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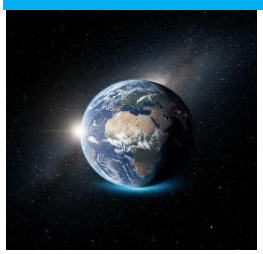

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Impact of Endocrine Disrupting Chemicals (EDCs) on Male Health: A Comprehensive Literature Review

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Abstract

Background: Endocrine disrupting chemicals (EDCs) impact human health by modulating endogenous hormones. While linked to metabolic, oncological, and reproductive disorders, literature often focuses narrowly on specific aspects of male health.

Objective: To provide a holistic analysis of EDC impact on male health (*Homo sapiens*) based on literature from 2000–2025, excluding *in vitro* and animal models.

Methods: A three-stage review of PubMed identified 51 records. After rigorous screening, 34 high-quality studies (systematic reviews, meta-analyses, and RCTs) addressing effects on the living male organism were synthesized.

Results: EDC impact is multidirectional and highly dependent on exposure windows. The prenatal period is critical for testicular cancer development and adult semen quality. Exposure to BPA, phthalates, and PAHs correlates with increased risk of ADHD and autistic behaviors in boys. Metabolically, PFAS and bisphenols correlate with abdominal obesity and diabetes, showing strong sexual dimorphism. Pathophysiological mechanisms include disruption of the HPG/HPT axes, oxidative stress, and epigenetic modifications.

Conclusions: EDCs are a systemic risk factor extending far beyond reproduction. Key research barriers include methodological heterogeneity and the neglect of the "cocktail effect." There is an urgent need for standardized, longitudinal prospective studies starting from the prenatal period to assess real-world anthropogenic impacts.

Keywords
Endocrine disrupting chemicals; Men's health; Environmental health; Homo sapiens; Bisphenol A; Phthalates; PFAS; Polycyclic aromatic hydrocarbons (PAHs); Semen quality; Testicular neoplasms; Metabolic syndrome; Neuropsychological disorders; Prenatal exposure; Sexual dimorphism; Cocktail effect; Epigenetics

Introduction

Endocrine Disrupting Chemicals (EDCs) represent a diverse group of natural and synthetic substances prevalent in the environment that interfere with hormonal homeostasis. The potential deleterious effects of EDCs on human health stem from their ability to disrupt endocrine signalling pathways, thereby increasing the risk of metabolic disorders, impaired reproductive function, and congenital anomalies. The potency of EDCs is rooted in the fundamental nature of the endocrine system: since endogenous hormones act as chemical messengers at extremely low physiological concentrations, even trace exposure to EDCs can trigger significant cellular responses. These substances exert their effects by mimicking natural hormones or by modulating their synthesis, transport, receptor binding, and elimination.

Throughout the life cycle, living organisms are chronically exposed to EDCs leaching from plastics, pharmaceuticals contaminating groundwater, or naturally occurring compounds such as phytoestrogens. Prolonged exposure leads to cumulative and complex interactions—including synergistic, additive, or antagonistic effects—resulting in unpredictable outcomes for the individual organism.

Notably, existing literature has predominantly focused on a narrow scope of male health, often limited to reproductive outcomes. Previous systematic reviews have addressed specific facets such as EDCs as carcinogens in prostate cancer [1], sex-specific impacts on cardiovascular health [2] and adipose tissue [3], or the systemic and fertile implications of specific agents like pesticides [4], bisphenols [5], and PFAS [6]. Furthermore, research has examined developmental origins of health and disease, including maternal exposure and subsequent male reproductive disorders [7,8], as well as the molecular mechanisms underlying these pathologies [9]. Despite these contributions, there remains a lack of comprehensive syntheses that integrate these diverse health outcomes into a holistic assessment of male health.

Objective The objective of this study is to analyse comprehensive literature published over the last 25 years regarding the impact of EDCs on male health. This review focuses specifically on observations in *Homo sapiens*, excluding studies involving isolated cell lines, tissues, or organs, to prioritize clinically relevant evidence of systemic effects in the male organism.

Methods

The methodology of this review was divided into three distinct stages to ensure a structured approach to the available literature.

Stage 1: Preliminary Search for Existing Syntheses Initially, the PubMed database was searched to identify existing reviews that holistically address the impact of various endocrine-disrupting chemicals (EDCs) on male health, specifically looking for works not limited to reproductive aspects or single organ systems. The search period was restricted to the last five years (January 1, 2020, to December 20, 2025) to capture only the most current scientific syntheses and clinical consensus. The search terms included: "Endocrine disrupting chemicals" OR "EDCs" OR "Endocrine disruptors", with filters for English language, human studies, and male subjects. This stage yielded 236 results - Link to search parameters:

https://pubmed.ncbi.nlm.nih.gov/?term=Endocrine+disrupting+chemicals+OR+EDCs+OR+Endocrine+disruptors&filter=dates.2020%2F1%2F1-2025%2F12%2F20&filter=simsearch2.ffrft&filter=pubt.review&filter=lang.english&filter=hum_ani.humans&filter=sex.male&filter=other.excludepreprints&format=abstract&size=20
A screening of these abstracts confirmed the absence of a comprehensive, up-to-date publication covering the full spectrum of EDCs' influence on general male health, which justified the need for the current review.

Stage 2: Identification of High-Level Evidence To construct a robust synthesis of knowledge, the search strategy was subsequently refined to focus on high-quality evidence. This stage targeted specific study designs: Systematic Reviews, Meta-Analyses, Randomized Controlled Trials (RCTs), and Clinical Trials. Given the niche nature of the topic and the stringent requirements for study quality, the temporal scope was expanded to cover the period from January 1, 2000, to December 20, 2025. This expansion was necessary to ensure a sufficient volume of high-level evidence, as the oldest identified relevant studies dated back to 2010. This search was also limited to "Free Full Text" publications and resulted in 51 records – search parameters available via link:
https://pubmed.ncbi.nlm.nih.gov/?term=Endocrine+disrupting+chemicals+OR+EDCs+OR+Endocrine+disruptors&filter=dates.2000%2F1%2F1-2025%2F12%2F20&filter=simsearch2.ffrft&filter=pubt.clinicaltrial&filter=pubt.meta-analysis&filter=pubt.randomizedcontrolledtrial&filter=pubt.systematicreview&filter=lang.english&filter=hum_ani.humans&filter=sex.male&filter=other.excludepreprints&format=abstract&size=20

Stage 3: Selection and Analysis A detailed analysis of the 51 identified records was performed. Studies were excluded if they did not directly investigate substances recognized as EDCs (e.g., studies regarding COVID-19 vaccines) or if they were not conducted on living human subjects (e.g., animal models, cell lines, or isolated human tissues). Following this rigorous screening, 34 studies were qualified for the final synthesis [10-44].

Limitations

Several limitations of this review must be noted. First, the search was restricted exclusively to the PubMed database and limited to "Free Full Text" publications. This approach may have introduced a selection bias by omitting relevant studies indexed in other databases (e.g., Embase, Scopus) or those available only through paid subscriptions. Second, the search strategy utilized broad thematic keywords such as "Endocrine disrupting chemicals" and "EDCs". Consequently, publications focusing on specific chemical agents (e.g., particular phthalates or bisphenols) that did not include these general umbrella terms in their titles, abstracts, or keywords might have been overlooked.

