transport, metabolism, binding, or elimination of natural hormones
- May temporarily or permanently alter feedback loops in the brain, pituitary, gonads, thyroid, and other components of the endocrine system

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement

Evanthia Diamanti-Kandarakis, Jean-Pierre Bourguignon, Linda C. Giudice, Russ Hauser, Gail S. Prins, Ana M. Soto, R. Thomas Zoeller, and Andrea C. Gore

Endocrine Section of First Department of Medicine (E.D.-K.), Laiko Hospital, Medical School University of Athens, 11527 Athens, Greece; Department of Pediatrics (J.-P.B.), Centre Hospitalier Universitaire de Liege, 4000 Liege, Belgium; Department of Obstetrics, Gynecology, and Reproductive Sciences (L.C.G.), University of California San Francisco, San Francisco, California 94131; Department of Environmental Health (R.H.), Harvard School of Public Health, Boston, Massachusetts 02115; Department of Urology (G.S.P.), University of Illinois at Chicago, Chicago, Illinois 60612; Department of Anatomy and Cell Biology (A.M.S.), Tufts University School of Medicine, Boston, Massachusetts 02111; Biology Department (R.T.Z.), University of Massachusetts, Amherst, Massachusetts 01003; and Division of Pharmacology and Toxicology (A.C.G.), The University of Texas at Austin, Austin, Texas 78712

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)**



Response to WHO/UNEP Report

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

- Footnote identifies only chemical and pesticide industries as having concerns about state of science
- Concerns voiced in response by Lamb et al rebutted by WHO/UNEP report authors in Reg Tox Pharm Bergman et al 2015

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

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

Pharmacology and Toxicology (A.C.G.), College of Pharmacy, The University of Texas at Austin, Austin, Texas 78734; Division of the National Toxicology Program (V.A.C., S.E.F.), National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709; Department of Comparative Biosciences (J.A.F.), University of Illinois at Urbana-Champaign, Urbana, Illinois 61802; Institute of Bioengineering and CIBERDEM (A.N.), Miguel Hernandez University of Elche, 03202 Elche, Alicante, Spain; Departments of Urology, Pathology, and Physiology & Biophysics (G.S.P.), College of Medicine, University of Illinois at Chicago, Chicago, Illinois 60612; Departments of Physiology and Pediatrics (J.T.), University of Turku and Turku University Hospital, 20520 Turku, Finland; and Biology Department (R.T.Z.), University of Massachusetts at Amherst, Amherst, Massachusetts 01003

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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Indirect Food Additives

Chemical	Food-Related Use	Health Concerns
Bisphenols (Bisphenol-A & related compounds)	• Polycarbonate plastic containers • Polymeric epoxy resins for food & beverage cans	• Endocrine disruption • Obesogenic activity • Neurodevelopmental disruption
Phthalates	• Clear plastic food wrap • Plastic tubing & storage containers for food production • Food manufacturing equipment	• Endocrine disruption • Obesogenic activity • Oxidative stress • Cardiotoxicity
Perfluoroalkyl chemicals (PFCs)	• Grease-proof paper and paperboard	• Immunosuppression • Endocrine disruption • Obesogenic activity
Perchlorate	• Antistatic agent in food packaging • Contamination from food manufacturing cleaning products	• Thyroid hormone disruption

Direct Food Additives

Chemical	Food-Related Use	Health Concerns
Nitrates/nitrites	• Preservative • Color enhancer	• Carcinogenicity • Thyroid hormone disruption
Artificial food coloring	• Coloring	• Potential effects on neurobehavioral outcomes; (ex: exacerbation of attention-deficit/hyperactivity disorders)

Policy Statement

Goals:

- Review regulatory system for food additives
- Provide guidance for pediatricians to incorporate into clinical visits
- Propose reforms to current regulatory process

https://www.helpsystems.com/blog/network-monitoring-government-agencies-areas-focus

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Regulatory Framework for Food Additives

Federal Food, Drug, and Cosmetic Act (FFDCA) (1938)

- Gave authority to US Food and Drug Administration (FDA) to oversee safety of food, drugs, medical devices, & cosmetics

FFDCA Food Additive Amendment (1958)

- Established food additives regulatory program
- Definition of “food additives”
- Exemption for substances *Generally Recognized as Safe (GRAS*)

Food and Drug Administration Modernization Act of 1997 (1997)

- Created approval process for food contact substances (FCS)

What is a “Food Additive?”

