Nutrizione e Disruptor Endocrini: Tiroide

Prof. Vincenzo Triggiani

Dipartimento Interdisciplinare di Medicina

Università degli Studi di Bari "A. Moro

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Sponsorizzazione per la partecipazione a congressi da parte di: Lilly, Sanofi, IBSA, Merck-Serono, Shire, Guidotti, Neo-Pharmed Gentili, Medtronic, Alpha-Sigma.

Generalità sugli EDs

- According to the US Environmental Protection Agency (EPA) an **endocrine disrupting compound** (EDC) is defined as "an **exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding, action or elimination of natural blood-borne hormones** that are present in the body and are responsible for homeostasis, reproduction, and developmental process"

Diamanti-Kandarakis, E et al. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. Endocr. Rev. **2009**, 30, 293–342

- A subsequent scientific statement from the Endocrine Society defined the EDC as **"an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action"**

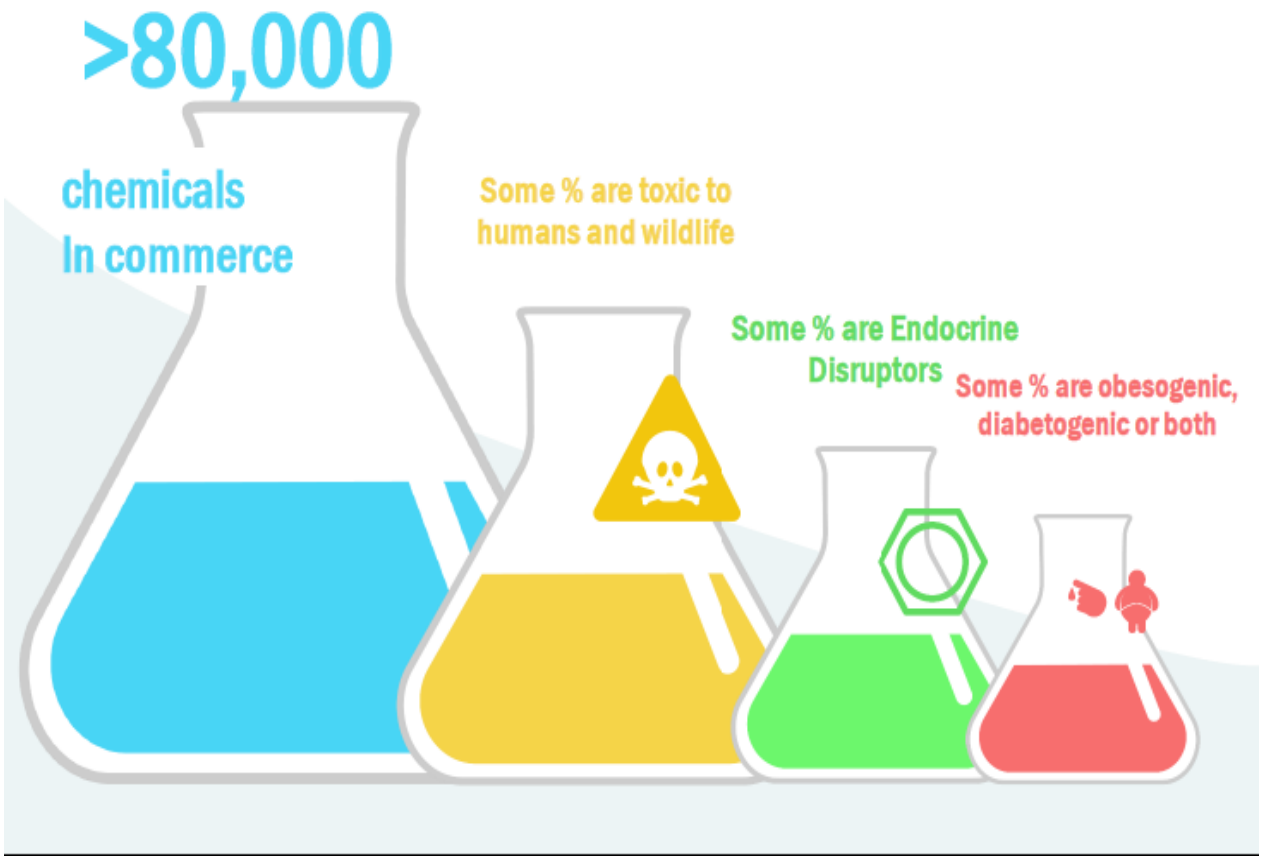
Zoeller, R.T. et al Endocrine-disrupting chemicals and public health protection: A statement of principles from The Endocrine Society. Endocrinology **2012**, 153, 4097–4110.