Abbreviations

2-MPA :: 2-Methoxypropionic acid
2,4-D :: 2,4-Dichlorophenoxyacetic acid
2,4-DCP :: 2,4-Dichlorophenol
2,4,5-T :: 2,4,5-Trichlorophenoxyacetic acid
2,4,5-TP :: 2,4,5-Trichlorophenoxy
2,5-DCP :: 2,5-Dichlorophenol
2OH-MiBP :: Mono-(2-hydroxy-iso-butyl) phthalate
3-PBA :: 3-Phenoxybenzoic acid
3,4-DHB :: 3,4-Dihydroxy benzoic acid
3OH-MnBP :: Mono-(3-hydroxybutyl) phthalate
4-HB :: 4-Hydroxy benzoic acid
4-OH-BP :: 4-Hydroxybenzophenone

4′-MAP :: 4′-Methoxyacetophenone
5cx-MEPP :: Mono-(2-ethyl-5-carboxypentyl) phthalate
5OH-MEHP :: Mono-(2-ethyl-5-hydroxyhexyl) phthalate (Alternative: MEHHP)
5oxo-MEHP :: Mono-(2-ethyl-5-oxohexyl) phthalate (Alternative: MEOHP)
6:2 diPAP :: 6:2 Polyfluoroalkyl phosphoric acid diesters
7cx-MMeHP :: Mono(4-ethyl-7-carboxylheptyl)phthalate [metabolite of DiNP]
8:2 diPAP :: 8:2 Polyfluoroalkyl phosphoric acid diesters
As :: Arsenic
BAA :: 2-Butoxyacetic acid
BBP :: Benzyl butyl phthalate
BBzP :: Butylbenzyl phthalate
BDE :: Bromodiphenyl ether
BDE-100 :: 2,2′,4,4′,6-Pentabromodiphenyl ether
BDE-153 :: 2,2′,4,4′,5,5′-Hexabromodiphenyl ether
BDE-154 :: 2,2′,4,4′,5,6′-Hexabromodiphenyl ether
BDE-28 :: 2,4,4′-Tribromodiphenyl ether
BDE-47 :: 2,2′,4,4′-Tetrabromodiphenyl ether
BDE-99 :: 2,2′,4,4′,5-Pentabromodiphenyl ether
BFRs :: Brominated flame retardants
BMI :: Body mass index
BP :: Butyl paraben
BP-1 :: 2,4-Dihydroxybenzophenone
BP-2 :: Benzophenone-2
BP-2 :: 2,2′,4,4′-Tetrahydroxybenzophenone
BP-3 :: Benzophenone-3
BP-8 :: 2,2′-Dihydroxy-4-methoxybenzophenone
BPA :: Bisphenol A
BPA-G :: Bisphenol A-G
BPAF :: Bisphenol AF
BPE :: Bisphenol E
BPF :: Bisphenol F
BPS :: Bisphenol S
BzBP :: Butyl benzyl phthalate
BzP :: Benzyl paraben
c-PAH :: Carcinogenic polycyclic aromatic hydrocarbons
CI :: Confidence Interval
CR :: Creatinine
cx-MiNP :: Mono-(carboxy-iso-nonyl) phthalate (Alternative: MCiNP)
cx-MiOP :: Mono-carboxy-iso-octyl phthalate (Alternative: MCiOP)
DBP :: Dibutyl phthalate
DDE :: Dichlorodiphenyldichloroethylene
DDT :: Dichlorodiphenyltrichloroethane
DEHP :: Di-(2-ethylhexyl) phthalate
DEP :: Diethyl phthalate
DiBP :: Di-isobutyl phthalate
DiDP :: Diisodecyl phthalate
DiNP :: Di-isononyl phthalate
DMP :: Dimethyl phthalate
DnOP :: Di-n-octyl phthalate
EAA :: Ethoxyacetic acid

EDC/EDCs :: Endocrine Disrupting Compounds
EEAA :: Ethoxyethoxyacetic acid
EHMC :: Ethyl-hexyl methoxycinnamate
EP :: Ethyl paraben
EPTC :: Ethyl dipropylthiocarbamate
Et-PFOSA-AcOH :: N-ethyl-perfluorooctane sulfonamido acetic acid
HBCDD :: Hexabromocyclododecane
HCB :: Hexachlorobenzene
HCCH :: Hexachlorocyclohexane
HCE :: Heptachlor epoxide
HCH :: Hexachlorohexane
Hg :: Mercury
HP :: Heptyl paraben
HRs :: Hazard ratios
MAA :: Methoxyacetic acid
MBP :: Monobutyl phthalate
MBzP :: Mono-benzyl phthalate
MCHP :: Mono-cyclo-hexyl phthalate
MCiDP :: Mono(carboxyisononyl) phthalate
MCiNP :: Mono(carboxyisooctyl) phthalate
MCMHP :: Mono(2-carboxymethylhexyl) phthalate
MCNP :: Mono-carboxynonyl phthalate
MCOP :: Mono-carboxyoctyl phthalate
MCPA :: Monochlorophenoxy acid
MCPP :: Mono-3-carboxylpropyl phthalate
Me-PFOSA-AcOH :: N-methyl-perfluorooctane sulfonamido acetic acid
MEAA :: Methoxyethoxyacetic acid
MECPP :: Mono(2-ethyl-5-carboxypentyl) phthalate
MeFOSAA :: Methyl perfluorooctane sulphonamido acetic acid
MEHP :: Mono-(2-ethyl-hexyl) phthalate
MEOHP :: Mono(2-ethyl-5-oxohexyl) phthalate
MEP :: Mono-ethyl phthalate
MePB :: Methyl paraben
MHiBP :: Mono(hydroxyisobutyl) phthalate
MHiDP :: Mono(hydroxyisodecyl) phthalate
MHiNP :: Mono(hydroxyisononyl) phthalate
MHnBP :: Mono(hydroxybutyl) phthalate
MHPP :: Mono-hydroxy-pentyl phthalate
MHxP :: Mono-hexyl phthalate
MiBP :: Mono-iso-butyl phthalate
MiDP :: Mono-iso-decyl phthalate
MiNP :: Mono-iso-nonyl phthalate
MMP :: Mono-methyl phthalate
MnBP :: Mono-n-butyl phthalate
MnOP :: Mono-n-octyl phthalate
MOiDP :: Mono(oxoisodecyl) phthalate
MOP :: Monooctyl phthalate
MP :: Methyl paraben
N-EtFOSAA :: N-Ethylperfluorooctane sulfonamidoacetic acid
N-MeFOSAA :: N-Methylperfluorooctane sulfonamidoacetic acid

n-NP :: n-Nonylphenol
n-PFOA :: Linear perfluorooctanoic acid
n-PFOS :: Linear perfluorooctanesulfonic acid
NMHC :: Non-methane hydrocarbons
NMOC :: Non-methane organic compounds
NPE :: Nonylphenol epoxide
o,p'-DDT :: o,p'-Dichloro-diphenyl-trichloroethane
o,p′-DDT :: 1,1,1-Tricholoro-2-(p-chlororphenyl)-2-(o-chlorophenyl)ethane
OCPs :: Organochlorine pesticides
OD-PABA :: Ethylhexyl dimethyl PABA
OH-Et-P :: Ethyl-protocatechuic acid
OH-Me-P :: Methyl-protocatechuic acid
OH-MiDP :: Mono-(hydroxy-iso-decyl) phthalate (Alternative: MHiDP)
OH-MiNP :: Hydroxy-mono-iso-nonyl phthalate
OH-MPHP :: Mono-hydroxy-propyl-heptyl phthalate
OR :: Odds Ratio
oxo-MiDP :: Mono-(oxo-iso-decyl) phthalate (Alternative: MOiDP)
oxo-MiNP :: Mono-oxo-iso-nonyl phthalate (Alternative: MOiNP)
p,p'-DDE :: p,p'-Dichlorodiphenyldichloroethylene
p,p′-DDE :: 2,2-Bis(4-chlorophenyl)-1,1-dichloroethylene
p,p′-DDT :: 1-Chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene
p,p′-DDT :: 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane
PA :: phthalic acid
PAA :: n-Propoxyacetic acid
PAEs :: Phthalates
PAHs :: Polycyclic aromatic hydrocarbons
PBB :: Polybrominated biphenyl
PBBs :: Polybrominated biphenyls
PBDE :: Polybrominated diphenyl ether
PBDEs :: Polybrominated Diphenyl Ethers
PBDEs/BDEs :: Polybrominated diphenyl ethers
PCB :: Polychlorinated biphenyl
PCBs :: Polychlorinated biphenyls
PCDD :: Polychlorinated dibenzo-p-dioxins
PCDD/Fs :: Polychlorinated dibenzo-p-dioxins/furans
PCDF :: Polychlorinated dibenzo-p-furans
PCDFs :: Polychlorinated dibenzofurans
PFAS :: Per- and polyfluorinated alkyl substances
PFAS / PFCs :: Perfluorinated compounds
PFASs :: Perfluoroalkyl and polyfluoroalkyl substances
PFBA :: Perfluorobutanoic acid
PFBS :: Perfluorobutanesulfonic acid
PFDA :: Perfluorodecanoic acid
PFDeA :: Perfluordecanoic acid
PFDoDA :: Perfluorododecanoic acid
PFDoDA/PFDoA :: Perfluorododecanoic acid
PFDS :: Perfluorodecane sulfonic acid
PFHpA :: Perfluoroheptanoic acid
PFHpS :: Perfluoroheptanesulfonic acid
PFHxA :: Perfluorohexanoic acid