Food additive: substances “*the intended use of which results or may reasonably be expected to result, directly or indirectly, in becoming a component or otherwise affecting the characteristics of any food*” (21 USC 321(s) and 21 CFR 170.3)

- Direct: intentionally added to food
  - ex: colorings, flavorings
- Indirect: not intentionally added to foods but reasonably expected to be part of food
  - ex: materials in food packaging & processing equipment

https://www.istockphoto.com/photo/american-grocery-collection-gm458413271-23870026

https://www.npr.org/sections/health-shots/2011/07/22/138606851/got-enhanced-meat-usda-rule-may-make-it-easier-to-tell

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Does the current regulatory system ensure food safety?

Most food additives have not been tested

- Neltner et al. 2013 study on 3941 direct food additives
  - 63.9% had no oral toxicology data
  - 93.3% had no reproductive toxicology data

Reasons for shortcomings

1. Extensive use of “GRAS” designation
2. Limitations to FDA authority & procedures

https://www.foodsafetynews.com/2014/04/report-identifies-chemicals-quietly-added-to-food-under-gras/

Neltner TG, Alger HM, Leonard JE, Maffini MV. Data gaps in toxicity testing of chemicals allowed in food in the United States. Reprod Toxicol. 2013;42:85 94pmid:23954440

Key Loophole: “GRAS”

Generally Recognized as Safe (GRAS): substances “*generally recognized, among experts qualified by scientific training and experience to evaluate the safety as having been adequately shown…to be safe under conditions of their intended use*” (21 USC 321(s))

No opportunity or legal obligation for FDA or public review

Intended for limited use, but now widespread (~1000 chemicals)

Extensive conflict of interest in GRAS designations

- Manufacturers or consultants can self-designate products as “GRAS”

Neltner TG, Alger HM, O’Reilly JT, Krimsky S, Bero LA, Maffini MV, Conflicts of interest in approvals of additives to food determined to be generally recognized as safe: out of balance. JAMA Intern Med.2013;173(22):2032–2036pmid:23925593

Limitations to FDA authority & procedures

No authority to obtain data or re-assess safety of chemicals already on the market

No consideration of cumulative or synergistic effects

Outdated toxicological testing recommendations may not be sufficiently protective for children

- Testing guidelines based on estimated daily exposure, without consideration of body weight
- Limited/no evaluation of neurobehavioral or endocrine endpoints

Recommendations for Pediatricians & Patients

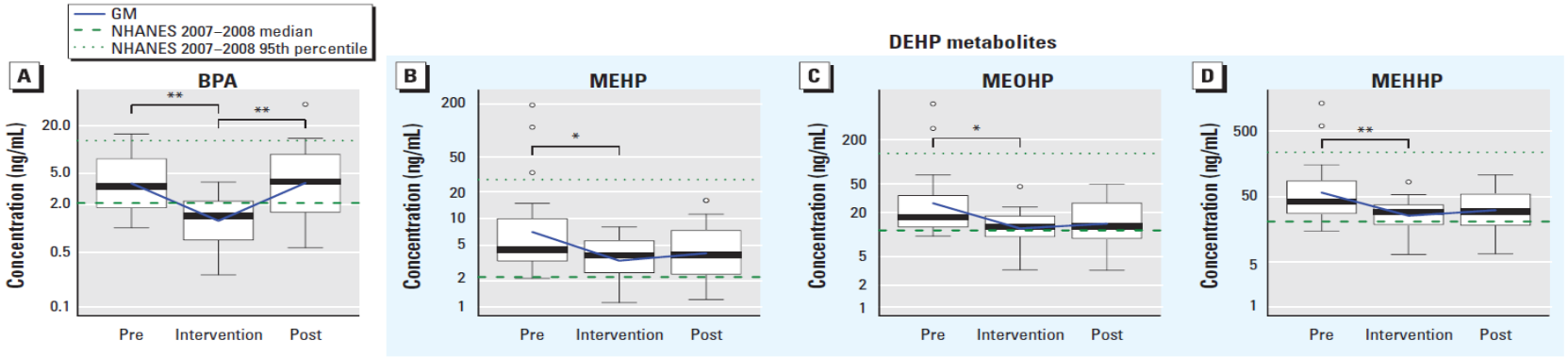
- Prioritize consumption of fresh or frozen fruits & vegetables
- Avoid processed meats, especially during pregnancy
- Avoid microwaving food or beverages in plastics
- Avoid putting plastics in dishwasher
- Avoid plastics with recycling codes 3 (phthalates), 6 (styrene), and 7 (bisphenols)
- Encourage hand-washing before handling foods
- Wash all fruits & vegetables that cannot be peeled

http://newsroom.ucla.edu/stories/ucla-faculty-voice-pediatricians-need-to-discuss-gun-safety-with-patients

Bisphenol and phthalate exposures are preventable

Limiting canned food consumption and avoiding processed foods

- Intervention reduced mean concentrations of BPA by 66% and DEHP metabolites by 53–56%.