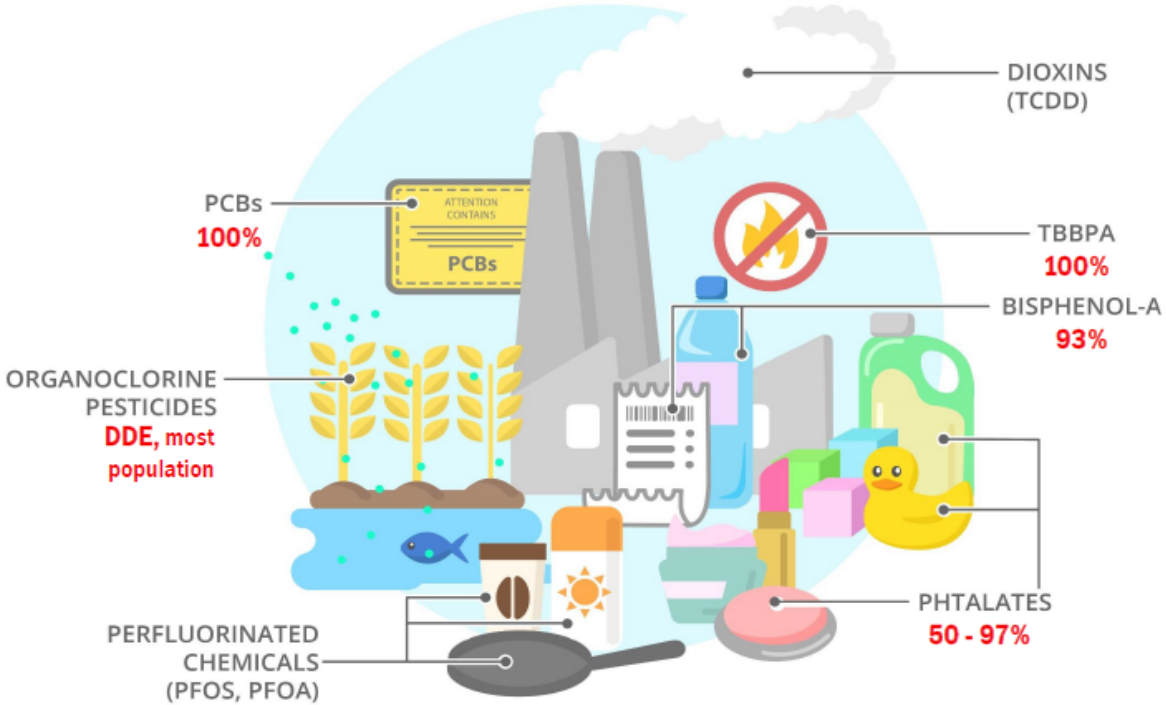
Endocrine Disruptors

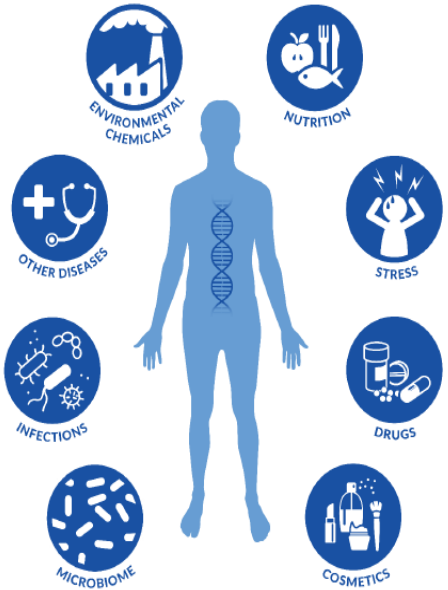
An **endocrine disruptor** is an exogenous chemical, or mixture of chemicals, that **interferes with any aspect of hormone action.**

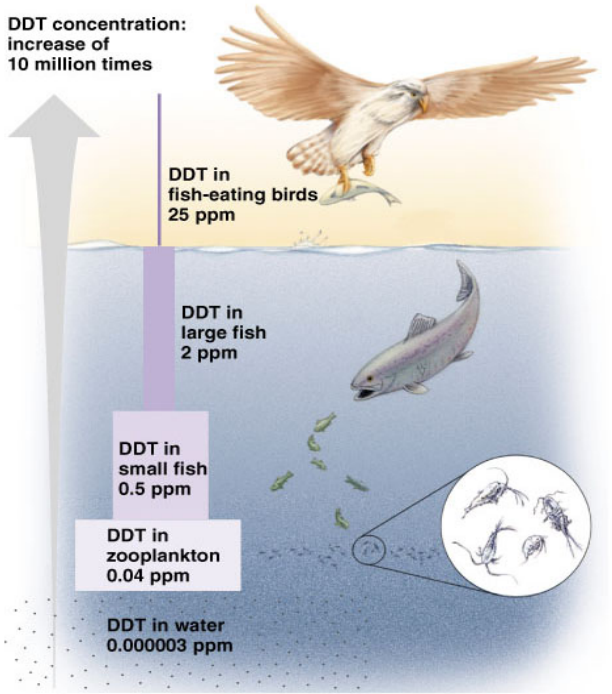
Zoeller et al, Endocrine Society Position Statement, Endocrinology 153: 4097–4110, 2012

Endocrine Disruptors




DIOXINS
(TCDD)
PCBs
100%
ATTENTION
CONTAINS
PCBs
TBBPA
100%
BISPHENOL-A
93%
ORGANOCLORINE
PESTICIDES
DDE, most
population
PHTALATES
50 - 97%
PERFLUORINATED
CHEMICALS
(PFOS, PFOA)
91 – 99%
% of people tested by CDC


ENVIRONMENTAL CHEMICALS
NUTRITION
OTHER DISEASES
STRESS
INFECTIONS
DRUGS
MICROBIOME
COSMETICS


DDT concentration: increase of 10 million times
DDT in fish-eating birds 25 ppm
DDT in large fish 2 ppm
DDT in small fish 0.5 ppm
DDT in zooplankton 0.04 ppm
DDT in water 0.000003 ppm


"DDT is good for me-e-e!"


WHERE YOU CAN FIND EDCs
PESTICIDES
CHILDREN'S PRODUCTS
FOOD CONTACT MATERIALS
ELECTRONICS AND BUILDING MATERIALS

Important variables for the final phenotype

Exposure levels on humans
Dosage on animal models

Timing of Exposure

Gender and Age

We all carry a Chemical Body Burden

287 chemicals in **cord blood**

47 chemicals in every **pregnant woman** tested

In **breast milk** (BPA, PCBs, dioxins, pesticides, mercury, flame retardants)

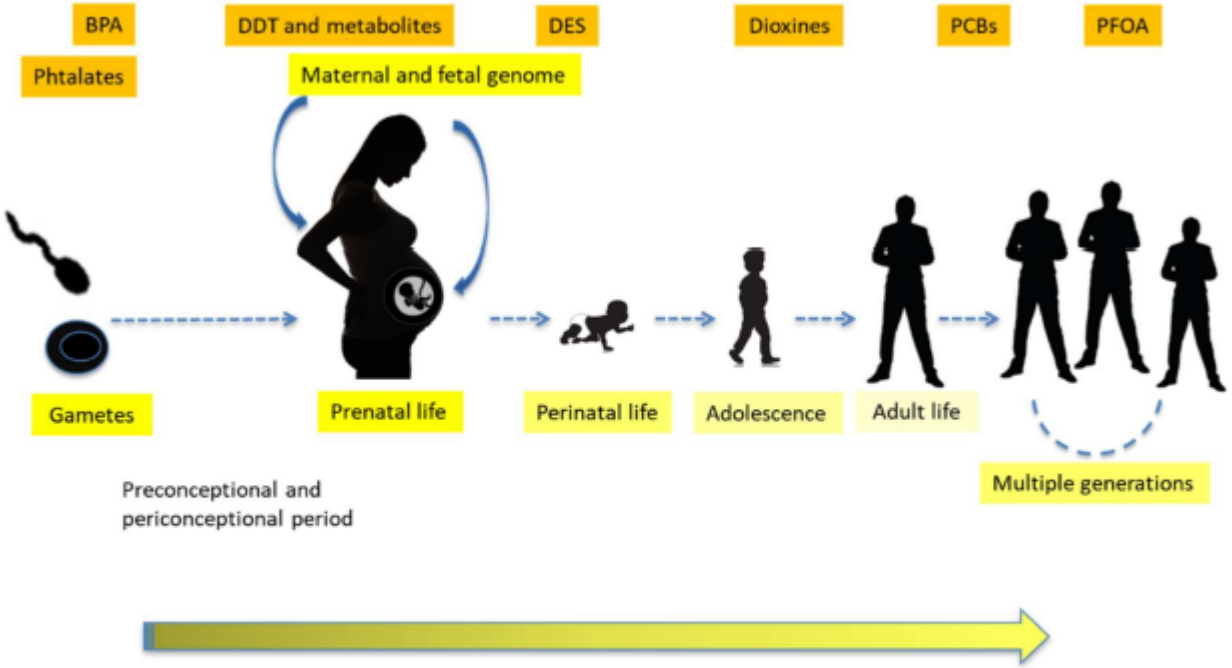
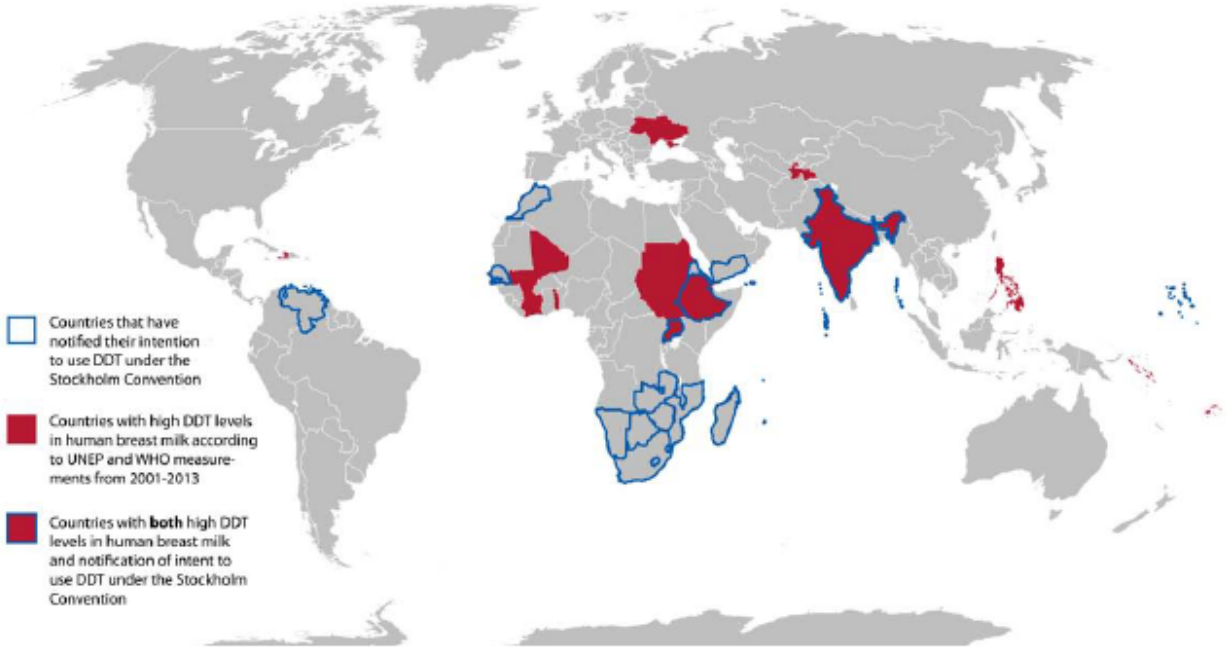