PFHxS :: Perfluorohexane sulfonate
PFHxS :: Perfluorohexanesulfonic acid
PFNA :: Perfluorononanoate
PFNA :: Perfluorononanoic acid
PFOA :: Perfluorooctanoic acid
PFOS :: Perfluorooctane sulfonic acid
PFOS :: Perfluorooctane sulfonate
PFOS :: Perfluorooctane sulphonic acid
PFOSA :: Perfluorooctane sulfonamide
PFPeA :: Perfluoropentanoic acid
PFTeDA :: Perfluorotetradecanoic acid
PFTrDA :: Perfluorotridecanoic acid
PFUnDA/PFUA :: Perfluoroundecanoic acid
PG :: Propylene glycol
PhAA :: Phenoxyacetic acid
PM10 :: Particulate matter
PM2.5 :: Fine particulate matter
PP :: Propyl paraben
PPAR :: Peroxisome proliferator-activated receptor
PrPB :: Propyl paraben
PVC :: Polyvinyl chloride
REACH :: Registration, Evaluation, Authorisation and Restriction of Chemicals
Sb-PFOA :: Sum of branched isomers of perfluorooctanoic acid
Sm-PFOS :: Sum of perfluoromethylheptane sulfonate isomers
SVHC :: Substances of Very High Concern
t-OP :: t-Octylphenol
TCBPA :: Tetrachlorobisphenol A
TCC :: Triclocarban
TCDD :: 2,3,7,8-Tetrachlorodibenzo-p-dioxins
TCEP :: Tris(2-chloroethyl) phosphate
TCS :: Triclosan
THC :: Total hydrocarbons
TSNAs :: Tobacco-specific nitrosamines
α-HCCH :: Alfa-Hexachlorocyclohexane
β-HCB :: Beta-hexachlorobenzene
β-HCCH :: Beta-Hexachlorocyclohexane
β-HCCH/β-HCH :: Beta-hexachlorocyclohexane
β-HCH :: Beta-hexachlorocyclohexane
γ-HCCH :: Gamma-Hexachlorocyclohexane
ΣDEHP :: Molar sum of di-ethyl-hexyl phthalate metabolites
ΣDiNP :: Molar sum of di-iso-nonyl phthalate metabolites
ΣDnOP :: Molar sum of di-n-octyl phthalate
ΣHMWP :: Sum of high molecular weight phthalates
ΣLMWP :: Sum of low molecular weight phthalates
ΣMBP :: Sum of MiBP and MnBP

List of EDCs from analysed publications

[10] BDE, BPA, BPAF, BPE, DEHP, DDT, DDE, MEHHP, MEHP, MEOHP, NPE, PCB, PFOA, PFOS, TCEP, Agent Orange, Atrazine, Chlordane, DDE/DDT, Heptachlor, Lindane, Malathion, Metalaxyl, Nonachlor, PCB 118, PCB 138, PCB 153, PCB 180,

Arsenic, Cadmium, Mercury, Strontium, Plastic, PVC, Benzene, BPA, BPAF, BPE, Perchloroethylene, Styrene, Tetrachloroethylene, Toluene, Xylene, Silica dust, BDE-28, BDE-47, BDE-153, BDE-209, PBB-153, Hexachlorodibenzofuran, Octachlorodibenzofuran, NPE, Perchlorate

[11] PAEs, BPA, Parabens, Pesticides, Dioxins, Furans, PCBs, Benzophenones, Metalloids, Pharmaceuticals, Triclosan, PFASs, Other phenols

[12] EDC, REACH, SVHC, BP-2, BP-3, EHMC, 4′-MAP, OD-PABA, BPA, BPA-G, PCDD, PCDF, TCDD, PBB, BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, MePB, PrPB, MMP, MEP, MiBP, 2OH-MiBP, MnBP, 3OH-MnBP, MBzP, MEHP, 5OH-MEHP, MEHHP, 5oxo-MEHP, MEOHP, 5cx-MEPP, MECPP, MCPP, MiNP, OH-MiNP, MHiNP, oxo-MiNP, MOiNP, cx-MiOP, MCiOP, OH-MiDP, MHiDP, oxo-MiDP, MOiDP, cx-MiNP, MCiNP, PCB, 2,4-DCP, 2,5-DCP, DDE, p,p′-DDE, DDT, p,p′-DDT, HCB, β-HCB, β-HCH, 3-PBA, PFHxS, PFNA, PFOA, PFOS, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFCs, PFAS, TCS.

[13] DDT, p,p’-DDT, o,p’-DDT, p,p’-DDE, HCCH, β-HCCH, α-HCCH, γ-HCCH, BDEs (hexa-BDEs), PFAS, PFOA, PFOS, 3M, BBzP, PVC, EU, BPA

[14] APCs, BFRs, BPA, EDC, PAHs, Polychlorinated organic compounds, Pesticides, Phthalates, Organic solvents, Metals, Miscellaneous chemicals

[15] BPA, MBP, DBP, DDE, o,p′-DDT, p,p′-DDT, DEHP, HCB, HCE, HCC, MEHP, 5cx-MEPP, 7cx-MMeHP, DiNP, n-NP, t-OP, PBB, PBDE, PCB, PCDD/Fs, PFOS, PFOA, TCDD

[16] MBP, MEP, MBzP, MMP, MCPP, MEHP, PCB-153, ΣPCB, PCB-138, DDE, DDT, 2,4-D

[17] Aldrin, DDE, DDT, Dieldrin, Endosulfan, HCB, HCH, Heptachlor, Heptachlor epoxide, Mirex, Oxychlordane, Trans-nonachlor, HBCDD, PBBs, PBDEs/BDEs, PCBs, PCDFs, TCDD, EtFOSAA, MeFOSAA, PFDA, PFDeA, PFDoDA, PFHpS, PFHxS, PFNA, PFOA, PFOS, PFOSA, PFTrDA, PFUnA/PFUnDA

[18] MBzP, MCHP, MCMHP, MCNP, MCOP, MCPP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MiNP, MMP, MnBP, MOP, BPA, TCS, TCC, BP-1, BP-2, BP-3, BP-8, 4-OH-BP, BP, BzP, EP, HP, MP, OH-Et-P, OH-Me-P, PP, 3,4-DHB, 4-HB, BAA, EAA, EEAA, MAA, MEAA, PAA, PhAA, 2-MPA