Rudel et al EHP 2011

Recommendations for Government & Policy

FDA should:

- Revise the “GRAS” process
- Coordinate with other agencies to address existing data gaps
- Establish requirements for prioritization and re-testing of approved chemicals
- Update safety assessment guidelines
  - Ex: endocrine disruption testing, safety factors for children, synergistic & cumulative effects
- Establish requirements for labeling of food additives with little or no toxicity data, and those not reviewed for safety by FDA

Congress should

- Provide FDA with authority to collect information about food additives (ex: use & toxicity data)
- Provide FDA with dedicated resources to support strengthened agency activities
- Support provisions to ensure transparency and minimize conflict of interest

Policy action on BPA

BPA banned in baby bottles and sippy cups

- But not in other food uses

Costs of BPA exposure

12,404 cases of childhood obesity

33,863 cases of newly incident coronary heart disease

Estimated social costs of $2.98 billion in 2008

Trasande Health Affairs 2014

Benefits and costs of replacing BPA

- Potential cost of one BPA alternative, oleoresin = $0.022 per can
  - 100 billion aluminum cans are produced annually
  - 100 billion x $0.022 = **$2.2 billion**

- Potential benefit of replacing BPA with lining free of health effects = **$1.74 billion**
  - Does not include other effects (cognitive, asthma, breast cancer)

- Sensitivity analyses suggest as high as $13.8 billion

Trasande Health Affairs 2014

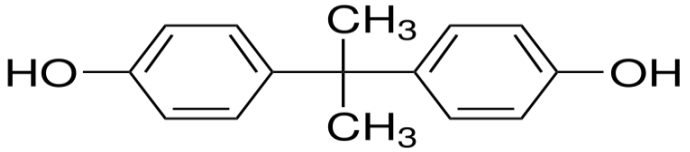
BPS replacing BPA?

Emerging evidence suggests replacement of BPA and BPS

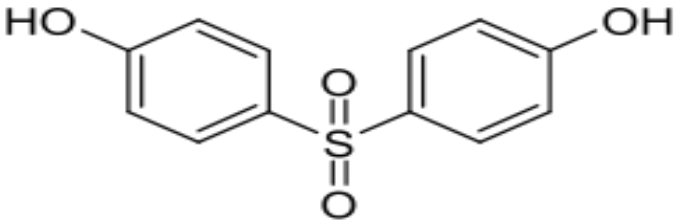
Similar, weak estrogen like BPA

Disrupts signaling of estrogen in animal studies

Does not degrade as easily in seawater



Bisphenol A



Bisphenol S

Liao et al Environ Sci Technol. 2012 Jun 19;46(12):6860-6.
Liao et al Environ Sci Technol. 2012 Jun 19;46(12):6515-22.
Grignard et al Toxicol In Vitro. 2012 Aug;26(5):727-31.
Vinas and Watson EHP doi:10.1289/ehp.1205826
Danzl et al Int J Environ Res Public Health. 2009 Apr;6(4):1472-84

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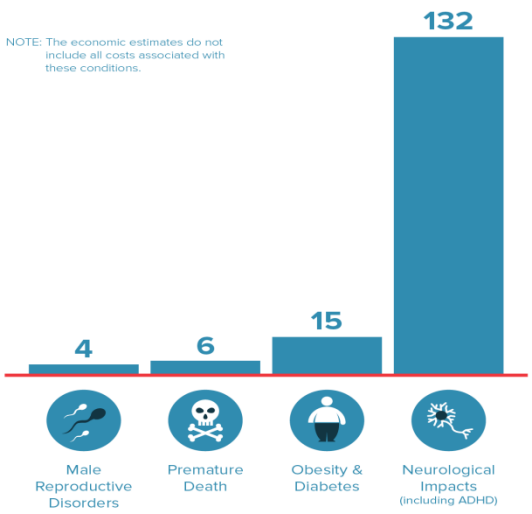
HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR.