Figure 2. Importance of EDCs driven epigenetic effects during life course and potential consequences across generations according to the Developmental Origins of Health and Disease (DOHaD) theory.

Int. J. Mol. Sci. **2018**, *19*, 1647

FIGURE 2 LEVELS OF DDT IN HUMAN MILK



Data reflects survey results over the period 2001-2013 and current DDT registry information from the Stockholm Convention

TABLE 2. SOME KNOWN EDCS AND THEIR USES

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterials	Triclosan
Textiles, clothing	Perfluorochemicals

Abbreviations: BPA: bisphenol A; 2,4-D: 2,4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls

TABLE 3. EXAMPLES OF EDC ROUTES OF EXPOSURES IN HUMANS

How we are exposed to EDCs	Where the EDCs come from	EDC example(s)
Oral consumption of contaminated food or water	Industrial waste or pesticides contaminating soil or ground-water	PCBs, dioxins, perfluori-nated compounds, DDT
Oral consumption of contaminated food or water	Leaching of chemicals from food or beverage containers; pesticide residues in food or beverage	BPA, phthalates, chlorpyrifos, DDT
Contact with skin and/ or inhalation	Household furniture treated with flame retardants	BFRs
Contact with skin and/ or inhalation	Pesticides used in agriculture, homes, or for public disease vector control	DDT, chlorpyrifos, vinclozolin, pyrethroids
Intravenous	Intravenous tubing	Phthalates
Application to skin	Some cosmetics, personal care products, anti-bacterials, sunscreens, medications	Phthalates, triclosan, Para-bens, insect repellants
Biological transfer from placenta	Maternal body burden due to prior/current exposures	Numerous EDCs can cross the placenta
Biological transfer from mother's milk	Maternal body burden due to prior/current exposures	Numerous EDCs are detected in milk

Abbreviations: BFR: brominated flame retardant; BPA: bisphenol A; PCBs: polychlorinated biphenyls

Table 1. Legacy Endocrine Dispurting Chemicals

Compound	Use/Source	Disease Links
BPA	Plastics, thermal receipts	Breast and other cancers, metabolism, puberty, neurobehavioral
Phthalates	Plastics, fragrances	Low sperm count, metabolism, birth defects, asthma, neurobehavioral
PCBs	Electrical coolant and other uses	Cancer, developmental issues
PBDEs	Flame retardants	Thyroid disruption, neurological issues
Lead	Drinking water, paint, gasoline	Neurological issues, premature birth, kidney disorders
Mercury	Burning coal, seafood	Neurological issues, diabetes
Dioxin	Formed in industrial processing	Cancers, sperm quality, fertility, neurobehavioral
DDT/DDE/DDD	Pesticides	Cancers, developmental toxicity
Arsenic	Drinking water, animal feed, herbicides, fertilizers	Cancers, diabetes, immune suppression, neurodevelopment, cardiovascular disease
Cadmium	Tobacco smoke, fertilizers	Cancers, reproductive issues
Atrazine	Herbicide	Alterations in pubertal development
Alkylphenols and p-Nonyl-phenol	Detergents, additives	Breast cancer

TABLE 4. TRADITIONAL CONCEPTS IN CHEMICAL TESTING AND WHY THEY ARE INADEQUATE TO DETERMINE ENDOCRINE-DISRUPTING ACTIVITY.

Traditional Approach to Chemical Testing: 'The Dose is the Poison'	Why this approach is insufficient for Endocrine-Disrupting Chemicals
Tests individual chemicals one at a time	Every person in the world now carries a body burden of chemicals that did not exist before 1940. Many more are being produced and released into the environment each year. Testing chemicals one at a time can't keep pace with exposure and doesn't take into account how combinations of chemicals within the body are impacting human development or health.
Assumes individual chemicals have a "safe or acceptable" level of exposure below which there are no adverse effects	The endocrine system regulates virtually every aspect of human health from development in the womb, to growth, to reproduction, and overall health. Recent science shows that even very small amounts of these chemicals or mixtures of these chemicals disrupt the endocrine system, reducing intelligence, disrupting reproductive systems, and causing other health problems. There may, in fact, be no safe level, especially when individuals have hundreds of these chemicals in their bodies.
Tests are focused on adult animals	Hormones regulate body systems beginning in the womb and throughout life. Tests conducted only on adult animals can't capture the impact of chemicals on the endocrine system throughout the body's life cycle.
Presumes doses below the amounts which cause test animals to die or develop a target disease (usually cancer) are 'safe'	Endocrine-disrupting chemicals have many impacts beyond death or disease.