[19] Soya isoflavones

[20] BPA, PAEs, PAHs, PFAS

[21] Triclosan

[22] PM2.5, PM10, SO2, NO2, O3

[23] 6:2 diPAP, 8:2 diPAP, N-EtFOSAA, N-MeFOSAA, n-PFOA, n-PFOS, PFBA, PFBS, PFDA, PFDoDA/PFDoA, PFDS, PFHpA, PFHpS, PFHxA, PFHxS, PFNA, PFOA, PFOS, PFOSA, PFPeA, PFTeDA, PFTrDA, PFUnDA/PFUA, Sb-PFOA, Sm-PFOS

[24] DEHP, MEHP, MEHHP, MEOHP, MECPP, DiNP, MiNP, MHiNP, MOiNP, MCiNP, DiDP, MiDP, MHiDP, MOiDP, MCiDP, DnOP, MnOP, MCPP, BBP, MBzP, DMP, MMP, DEP, MEP, DBP, MnBP, MHnBP, DiBP, MiBP, MHiBP

[25] LMW, HMW, MnBP, MEP, MiBP, MMP, MCNP, MCOP, MiNP, MCPP, MBzP, ΣDEHP, MECPP, MEHHP, MEHP, MEOHP, MCMHP, DBP, DEP, DiBP, DMP, DiDP, DiNP, DnOP, BzBP, DEHP

[26] BPA, BPS, BPF, BPAF, Phtalathes, PFOS, PFOA, Mercury, Selenium, Zinc, MEP, Parabens, BP3, BDE-154, BDE-153, BDE-100, BDE-28

[27] Fossil fuel mixtures

[28] 2,4,5-T, 2,4,5-TP, As, DDT, DEHP, EPTC, HCB, Hg, PBDEs, β-HCCH/β-HCH

[29] PCB, Dioxin

[30] BBzP, BPA, BPF, BPS, DEHP, MBzP, MCNP, MCOP, MCPP, MECPP, MEHP, MEHHP, MEOHP, MEP, MHPP, MHxP, MiBP, MiDP, MiNP, MMP, MnBP, OH-MiNP, OH-MPHP, oxo-MiNP, PA, ΣDEHP, ΣDiNP, ΣDnOP, ΣHMWP, ΣLMWP, ΣMBP
[31] BPA
[32] Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFASs, PFHxS, PFNA, PFOA, PFOS
[33] Malathion, Paraquat, Methylparathion, Metamidiphis, Endosulfan, Dimethoate, Diazinon, Cadusaphos, Ethoprophos, Isazophos, Pyrimiphos-ethyl, Terbulos, Methamidophis, Fentothion, Dichlorvos, Chlorpyrifos, Chlorpyrifos-methyl, Propetanphis, Ethyl parathion, Methyl parathion
[34] BPA
[35] PM2.5, PM10, SO2, NO2, O3, CO2, CH4, CO, H2S, NMHC, NMOC, sulphur, THC, c-PAH, PMcoarse, NOx, PM2.5, PM25-10, PM25
[36] Nicotine, PG, Glycerol, Vegetable glycerine, Formaldehyde, Acetaldehyde, Methylglyoxal, Acrolein, Acetone, Benzaldehyde, Benzene, Toluene, Ethylbenzene, Xylenes, Lead, Chromium, Tin, Silver, Nickel, Copper, Aluminum, Cadmium, Mercury, TSNAs, Hydroxycarbons, PAHs, Phenols, Aldehydes, Pesticides, Vanillin, Ethyl Maltol, Ethyl vanillin, Menthol.
[37] Caffeine, Alcohol, Heavy metals, Xenobiotics, Estrogen, Lead, Arsenic, Mercury, Organic solvents, Pesticides
[38] PFOS, PFOA, PFHxS, EtFOSAA, MeFOSAA, PFNA
[39] Chloropicrin, Chlorothalonil, Triforine, Myclobutanil, Ziram, MCPA, Carbofuran, Formetanate hydrochloride, Methomyl, Aldicarb, Endosulfan, Diazinon, Dimethoate, Phosmet, Methyl parathion, Phorate, Methidathion, Cacodylic acid, Sodium cacodylate, Fenbutatin-oxide, Aluminum phosphide, Petroleum distillates, Paraffin-based petroleum oil, Polyoxyethylene sorbitol, mixed ethyl ester, α-(p-Nonylphenyl)-omega-hydroxypoly (oxyethylene) with an average of 4.2 mol of ethylene oxide, Cyhalothrin, Bifenthrin, Streptomycin, Benomyl, Oxyfluorfen , Copper hydroxide, Copper sulfate (basic), Acephate, Nonyl phenoxy poly (ethylene oxy) ethanol
[40] BPA, BPF, BPS, BPAF, TCBPA
[41] PFAS, PFDA, PFHxS, PFNA, PFOA, PFOS
[42] Lead
[43] BPA
[44] PCBs, DDE

EDCs and Carcinogenesis

The impact of Endocrine Disrupting Chemicals (EDCs) on cancer development is characterized by significant heterogeneity, yet several trends emerge across meta-analyses and systematic reviews. Research indicates that the strongest associations between EDC exposure and malignancy are observed in the thyroid (up to 67% of studies showing positive correlations) and male reproductive organs, specifically the prostate (48%) and testes (47%) [10]. Notably, the risk for male-specific cancers often mirrors or slightly exceeds that of female reproductive cancers, such as uterine (44%) or ovarian (43%) [10].

Specific Substances and Risk Magnitudes

Certain chemical classes demonstrate a more pronounced carcinogenic potential:

- **Phthalates and Heavy Metals:** Phthalates (63% positive results) and heavy metals (54%) are among the most frequently implicated substances [10].
- **Odds Ratios (OR):** High-risk correlations have been identified for heavy metals (OR > 10) and specific compounds like **PCB 153**, particularly in patients with elevated PSA levels (OR = 30.3) [10].

- **Organohalogens:** These compounds show a strong link to non-seminoma testicular cancers (OR = 2.96), while organochlorine compounds are associated with both seminoma and non-seminoma types [13].

The Role of Timing: Prenatal vs. Adult Exposure

A critical factor in EDC-induced carcinogenesis is the **window of exposure**. Evidence suggests a significant **two-fold increase** in genital cancer risk (specifically seminomas) for men exposed prenatally to EDCs; however, this association is often absent when exposure occurs only during adulthood [13]. The stronger impact on non-seminoma risks may be attributed to their later clinical presentation (approximately 10 years later than seminomas), allowing long-lived EDCs—measured in maternal blood—more time to exert pathological effects [13]. While most single compounds show statistically insignificant trends, p,p′-DDE remains a notable exception, showing moderate risk particularly during prenatal stages [15].

Industry-Specific Risks and Thyroid Health

Environmental and occupational exposure related to the **fossil fuel industry** is linked to a moderately increased risk of prostate cancer [27]. Furthermore, long-term exposure to agricultural chemicals significantly impacts the thyroid, particularly the **papillary subtype**. Fungicides (OR = 1.21) and herbicides (OR = 1.1) show stable negative effects across populations, whereas the evidence for insecticides remains contradictory [28]. Interestingly, the thyroid cancer risk appears lower in men than in women, likely due to the mediating role of estrogenic receptors [28].

Proposed Biological Mechanisms

The transition from EDC exposure to malignancy is driven by several complex pathways:

1. **Hormonal Interference:** Primarily through the antagonism of androgen and progesterone receptors, and mixed agonist/antagonist effects on estrogenic receptors [10, 27, 28].
2. **Cellular Dysregulation:** Disruption of intracellular signalling pathways and the induction of oxidative stress and inflammatory responses [10, 28].
3. **Genotoxicity:** Direct damage to genetic material and disruption of the Hypothalamic-Pituitary-Thyroid (HPT) axis [10, 28].