This is the tip of the iceberg: Costs may be as high as €270B.

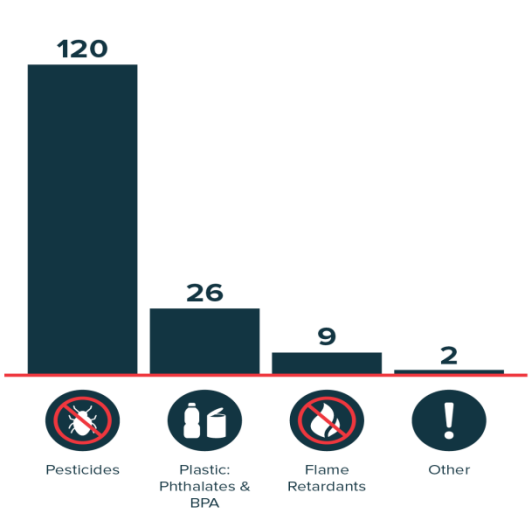
€157B Cost by Health Effect



SOME EDC-RELATED HEALTH OUTCOMES NOT INCLUDED:

- Breast Cancer
- Prostate Cancer
- Immune Disorders
- Female Reproductive Disorders
- Liver Cancer
- Parkinson's Disease
- Osteoporosis
- Endometriosis
- Thyroid Disorders

€157B Cost by EDC Type



SOME EDCs NOT INCLUDED:

- Atrazine
- 2, 4-D
- Styrene
- Triclosan
- Nonylphenol
- Polycyclic Aromatic Hydrocarbons
- Bisphenol S
- Cadmium
- Arsenic
- Ethylene glycol

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Endocrine Disrupting Chemicals (EDCs) interfere with hormone action to cause adverse health effects in people.

"THE TIP OF THE ICEBERG"

The data shown to the left are based on fewer than 5% of likely EDCs. Many EDC health conditions were not included in this study because key data are lacking. Other health outcomes will be the focus of future research.

See Trasande et al. The Journal of Clinical Endocrinology & Metabolism
http://press.endocrine.org/edc

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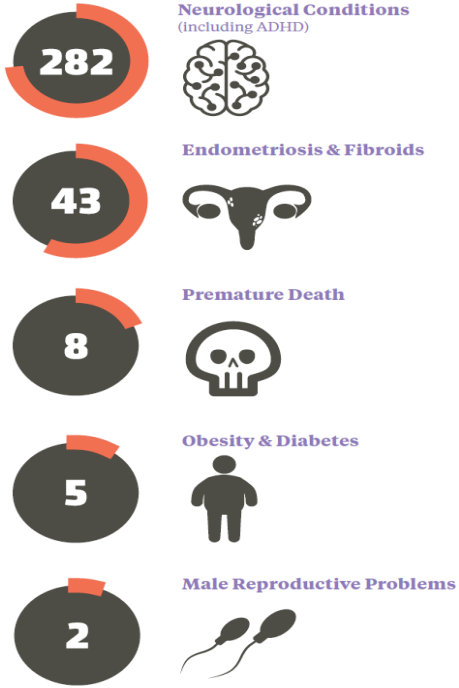
Health Effects From Endocrine Disrupting Chemicals Cost The U.S.

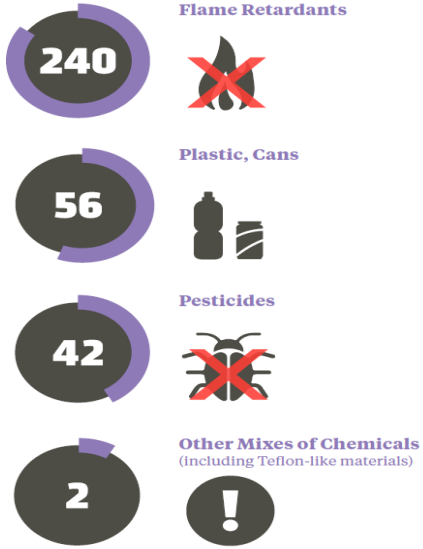
$340 Billion Annually

Endocrine Disrupting Chemicals (EDCs) interfere with hormone action to cause adverse health effects in people.

$340 Billion by Health Effect



$340 Billion by EDC Type



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Thank you

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