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

Endocrine Reviews 36: E1-E150, 2015

ENDOCRINE SOCIETY

Goitrogens

- **perchlorate**
- **sulphurated organics** (thocyanate, isothiocyanate, etc.)
- **flavonoids** (polyphenols)
- **pyridines**
- **phtalate esters**
- **polychlorinated and polybrominated biphenyls**
- **organochlorines** like DDT
- **polycyclic aromatic hydrocarbons**
- **excess iodine**
- **lithium**

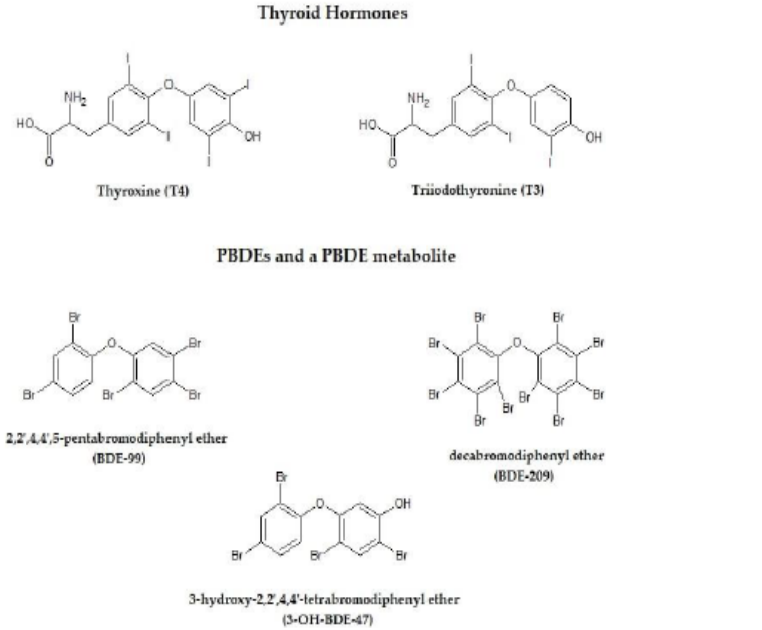


Figure 1. Chemical structures of thyroid hormones thyroxine and triiodothyronine and the main polybrominated diphenyl ethers (PBDEs) (modified from [16]).

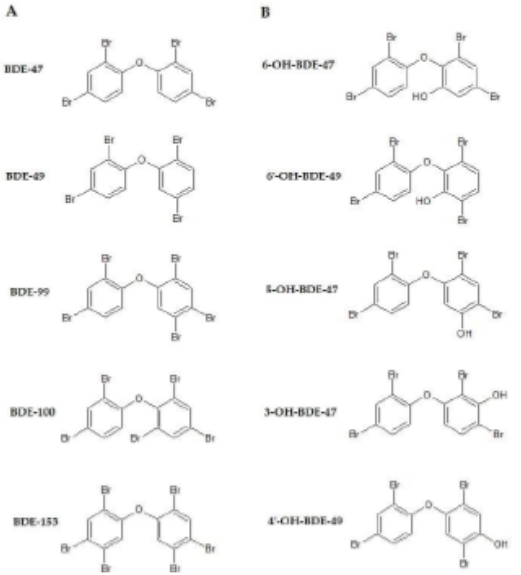


Figure 2. Molecular structure of (**A**) the PBDEs (BDE-47, BDE-49, BDE-99, BDE-100, BDE-153) and (**B**) the metabolites of BDE-47 (6-OH-BDE-47, 6′-OH-BDE-49, 5-OH-BDE-47, 3-OH-BDE-47, and 4′-OH-BDE-49) (modified from [141]).

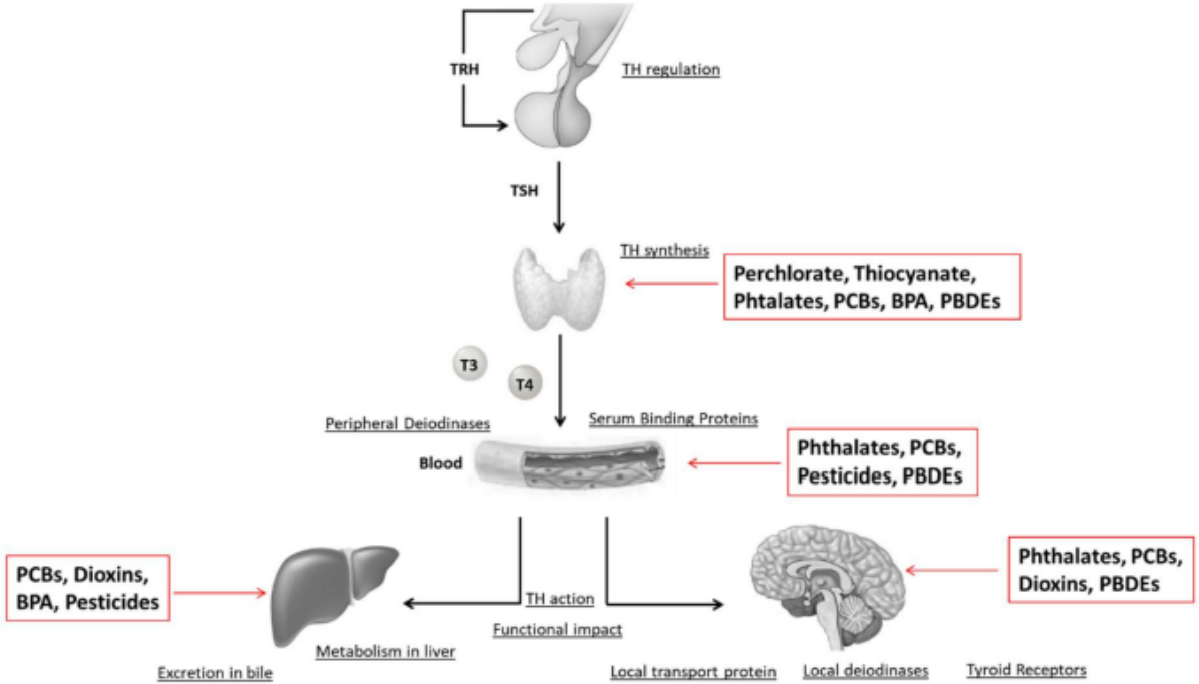


Figure 1. Action of EDCs on the HPT Axis. The black arrows indicate arrows indicate the organs/tissues targeted by the EDCs.