Methodological Limitations in Current Research

The reliability of these findings is frequently hampered by common limitations across the literature:

- **Exposure Assessment:** A lack of objective, quantified measurements; many studies rely on subjective questionnaires or environmental proxies rather than individual biomarkers [10, 27, 28].
- **The "Cocktail Effect":** Most research focuses on single, persistent EDCs (often ignoring fast-metabolizing substances), failing to account for the synergistic effects of chemical mixtures [13, 15, 27].
- **Study Design:** Significant methodological heterogeneity, small sample sizes, and the failure to control for variables such as family history or breastfeeding duration [10, 13].

EDCs and Semen quality

The relationship between exposure to Endocrine Disrupting Chemicals (EDCs) and male fertility remains a subject of complex debate due to methodological inconsistencies across studies. While some systematic reviews and meta-analyses have failed to demonstrate statistically significant correlations between general EDC exposure and key semen parameters (such as concentration, total count, motility, and morphology), these results are often hindered by the inclusion of diverse substances and varying clinical endpoints [11]. Consequently, researchers emphasize the necessity of structured studies focusing on chemical mixtures rather than isolated substances to better reflect real-world exposure [11, 37].

Specific Substances and Observed Effects

Despite the lack of a universal consensus, specific categories of EDCs and pollutants have shown distinct negative impacts on reproductive health:

- **Persistent Organic Pollutants and Plasticizers:** Exposure to **PCB-153** is associated with reduced sperm motility, while **DDE/DDT** negatively affects concentration, motility, and morphology. Similarly, phthalate metabolites such as **MBP and MBzP** are linked to lower sperm concentration and motility [16].
- **Heavy Metals and Pesticides:** Lead exposure significantly reduces ejaculate volume, sperm concentration, total count, motility, and the percentage of normal morphology [42]. Organophosphorus pesticides are linked to substantial decreases in count, concentration, motility, and morphology, alongside a non-significant increase in seminal leukocyte levels [33].
- **Atmospheric Pollutants:** Air pollutants, including **PAHs (Polycyclic Aromatic Hydrocarbons), PM2.5, NO2, and SO2**, impair overall human fertility. Specifically, **PM10, PM2.5, and SO2** significantly reduce the success rates of *in vitro* fertilization [22]. While EDCs in the air adversely affect morphology (particularly head defects), motility, and vitality, their impact on sperm concentration and total count remains inconclusive [22].
- **Industrial and Lifestyle Factors:** Fossil fuel industry-related EDCs present a moderate risk of declining sperm concentration, motility, and vitality, though quantifying these risks is difficult due to the lack of exposure quantification in many studies [27]. Furthermore, **e-cigarette "e-liquids"** have been shown to increase the risk of decreased testosterone levels and lower sperm count, vitality, and motility [36].
- **Phytoestrogens:** In contrast to synthetic EDCs, studies on **soy isoflavones** have not found a significant impact on testosterone, estrogen levels, or semen quality, nor have they demonstrated feminizing effects in men [19].

Pathophysiological Mechanisms

The literature identifies several primary pathways through which these substances exert their deleterious effects:

1. **Oxidative Stress:** A recurring mechanism across various exposures (pesticides, heavy metals, e-cigarettes, and fossil fuel EDCs) is the induction of **reactive oxygen species (ROS)**, leading to DNA fragmentation and cellular damage [27, 33, 36, 42].
2. **Hormonal and Signal Disruption:** EDCs interfere with androgen and estrogenic receptors, disrupt steroidogenesis, and may impair the **hypothalamus-pituitary-gonadal (HPG) axis** [16, 42]. Notably, some pesticide-induced damage appears to be testosterone-independent, suggesting direct suppressive toxicity or altered intracellular signalling and gene regulation [33].
3. **Structural Damage:** Several substances, particularly lead and organophosphorus pesticides, compromise the integrity of the **blood-testis barrier** and induce endoplasmic reticulum stress or systemic inflammation [16, 33, 42].

Critical Periods and Limitations

The timing of exposure is a crucial factor; foetal exposure to EDCs is particularly significant and has been linked to both diminished semen quality in adulthood and the feminization of male foetuses [18].

However, the field faces significant research challenges. Many studies suffer from high heterogeneity, small sample sizes, a lack of standardized methodologies, and a failure to account for multi-component (mixture) exposures [16, 27, 33, 42]. The absence of comprehensive exposure quantification remains a major barrier to establishing definitive causal relationships [27, 33].

EDCs and Reproductive Health

The relationship between exposure to Endocrine Disrupting Chemicals (EDCs) and reproductive outcomes is characterized by significant complexity and heterogeneity. Meta-analytical data indicates that while statistically significant correlations between general EDC exposure and reproductive disorders are sometimes elusive, prenatal exposure often yields stronger effects. A notable exception is p,p'-DDE, which is consistently associated with an increased risk of reproductive dysfunction [15].

Impact on Female Fertility and Pregnancy Outcomes

Research highlights a significant link between exposure to Polychlorinated Biphenyls (PCBs) and Brominated Flame Retardants (BFRs) and a prolonged Time to Pregnancy (TTP) in women. Conversely, Organochlorine pesticides (OC) and Perfluoroalkyl substances (PFAS) have not shown a clear impact on TTP [17]. Further evidence suggests that while Bisphenol A (BPA), Triclosan (TCS), and Triclocarban (TCC) have negligible effects on TTP, parabens and glycol ethers are negatively associated with female fertility [18]. Beyond conception, EDCs significantly impair overall fecundity by increasing the rates of miscarriage and stillbirth, likely through damage to the embryo, placenta, and the uterine environment [35]. Notably, a delayed TTP serves not only as a marker of subfecundity but also as a predictor for metabolic syndrome, cardiovascular disease, and increased overall mortality [17].

Male Reproductive Health and Semen Quality

The impact of EDCs on male fertility is frequently observed through changes in semen quality rather than TTP [17, 35]. Exposure—particularly during the critical foetal period—is linked to a decline in semen parameters and the feminization of male foetuses [18]. Specific substances such as Benzophenone have been identified as potential drivers of male infertility [18].

BPA, even at low doses, negatively affects male reproductive health by reducing sperm motility and count, inhibiting Leydig cells, and contributing to clinical dysfunctions such as decreased libido, premature ejaculation, and erectile dysfunction [34]. Phthalate exposure is similarly linked to sex hormone imbalances (reduced testosterone and oestradiol) and poor semen quality [24]. Furthermore, air pollutants—including Polycyclic Aromatic Hydrocarbons (PAHs), $PM_{2.5}$, NO_2, and SO_2—adversely affect general fertility, with PM_{10}, $PM_{2.5}$, and SO_2 specifically reducing the success rates of *in vitro* fertilization (IVF) [22].

Physiological Mechanisms

The literature identifies several overlapping pathways through which EDCs and pollutants exert their effects:

1. **Hormonal Disruption:** Mimicry of oestrogens (e.g., BPA), interference with the hypothalamus-pituitary-testis axis, and general endocrine signalling imbalance [22, 24, 34, 35].
2. **Oxidative Stress and Cellular Damage:** Induction of reactive oxygen species leading to DNA damage and apoptosis [22, 24, 34].
3. **Epigenetic and Structural Changes:** Alterations in gene expression and structural damage to reproductive organs [22, 24, 35].
4. **Developmental Timing:** Phthalate exposure shows a dimorphic effect on puberty, delaying maturation in boys while accelerating it in girls [24].

Methodological Challenges and Future Directions

A recurring theme across studies is the difficulty in establishing definitive causal links due to high biological variability and methodological limitations [37]. Many substances, such as phthalates and certain EDCs, have short half-lives (measured in hours), making accurate exposure assessment difficult without high-frequency sampling [15, 18, 24]. Furthermore, many reviews suffer from:

- A lack of standardization in quantifying concentrations and defining infertility [17, 18, 35].

- Failure to account for "cocktail effects" (simultaneous exposure to multiple EDCs) [17, 22, 24].
- Inadequate stratification for confounding factors such as age and workplace versus home exposure [17, 35, 37].