Int. J. Mol. Sci. **2018**, *19*, 1647

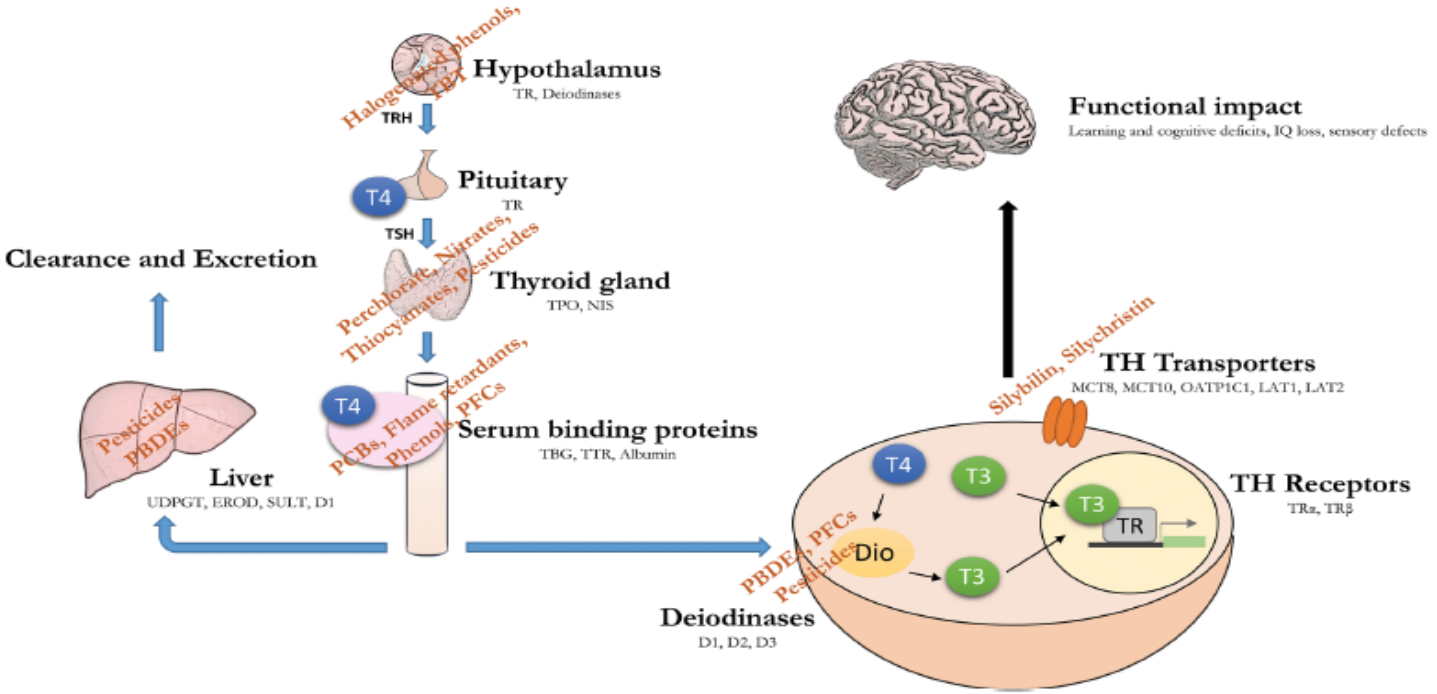


Figure 1
Endocrine-disrupting chemicals (EDCs) act at multiple levels of the hypothalamus–pituitary–thyroid (HPT) axis. Environmental chemicals have the potential to disrupt the HPT axis, alone or in combination. Given the crucial role for thyroid hormone in brain development, such disruption can have a long-lasting functional impact, such as IQ loss and increased risk of neurodevelopmental disease (note: targets not drawn to scale).

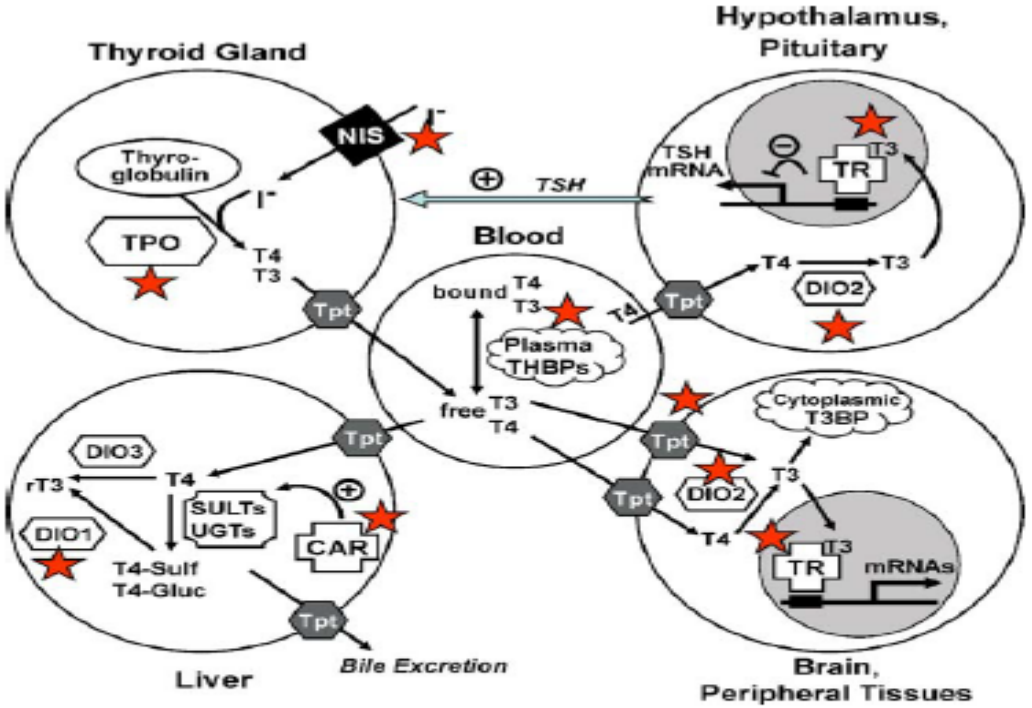
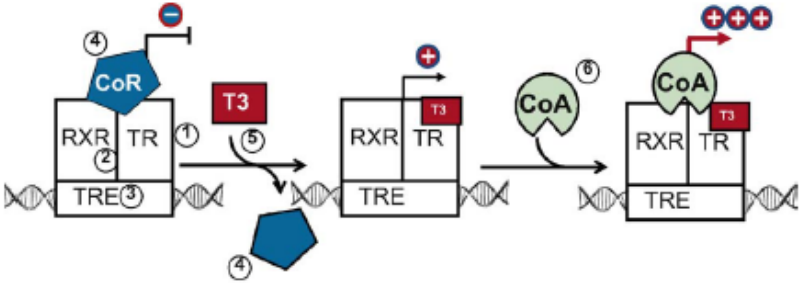


Fig. 1. A schematic view of the thyroid hormone regulatory network and thyroid disruption endpoints. Cytoplasmic T3BP: Cytoplasmic T3-binding protein; DIO1,2,3: deiodinases type 1, 2, 3; NIS: sodium iodide symporter; Plasma THBPs: plasma thyroid hormone-binding proteins; rT3: reverse-T3 (inactive); SULT: sulfotransferase; T4-Gluc: T4 glucuronide (inactive); T4-Sulf: T4-Sulfate (inactive); TPO: thyroperoxidase; Tpt: membrane transporter; TR: thyroid hormone receptor; TSH: thyrotropin; UGT, glucuronosyltransferase; (★) thyroid disruption endpoints.



Endpoints	Chemicals	References
1. Expression of TR	Phthalates Bisphenol A	[86] [87]
2/ TR/RXRheterodimerization	No data	[80]
3/ Interaction of TRE with RXR/TR	OH-PCB	[78]
4/ Recruitment/release of corepressors	Bisphenol A Anti-thyroid drugs NH-3	[70] [71] [69]
5/ T3 binding to TR	OH-PBDE Pentabromophenol Phthalates	[59-60] [60] [67]
6/ Recruitment of coactivators:transcriptional activation	OH-PCB	[72]

Fig. 2. Regulation of transcription by the thyroid hormone receptor (TR). In the absence of T3, the heterodimer TR-RXR, bound to a T3-responsive element (TRE) on DNA, recruits corepressors (CoR) and represses basal transcription. T3 binding to TR induces the release of CoR, and restores the basal transcription level. Coactivators (CoA) can then be recruited and stimulate transcription. Table inset: Environmental chemicals may target various levels of the TH-related transcriptional process.

Table 3: TH signaling targets of different classes of TH-EDCs.

TH-EDCs	Iodine uptake	Inhibition of TPO	Binding to TTR	TH levels	TSH levels	Deiodinase activity	Sulfotransferase activity	Transporter/receptor
PBDE				x	x	x	x	
PCB			x	x	x			x
TCDD							x	
Triclosan							x	x
Perchlorate	x			x	x			
Flavonoids	x	x		x				x
BPA		x	x	x			x	
Dioxin		x	x	x				x
Phthalates	x			x				

Table 2: Risk assessment of TH-EDCs and their effect on TH regulation in pregnancy.

Endocrine disruptors	Thyroid hormone-EDCs	Sources of exposure	Mode of exposure	Target tissues	Effect on TH regulation	References
Nonpersistent organic chemicals	Phthalates	Medical equipment, pesticides, and cosmetics	Ingestion, inhalation, and dermal exposures	Placenta, cord blood, and neonatal meconium	Impaired iodine uptake, inhibition of TH homeostasis	[16–18]
	Bisphenol A	Food can linings, dental sealants, and plastics	Ingestion, dermal exposures	Serum, amniotic fluid, and placenta	Binds TTR and inhibits TPO, T3 antagonist	[16, 19–21]
	Triclosan	Clothing, cosmetics, and detergents	Ingestion, dermal exposures	Urine, serum, and breast milk	Alters TH actions	[22–24]
Persistent organic chemicals	Flame retardants	Furniture, electronics, house dust, and foods	Inhalation, ingestion	Serum, milk, and cord blood	Disrupt TH signalling, alter TH levels, and inhibit TH sulfotransferase, TSH, and deiodinase activities	[25–27]
	Dioxins	By-products of industrial and environmental processes	Ingestion of contaminated dairy products	Fat tissue, breast milk	Alter TH and TSH levels and TPO and bind TTR	[28, 29]
	Polychlorinated biphenyls	Insulating materials, heat-transfer systems, lubricants, and paints	Dermal exposures, ingestion, and inhalation	Placenta, serum, adipose, and breast milk	Alter TH and TSH levels, bind TTR, and alter TH-responsive genes	[30–32]
	Perchlorates	Inflation systems, fireworks, nitrate fertilizers, and oxidants in propelling rockets and missiles	Drinking contaminated water, ingestion, and inhalation	Breast milk, urine	Inhibit iodine uptake via sodium iodide symporter (NIS) and alter TH and TSH levels	[33–35]
	Phytoestrogens	Soy rich foods	Ingestion		Decrease iodine accumulation, inhibit TPO activity, act as TR agonist or antagonist, and alter TH levels	[36, 37]

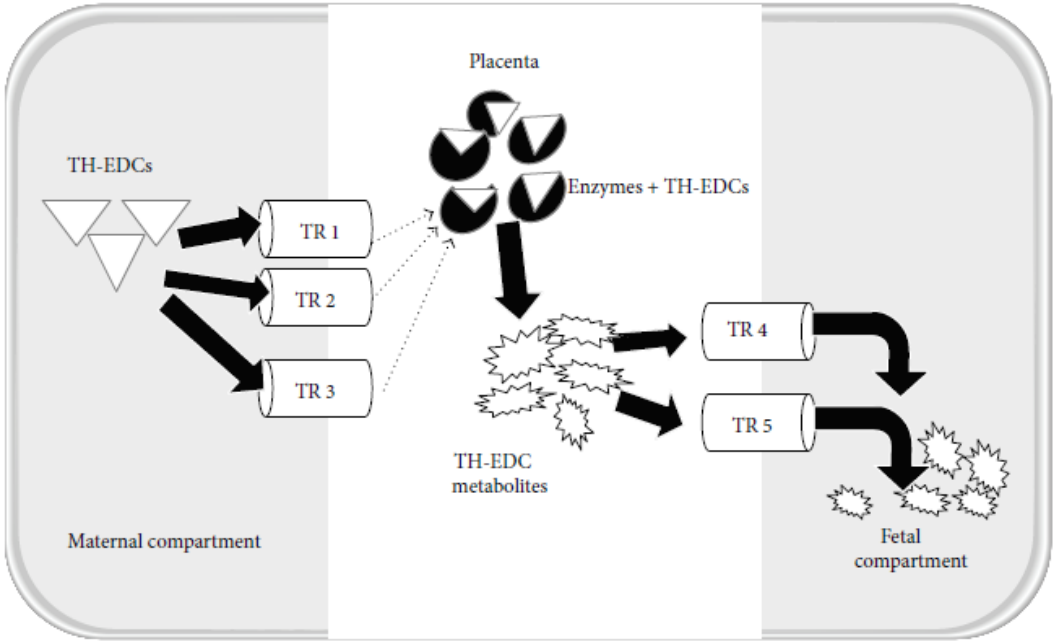


FIGURE 3: Placental transfer and biotransformation of TH-EDCs. Thyroid hormone endocrine disrupting chemicals (TH-EDCs) enter the placenta from the maternal compartment via various transporters located at the maternal interface of the placenta and are biotransformed by metabolizing enzymes to various metabolites that then enter the fetal compartment through transporters located at the fetal interface of the placenta. TR indicates transporters.

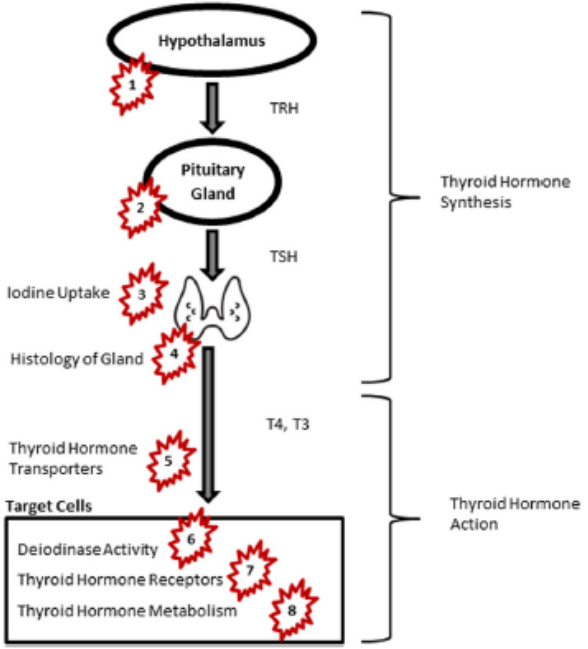


FIGURE 1 | Thyroid signaling pathway and endocrine-disrupting chemicals. Groups of chemicals act at: PCB and PCDD: 5, 7; PBDEs: 5, 6, 7, 8; pesticides: 4, 5, 7; PFASs: 5, 6; NIS: 3; BPA: 2, 7; phthalates: 1, 2, 5, 8. Abbreviations: BPA, bisphenol A; NIS, sodium iodide symporters; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxins; PFAS, perfluoroalkyl substances; TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine. Image of thyroid: by P. J. Witt, AU from the Noun Project, Creative Commons.

TABLE 1 | Endocrine disrupting chemicals (EDCs) and target of action in the hypothalamus–pituitary–thyroid axis.