To address these gaps, authors advocate for standardized, long-term prospective studies that begin in childhood. Such research should utilize high-frequency sampling, account for EDC mixtures, and evaluate both partners simultaneously to treat fertility as a shared reproductive unit [17, 18, 24, 34].

EDCs and Pubertal Development

A systematic review and meta-analysis investigating the effects of prenatal and postnatal exposure to **Endocrine Disrupting Chemicals (EDCs)** found no statistically significant correlation between EDC exposure and pubertal disorders in the male population. Furthermore, the analysis was unable to identify a specific developmental window of heightened sensitivity to these substances.

In the female population, a weak trend suggests that prenatal exposure may be associated with **accelerated maturation**. However, the strength of these findings is limited by several critical factors:

- **Inconsistent Data:** Conflicting directions of influence for the same chemical compounds across different studies.
- **Methodological Heterogeneity:** Variations in the methods used to quantify EDC exposure and differing clinical definitions of puberty.
- **Chemical Complexity:** A general failure to account for the synergistic or antagonistic effects inherent in mixtures of EDCs and other substances **[12]**.

Regarding dietary components, current evidence does not support a causal link between **isoflavone intake** and the onset of precocious puberty **[19]**.

EDCs and Prenatal Health

The cumulative evidence from recent systematic reviews and meta-analyses underscores a significant correlation between exposure to Endocrine Disrupting Chemicals (EDCs) and adverse prenatal outcomes, most notably reductions in birth weight and increased risks of preterm birth.

Impact on Birth Weight and Gestational Age

Meta-analytical data indicate that prenatal exposure to EDCs is associated with a decrease in foetal birth weight [14]. This association appears to be modulated by socioeconomic and lifestyle factors; the stability and strength of these observations are more pronounced among mothers with lower educational attainment and those who smoke tobacco [14]. Notably, the risk profile follows a dose-response pattern regarding chemical variety: the risk of low birth weight doubles when the mother is exposed to four or more different EDCs [14].

While some studies report inconsistent results regarding the magnitude of birth weight reduction for specific substances, others quantify these effects more precisely. For instance, a ten-fold increase in exposure to Per- and polyfluoroalkyl substances (PFAS) was linked to an average weight reduction of 11g, while Lead (Pb) and Dimethyl phthalate (DMP) were associated with reductions of 45g and 57g, respectively [44]. Furthermore, exposure to Bisphenol A (BPA) and substances related to the fossil fuel industry has been specifically linked to an increased risk of preterm birth and miscarriage [27, 34].

Pathophysiological Mechanisms

The detrimental effects of EDCs on the foetus are thought to be driven by several complex biological pathways:

- Hormonal Disruption: EDCs act via estrogenic mimicry and the disruption of the hypothalamus-pituitary-gonadal (HPG) axis, interfering with endocrine signalling and lipid metabolism [34, 44].
- Oxidative Stress and DNA Integrity: A primary proposed mechanism is the induction of oxidative stress through reactive oxygen species (ROS), which compromises DNA integrity and causes direct cellular toxicity [27, 34].
- Adipose Tissue Development: Some substances may interfere with the normal development of foetal adipose tissue [44].

Interestingly, across multiple studies, no significant differences in vulnerability based on foetal sex have been established [14, 27].

Methodological Limitations in Current Research

The synthesis of data on EDCs remains challenging due to several systemic limitations in the existing literature:

- **Exposure Quantification:** Many studies lack rigorous quantification of exposure, often relying on self-reported questionnaires rather than standardized biomarkers [27, 34].
- **Chemical Complexity:** The vast number of EDCs—particularly those derived from the fossil fuel industry—makes it difficult to isolate the impact of individual substances or assess synergistic "cocktail effects" [27, 44].
- **Standardization:** Variations in study protocols and population groups hinder the ability to conduct robust meta-analyses [34].
- **Research Scope:** Most current data focuses on exposition during conventional fossil fuel extraction, potentially overlooking newer industrial processes [27].

EDCs and Congenital Abnormalities

The relationship between exposure to Endocrine Disrupting Chemicals (EDCs) and the incidence of congenital malformations remains a complex area of research characterized by significant heterogeneity and methodological challenges.

Meta-Analysis Findings and Specific Substances

Current meta-analyses generally report a lack of statistically significant associations between EDC exposure and the risk of hypospadias or cryptorchidism for most investigated substances. A notable exception is p,p′-DDE, which demonstrates a moderate risk, particularly when prenatal exposure is involved [15]. However, the impact of individual EDCs varies widely. Research is often limited by a failure to account for chemicals with short half-lives and the difficulty of determining precise prenatal exposure levels [15].

Regarding Bisphenol A (BPA), maternal exposure is linked to an increased risk of several congenital defects, including:

- Male feminization: Hypospadias, cryptorchidism, and reduced anogenital distance[34].
- Organ-specific changes: Testicular hypertrophy or atrophy (including the epididymis) and prostate enlargement [34].

The proposed mechanisms for these effects include oestrogen mimicry, disruption of the hypothalamus-pituitary-testicular axis, induction of oxidative stress, and direct cellular toxicity [34].

Industrial and Environmental Exposure

Research into the fossil fuel industry suggests a likely increased risk of birth defects, though findings across studies remain inconsistent. These negative effects appear to stem from both environmental and occupational exposure, with no clear consensus on which sex is more vulnerable [27]. Evaluation is further complicated by the vast number of EDCs produced by the fossil fuel industry, making it difficult to isolate the effects of single substances or assess specific endpoints due to small sample sizes for individual diseases [27].

In agricultural contexts, studies on male neonates (e.g., in Central California) have largely found no correlation between general environmental EDC exposure and hypospadias frequency. However, specific exceptions exist where certain substances correlate with varying degrees of severity:

- Mild severity: Associated with specific EDCs.
- Significant severity: Linked to herbicides from the monochlorophenoxyacetic acid or ester groups, aldicarb, dimethoate, phorate, paraffin-based petroleum oil, and polyoxyethylenesorbitol [39].

Methodological Limitations and Future Directions

A recurring theme in the literature is the lack of standardized exposure quantification. Many studies rely on environmental measurements rather than tissue-based analysis [39] or use self-reported questionnaires, which introduces significant variability and hinders robust meta-analysis [34]. Furthermore, previous research on fossil fuels has focused primarily on conventional extraction methods and may have missed relevant data due to incomplete search terminology [27].

To address these gaps, authors emphasize the need for long-term, standardized studies that move beyond single-substance analysis (like BPA) to evaluate the cumulative impact of the full spectrum of EDCs and other hazardous materials [34].

EDCs and Mental Health

Recent meta-analytical data confirms that exposure to endocrine-disrupting chemicals (EDCs) significantly elevates the risk of Attention-Deficit/Hyperactivity Disorder (ADHD), with a notably more pronounced effect observed in males. The strength of this association varies by chemical class, with the highest risks linked to Polycyclic Aromatic Hydrocarbons (PAHs; OR = 1.40), Bisphenol A (BPA; OR = 1.35), and Phthalates (PAEs; OR = 1.11)[20]. Furthermore, prenatal exposure to these substances is linked to an increase in autistic behaviours and general hyperactivity across both genders [20, 34].

Exposure Windows and Compound-Specific Risks

The developmental impact of EDCs is highly sensitive to the timing of exposure:

- PAHs and PAEs: These compounds demonstrate a significant association with ADHD risk primarily during the prenatal period, with Odds Ratios (OR) of 1.52 and 1.13, respectively [20].
- BPA: Increased risk is persistent across both prenatal (OR = 1.22) and postnatal (OR = 1.18) windows [20]. Beyond ADHD, maternal urinary BPA levels are specifically correlated with increased anxiety and depression in boys by age seven [34].
- PFAS: Conversely, Per- and polyfluoroalkyl substances (PFAS) have shown an inverse correlation with ADHD risk, highlighting the complexity of chemical interactions with the nervous system [20].