Groups of EDCs	Target of action
Polychlorinated biphenyls and polychlorinated dibenzodioxins (PCDD)	Thyroid hormone transportation Thyroid hormone receptors
Polybrominated diphenyl ethers	Thyroid hormone transporters Deiodinase activity in the thyroid gland Thyroid hormone receptors Thyroid hormone metabolism
Pesticides	Histology of thyroid gland Thyroid hormone transportation Thyroid hormone receptors
Perfluoroalkyl substances (PFASs)	Thyroid hormone transportation Deiodinase activity in the thyroid gland
Sodium iodide symporters (NIS)	Iodine uptake into the thyroid gland
Bisphenol A and other phenols	Expression of thyroid receptor genes in the pituitary Thyroid hormone receptors
Phthalates	Thyroid-releasing hormone receptor in the hypothalamus and pituitary Thyroid-stimulating hormone receptor in the thyroid gland Expression of genes related to thyroid hormone metabolism, synthesis, and transportation

Thyroid Disruption

- A large number of chemicals and chemical classes are known to affect the thyroid system.
- Animal studies have also demonstrated that a number of chemicals, including but not limited to PCBs, PBDEs, some phthalates, and perchlorate, can reduce circulating levels of thyroid hormone. Interestingly, not all of these chemicals also cause an increase in serum TSH.
- Some chemicals that affect the thyroid system in animals have been shown to be associated with cognitive deficits in humans. However, exposure is not always correlated with reductions in thyroid hormone in humans.
- Thyroid hormone produces different effects at different developmental stages—in humans as well as in animals—and the consequences of disruption are stage-specific.
- Some chemicals clearly exert actions on the thyroid system in humans and animals at environmentally relevant concentrations. The mechanism(s) by which chemicals can produce this effect varies.
- Three key areas of research are urgently needed: 1) identify biomarkers of thyroid hormone action in tissues to test the ability of chemicals to interfere with hormone action in the absence of effects on serum hormone concentrations; 2) determine whether chemicals with different mechanisms of action on the thyroid system can synergize to cause adverse effects; and 3) identify high throughput assays that predict thyroid "disruption."

Table 1. Synthetic chemicals that interfere with the production, transport, and metabolism of thyroid hormone.

Thyroid mechanism and interfering chemical

Uptake of iodide by thyroid gland
2,4-D (*137*)
3-Amino-1,2,4-triazole (*138,139*)
Aldrin (*140*)
Amitrole (*141,142*)
Aroclor 1254 (*143,145*)
1,2-Dihydroxybenzene (catechol) (*146*)
4-Chlororesorcinol (*146*)
Clofentezine (*141*)
o-Cresol (*146*)
p-Cresol (*146*)
Cythion (*96,147*)
1,3-Dihydroxynaphthalene (*146*)
1,5-Dihydroxynaphthalene (*146*)
2,3-Dihydroxynaphthalene (*146*)
2,7-Dihydroxynaphthalene (*146*)
2,4-Dihydroxybenzaldehyde (*146*)
2,4-Dihydroxybenzoic acid (*146*)
Ethiozin (*141*)
Ethylene thiourea (*141,148*)
Fipronil (*141*)
Hexachlorobenzene (*149,150*)
Hexadrin (*147*)
4-Hexylresorcinol (*146*)
1,3,4-Trihydroxybenzene (hydroxyquinol) (*146*)
Hydroxyquinol triacetate (*146*)
Lead (*151*)
Mancozeb (*152*)
Mercuric chloride (*153,154*)
3-Methylcholanthrene (*143,155*)
Methylmercuric chloride (*154*)
Methylparathion (*156*)
2-Methylresorcinol (*146*)
Mull-Soy (*157*)
Nabam (*140*)
5-Methylresorcinol (orcinol) (*146*)
Pendimethalin (*141*)
Pentachloronitrobenzene (*141*)
Phenobarbital (*143*)
Phenol (*146*)
1,3,5-Trihydroxybenzene (phloroglucinol) (*146*)
Polybrominated biphenyls (*158*)
Pregnenolone-16α-carbonitrile (*143*)
Propylthiouracil (*139,158*)
1,2,3-Trihydroxybenzene (pyrogallol) (146)
Pyrimenthanil (*141*)
1,3-Dihyroxybenzene (resorcinol) (*146*)
o-Hydroxybenzyl alcohol (saligenin) (*146*)
Selenium (*151*)
Thiocyanate (*141*)

Sodium/iodide symporter
Perchlorate (*94,159*)
Perrhenate (*159*)

Serum protein–bound iodide level
2,4-D (*137*)
2,4-Dinitrophenol (*96*)
3-Methylcholanthrene (*155*)
Amitrole (*142*)
Aroclor 1254 (*144*)
Cythion (*96,147*)
Malathion (*160*)
Mancozeb (*152*)
Mercuric chloride (*153*)
o,p′-DDD (*161,162*)
Hexadrin (147)

Thyroid peroxidase action—general information
Amitrole (*141*)
Ammonia (*163*)
Ethylene thiourea (*141*)
Fipronil (*141*)
Mancozeb (*141*)
4,4′-Methylenedianiline (*141*)
Thiocyanate (*141*)

Thyroid peroxidase action—oxidation of iodide
Aminotriazole (*97,164*)
Ammonia (*163*)
Cadmium chloride (*163,165*)
Endosulfan (*166*)
Ethylene thiourea (*98*)
1,2,3,4,5,6-Hexachlorocyclohexane (lindane) (*167*)
Malathion (*167*)
Mancozeb (*152*)
Mercury chloride (*165*)
Methamizole (*97*)
Polybrominated biphenyls (*158*)
Thiourea (*166*)

Thyroid peroxidase action—iodination of tyrosine
Polybrominated biphenyls (*158*)

Binding to thyroglobulin
o,p′-DDD (*161*)
Pentachlorophenol (*168*)

Binding to transthyretin
Bromoxynil (3,5-bibromo-4-hydroxybenzonitril) (*99*)
4-(Chloro-*o*-tolyloxy) acetic acid (*99*)
4-(4-Chloro-2-methylphenoxy) butyric acid (*99*)
Chlorophenol (*99,169*)
Chloroxuron (*99*)
2,4-D (*99*)
2,4-Dichlorophenoxybutric acid (*99*)
Dioxtylphthalate (*99*)
o,p′-DDD (99)
p,p′-DDD (*99*)
2,3-Dichlorophenol (*99,169*)
2,4-Dichlorophenol (*99*)
2,6-Dichlorophenol (*99,169,170*)
2-(2,4-Dichlorophenoxy) propionic acid [dichloroprop] (*99*)
1,1,1-Trichloro-2,2-bis (chlorophenol) ethanol [difocol] (*99*)
2,4-Dinitrophenol (*99*)
2,4-Dinitro-6-methylphenol (*99*)
Ethyl-bromophos (*99*)
Ethyl-parathion (*99*)
2-(2,4,5-Trichlorophenoxyl propionic acid [fenoprop] (*99*)
Hexachlorobenzene (*99*)
Hexachlorophene (*99,169*)
2-Hydroxybiphenyl (*99*)
4-Hydroxybiphenyl (*99,169*)
Lindane (*99*)
Linuron (*99*)
Malathion (*99*)
Pentachlorophenol (*99,169,170*)
Phenol (*169*)
Pyrogallol (*99*)
2,4,5-Trichlorophenoxyacetic acid (*99*)
1,4-Tetrachlorophenol (*99,170*)
PCB-77 (*99,105,169*)
Trichloroacetic acid (*99*)
Trichlorobenzene (*99*)
2,3,4-Trichlorophenol (*170*)
2,4,5-Trichlorophenol (*99,169,170*)
2,4,6-Trichlorophenol (*99,170*)
2,4,5-Trichlorophenoxyacetic acid methyl ester (*99*)