Pathophysiological Mechanisms

The neurotoxic effects of EDCs on the developing nervous system are driven by several key biological pathways:

1. Endocrine Disruption: Alteration of thyroid and sex hormone homeostasis.
2. Neurotransmitter Interference: Dysregulation of the dopaminergic system and a reduction in Brain-Derived Neurotrophic Factor (BDNF) expression.
3. Epigenetic Modifications: Potential for transgenerational effects through altered gene expression.
4. Cellular Stress: Induction of oxidative stress pathways [20].

Methodological Considerations

Despite these findings, the current body of evidence is constrained by high study heterogeneity, particularly regarding varying ADHD diagnostic criteria. Furthermore, there is a critical

shortage of data addressing co-exposure with heavy metals or particulate matter. Future prospective longitudinal studies are essential to fully evaluate the long-term cumulative effects of EDCs on mental health [20].

EDCs and Endocrine Health

The influence of Endocrine Disrupting Chemicals (EDCs) on the hypothalamic-pituitary-thyroid (HPT) axis remains a complex area of study, characterized by varying results across different compounds and life stages. While certain substances like isoflavones show no discernible impact on T4 or T3 levels in euthyroid individuals—even those with marginal iodine intake [19]—other synthetic compounds such as triclosan and bisphenols suggest more significant disruption.

Triclosan and Thyroid Regulation

Research regarding **triclosan** has yet to yield a definitive consensus on its impact on the human thyroid system at current exposure levels [21]. However, studies have indicated a slight association between triclosan exposure and a decrease in T3 and T4 levels alongside a concomitant increase in TSH, with these effects appearing more pronounced in females.

The interpretation of these findings is complicated by the presence of other EDCs and the ethical impossibility of controlled administration in human subjects. Methodological limitations, such as the use of single-point urine or blood samples, often fail to account for the dynamic nature of the HPT axis. This is particularly relevant during **pregnancy**, which is hypothesized to be a window of heightened vulnerability. Proposed mechanisms for triclosan-induced disruption include:

- **Structural Mimicry:** Mimicking T3 and T4 to trigger negative feedback loops in the pituitary and hypothalamus.
- **Receptor Antagonism:** Blocking TSH and TRH receptors.
- **Enzymatic Inhibition:** Inhibiting deiodinases and transporters [21].

Bisphenol A (BPA) and Related Bisphenols

The impact of bisphenols, particularly **BPA**, demonstrates significant correlation with altered thyroid markers, though the directionality of these changes often varies by study and sex. Increased BPA exposure generally correlates with a decrease in TSH levels, while its effect on T3 and T4 remains inconsistent across systematic reviews [31].

The susceptibility to bisphenols is highly dependent on the **developmental window**, with the third trimester of pregnancy and early childhood identified as critical periods. Observed effects include:

- **Maternal and Neonatal Impact:** BPA is linked to decreased total thyroxine in pregnant women and lower TSH levels in male neonates [34].
- **Sex-Specific Variability:** General bisphenol exposure has been associated with TSH reduction in both sexes; however, it may lead to an increase in T3 in girls while causing a decrease in boys [40].
- **Dosage Thresholds:** High exposure to bisphenol mixtures (>1.5 μg/g creatinine) is associated with a decrease in FT3 levels in offspring of both sexes [40].

Mechanistically, bisphenols are thought to interfere with the HPT axis due to their **structural similarity to T3, T4, and TSH**. This similarity allows them to influence receptors in the pituitary and hypothalamus—promoting negative feedback—and to inhibit iodine uptake by interacting with the sodium-iodide symporter (NIS). Furthermore, bisphenols may alter the expression of genes essential for thyroid hormone synthesis [31, 40].

Conclusion and Future Directions

While an association between BPA and thyroid autoimmunity in children remains inconclusive, a correlation begins to emerge after the age of 15 [31]. Given the current limitations in data,

there is a clear necessity for large-scale cohort studies utilizing multi-point exposure measurements and considering the cumulative effects of EDC mixtures [21].

EDCs and Metabolic Health

The Impact of PFAS on Body Composition and Metabolism

Research regarding the association between prenatal exposure to Per- and Polyfluoroalkyl Substances (PFAS) and metabolic outcomes remains largely inconsistent. However, a relatively stable negative correlation has been observed between childhood concentrations of PFOA and PFOS and BMI, particularly up to the age of three. Sex-specific effects have also emerged: newer compounds such as PFBA and PFBS appear to negatively impact only girls, while PFNA shows a similar effect in boys [23]. In adult populations (ages 40–60), higher PFAS levels are associated with longitudinal increases in body weight and hip circumference, though these effects are mitigated by diet and physical activity. Notably, higher concentrations have been recorded in Black men [32].

PFAS also appear to interfere with weight management by exacerbating the "yo-yo effect." High concentrations are linked to a decrease in resting metabolic rate (RMR) during weight loss and a slower RMR recovery during weight regain, an effect more pronounced in women than men. Proposed mechanisms include oestrogen mimicry, activation of PPARα and PPARγ receptors, and interference with proteins regulated by hepatocyte nuclear factor 4α [41].

PFAS and Glycaemic Regulation

Exposure to specific PFAS compounds significantly influences diabetes risk. For instance, Sb-PFOA is associated with a 14% increase in diabetes risk compared to placebo, though this risk can be reduced to 1% through lifestyle interventions. Conversely, EtFOSAA and PFHxS increase the risk of microangiopathy by 17% and 18%, respectively, regardless of behavioural interventions [38]. Postulated mechanisms for these effects include enhanced fatty acid oxidation, increased glycogenolysis, and pancreatic inflammation [38].

Phthalates and Bisphenols: Sex-Specific Observations

Phthalates have been shown to increase the risk of metabolic syndrome (MetS), with high-molecular-weight compounds (MBzP: 16%, DEHP: 16%, MCOP: 12%, MCPP: 9%) showing a slightly stronger influence than low-molecular-weight ones (e.g., MMP, which shows an 89% association in men) [25]. The proposed mechanisms involve the activation of PPARγ induction of insulin resistance via FoxO1 overexpression, activation of angiotensin-converting enzyme (ACE), and inhibition of the bradykinin-nitric oxide pathway [25].

Regarding prenatal exposure to BPA and BP3, strong positive correlations with BMI, waist circumference, and subscapular skinfold thickness have been noted in girls, while results for boys remain ambiguous or negative. In contrast, parabens and PBDEs appear to disproportionately affect boys. During childhood and adolescence, bisphenols correlate with abdominal obesity specifically in boys, whereas phthalates affect body mass in both sexes. A specific susceptibility window for boys has been identified between 4 months and 3 years of age [26].

Persistent Organic Pollutants (PCBs and Dioxins)

Exposure to Polychlorinated Biphenyls (PCBs) shows a high correlation with diabetes (particularly in Asian countries) and hypertriglyceridemia (in North America). While dioxins are also linked to MetS, the limited number of studies prevents definitive confirmation. It is suggested that PCBs induce individual components of MetS sequentially rather than the full syndrome simultaneously. Underlying mechanisms may include adipocyte hypertrophy, impaired differentiation, activation of NF- κ/β signalling leading to systemic inflammation, disruption of leptin signalling, and mitochondrial damage [29].

Limitations and Methodological Challenges

These researches faces several significant limitations:

- Sample Size and Diversity: Small cohorts in certain studies and a lack of analysis regarding the synergistic effects of EDC mixtures [23, 26].
- Study Design: Many studies, such as those regarding BPA and lipid levels, are cross-sectional, preventing the establishment of causality. Furthermore, single-spot urine samples may not accurately reflect long-term exposure [43].
- Population Specificity: Several PFAS studies focused exclusively on individuals who were already overweight or prediabetic, which may limit generalizability [32, 38].
- Confounding Factors: Inconsistent definitions of overweight, inaccurate exclusion of dietary factors, and measurement errors in physical activity assessments (e.g., self-reported questionnaires) [23, 41].