Binding to albumin
Pentachlorophenol (*169*)

Catabolism of T_4 or T_3: type I or II 5′-deiodinase
3,3′,4,4′,5,5′-Hexachlorobiphenyl (*107*)
3-Methylcholanthrene (*171,172*)
Aminotriazole (*106*)
Amiodarone (*94,172*)
Aroclor 1254 (*109*)
Cadmium chloride (*173*)
Diphenylthiohydantoin (*141,172*)
Dimethoate (*100,174*)
Fenvalerate (*175,176*)
Hexachlorobenzene (*102*)
Lead (*177*)
Phenobarbital (*172*)
Propylthiouracil (*172*)
PCB 77 (*107,171*)
TCDD (*171,178*)

Glucuronidation of T_4/T_3
Acetochlor (*141*)
Aroclor 1254 (*109,143–145,179*)
3,4-Benzpyrene (*180*)
Clofentenzine (*141*)
Clofibrate (*141*)
DDT (*144*)
Fenbuconazole (*141*)
3,3′,4,4′,5,5′-Hexabromobiphenyl (*101*)
Hexachlorobenzene (*102,183*)
2,3,3′,4,4′,5-Hexachlorobiphenyl (*182*)
3,3′,4,4′,5,5′-Hexachlorobiphenyl (*107*)
3-Methylcholanthrene (*141,143,155,171,179*)
Pendimethalin (*141*)
PCB 126 (*108,182*)
Phenobarbital (*141,143,172,180,181,183*)
Polybrominated biphenyls (*184*)
PCBs (*141*)
Pregnenolone-16α-carbonitrile (*141,143,179*)
Promadiamine (*141*)
Pyrimethanil (*141*)
PCB 77 (*108,171*)
TCDD (*108,141,178,182*)
Thiazopyr (*141*)

Catabolism and biliary elimination of T_4/T_3 in the liver
Aroclor 1254 (*144,145*)
3,4-Benzopyrene (*180*)
DDT (*144*)
Hexachlorobenzene (*102*)
3-Methylcholanthrene (*155*)
Phenobarbital (*180,183*)
Polybrominated biphenyls (*184*)

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; DDD, 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethane.

Table 2. Thyroid volume and urinary BPA concentration of participants characterized by sex, age, BSA, area and iodine nutrition status.

Characteristics	Thyroid Volume		Urinary BPA concentration [a]	
	Median (IQR)	*P*-value	Median (IQR)	*P*-value
All	3.14(2.44–4.11)		2.45(1.09–5.97)	
Sex		0.263		0.126
Male	3.05(2.43–4.03)		2.64(1.13–6.40)	
Female	3.21(2.45–4.25)		2.35(1.04–5.40)	
Age (years)		<0.0001		0.028
9	2.92(2.25–3.85)		2.24(1.04–5.34)	
10	3.74(2.75–4.70)		2.54(0.98–6.41)	
11	3.02(2.46–3.58)		2.89(1.27–6.34)	
BSA[b]		<0.0001		0.050
T1 (<1.06 m^2)	2.57(2.05–3.45)		2.26(1.01–5.12)	
T2 (1.06–1.19 m^2)	3.31(2.59–4.41)		2.49(1.05–5.58)	
T3 (> = 1.20 m^2)	3.42(2.70–4.54)		3.02(1.27–6.85)	
Iodized salt consumption		<0.0001		<0.0001
No	2.73(2.16–3.50)		3.44(1.74–7.02)	
Yes	3.35(2.61–4.43)		2.14(0.85–5.21)	
Urinary iodine(μg/l)		0.0003		0.783
<100	2.75(2.21–3.55)		2.29(1.10–4.58)	
100–200	3.18(2.45–4.11)		2.44(1.02–6.35)	
>200	3.33(2.55–4.43)		2.49(1.15–6.36)	
Area		<0.0001		<0.0001
Minhang	4.25(3.44–5.17)		1.74(0.94–3.43)	
Haimen	3.13(2.46–4.07)		2.22(0.78–5.20)	
Taizhou	2.52(2.02–3.07)		3.95(2.04–10.48)	

BPA: Bisphenol A; BSA: Body Surface Area; IDR: Inter-quartile range

[a]: Creatinine adjusted (μg/mg)

[b]: In tertiles

doi:10.1371/journal.pone.0141248.t002

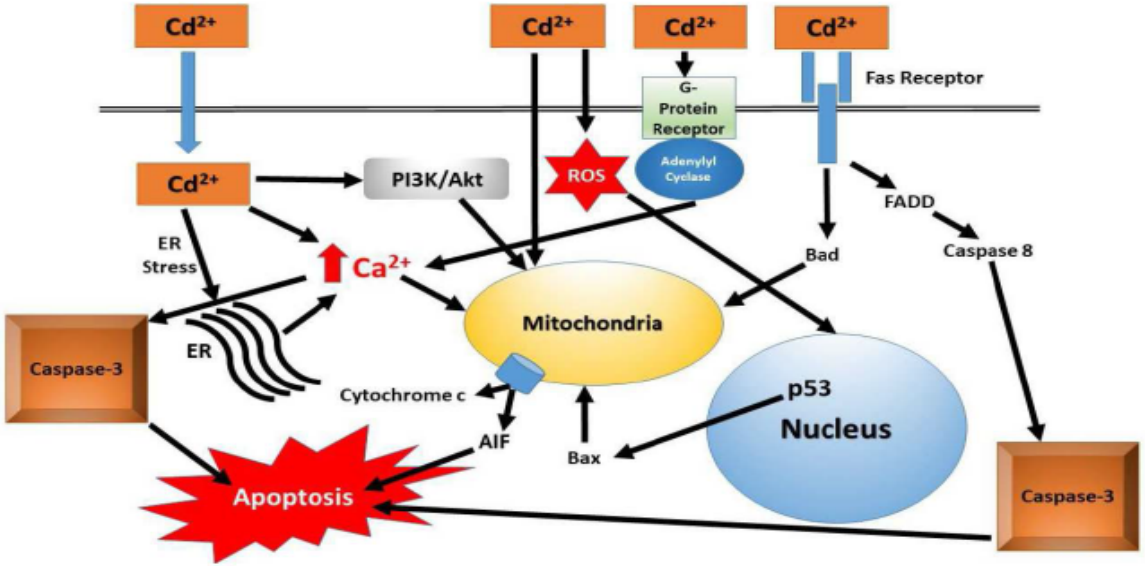


Figure 1. Schematic of Cd-mediated cellular effects. The primary pathways are to induce apoptosis when there is a cellular challenge from Cd exposure. When the ability of the cells to efficiently enter apoptosis for repair, or if apoptosis is blocked, the cell will continue to proliferate and perpetuate the genetic damage caused by oxidative stress. Damage to the mitochondrial will occur over time, membrane permeability will change and normal respiration resulting in the generation of ATP will cease. Abbreviations: ROS = Reactive Oxygen Species; FADD = Fas-Associated protein with Death Domain; ER = Endoplasmic Reticulum; AIF = Apoptosis-Inducing Factor; PI3K/Akt = Phosphoinositide 3-Kinase/Protein Kinase B.