While EDCs clearly exert sex-specific effects, it is currently impossible to determine which sex is more vulnerable due to these methodological gaps. Future research must include both sexes and account for both biological sex and socio-cultural gender factors [26].

EDCs and Pulmonological Health

A systematic review and meta-analysis of 15,123 subjects indicated weak associations between specific endocrine-disrupting chemicals (EDCs)—namely **MBzP, MEOHP, and MCNP**—and reduced lung function parameters (FEV1, FVC, FEF25-75, PEF). Although the observed declines were below the clinical significance threshold (100–140 mL or >10% for FEV1), such early-life impairments may irreversibly alter long-term respiratory trajectories.

The impact of EDCs appeared to be sex- and age-dependent, with males and those postnatally exposed showing higher susceptibility. Proposed biological mechanisms include:

- **Immunomodulation:** Promotion of Th2-driven pro-allergic responses.
- **Oxidative Stress:** Induction of airway inflammation and remodelling via the p38 MAPK pathway.
- **Hormonal Pathways:** Interactions with oestrogen receptors expressed in immune cells.

However, the findings are limited by significant methodological constraints, including exposure misclassification (due to single spot-urine sampling), reverse causation (EDCs in inhalation medications), and inadequate adjustment for confounders like height and socioeconomic status. Future research should prioritize longitudinal data, repeated exposure measurements, and cohorts of children under four years of age to strengthen causal inferences.[30]

Conclusions

EDCs influence on male health:

Endocrine Disrupting Chemicals (EDCs) collectively exert a distinct influence on **carcinogenesis**, particularly regarding thyroid and reproductive organ malignancies. However, the available literature lacks meta-analyses or systematic reviews concerning cancers other than those of the reproductive system, sex-specific organs, and the thyroid—a gap resulting from the paucity of original research on other types of neoplasms [10]. A very strong impact has also been reported for **heavy metals** and certain **PCBs** [13], where prenatal exposure is associated with a twofold higher risk, notably for testicular cancer [15]. The risk of reproductive system cancers is slightly higher in men, in contrast to thyroid cancer, where women are more susceptible—a phenomenon attributed to the modulation of susceptibility by oestrogens [28].

The impact of EDCs on **male fertility** has been confirmed for specific substances; however, the general assessment of this phenomenon remains a subject of debate due to methodological heterogeneity across studies [11, 37]. A negative impact has been observed for PCBs, phthalates, metals, pesticides, and air pollutants [16, 42, 33, 22, 27, 36], while a neutral effect was noted for phytoestrogens (specifically soy isoflavones) [19]. Furthermore, **foetal exposure** is critical, as it leads to the feminization of male foetuses and a permanent reduction in semen quality in adulthood [18].

The influence of EDCs on the reproductive system is well-documented but characterized by significant complexity. The key factors determining the severity of effects are the **exposure window** (particularly the prenatal period) and the specific type of substance. Notably, female fertility is often utilized as a studied endpoint representing couple fertility. Research in this field distinguishes between the impact on **couple fertility** through the male factor (semen quality, libido, and erectile dysfunction) [17, 18, 22, 24, 34, 35] and the impact where the male partner's role is not specified, resulting in a dominance of female factors: prolonged time to pregnancy (TTP), reduced fecundity, and pregnancy complications (e.g., miscarriage, placental damage) [17, 18, 35]. The strength of evidence remains mixed, with few exceptions: p,p'-DDE [15], PCBs and BFRs [17], and BPA, phthalates, and benzophenone [18, 24, 34].

The effect of EDCs on **puberty** remains uncertain; no significant correlation has been established in boys, whereas a weak trend toward accelerated maturation is observable in girls—likely linked to the estrogenic mimicry of EDCs [12]. Notably, a diet rich in soy isoflavones does not appear to influence this process [19]. Conversely, a strong correlation exists between **birth weight**, premature birth, and EDC exposure [14, 27, 44], with higher concentrations of EDCs correlating with an increased risk of low birth weight [14].

The relationship between exposure to EDCs and the occurrence of **developmental malformations** is complex and ambiguous, primarily due to the methodological diversity of studies. Within this context, exposure to EDCs derived from agricultural activities shows low significance for certain compounds [39], similar to exposure related to fossil fuel processing [27]. Nevertheless, the potentially stronger impact of the full environmental mixture must be considered, given the limitations of studies that evaluate only a fraction of possible EDCs [34, 39]. For p,p′-DDE, a moderate risk of **hypospadias/cryptorchidism** is noted, while for BPA, there is a clear association with the feminization of male foetuses and alterations in genital organs [15, 34].

A significant influence of EDCs on the increased risk of **ADHD, autistic behaviours, and anxiety** has been confirmed in relation to PAHs, BPA, and phthalates, with this dependency being markedly more pronounced in boys [20]. PAHs and phthalates are dangerous primarily during foetal exposure, whereas BPA also poses risks postnatally [20]. Foetal BPA exposure results in negative consequences almost exclusively in male offspring [34].

The influence of EDCs on **thyroid hormonal function** is probable but remains inconclusive; while biological mechanisms suggest disruption, human studies are often contradictory or dose-dependent. Triclosan is reported to cause a decrease in T_3/T_4 and an increase in TSH, an effect stronger in women [21]. In contrast, prenatal exposure to bisphenols leads to a decrease in TSH [31, 40], and high doses result in decreased T_3 in offspring [40]. For hormonal functions of organs other than the thyroid, there is a lack of meta-analyses and systematic reviews.

The impact of EDCs on **metabolic health** is evident, although the level of confirmation varies by substance and research area. A common phenomenon is strong **sexual dimorphism** in response to exposure. Effects are confirmed for PCBs (diabetes, hypertriglyceridemia) and dioxins (the latter being presumptive due to limited sources) [29]. Phthalates and bisphenols are linked to an increased risk of metabolic syndrome and abdominal obesity: in girls, a correlation exists between BPA/BP3 and BMI, while boys show sensitivity to parabens, PBDEs, and bisphenols (specifically regarding abdominal obesity) [25, 26]. Conversely, **PFAS** exposure leads to either a decrease in BMI (up to age 3) or weight gain and disturbances in resting metabolic rate (RMR) in adults. Susceptibility is sex-dominant for girls (PFBA, PFBS) and boys (PFNA), with women also being more susceptible to RMR disturbances [23, 32, 41]. PFAS exposure increases the risk of diabetes and microangiopathy without showing a stronger influence in either sex [38].

Finally, a weak association exists between exposure to selected phthalates (MBzP, MEOHP, MCNP) and a reduction in lung functional parameters (FEV_1, FVC, FEF_{25-75}, PEF). Although

this association is clinically non-significant regarding acute symptoms, it may have significant implications for cumulative lifelong exposure. Men demonstrate greater susceptibility in this regard [30].

Integrative Pathophysiological Mechanisms of EDC Action

The transition from environmental exposure to clinically observable pathology is driven by a complex, multi-layered network of biological mechanisms. Central to these effects is the capacity of Endocrine Disrupting Chemicals (EDCs) to act as molecular mimics or antagonists, primarily targeting the hypothalamic-pituitary-gonadal (HPG) and thyroid (HPT) axes, thereby disrupting hormonal homeostasis and steroidogenesis. Beyond classical endocrine signalling, EDCs exert significant cellular toxicity through the induction of oxidative stress and reactive oxygen species (ROS), which results in DNA fragmentation, epigenetic modifications, and the triggering of pro-inflammatory pathways such as NF-κ/β and p38 MAPK. Furthermore, metabolic dysregulation is facilitated through the activation of nuclear receptors (e.g., PPARγ) and the impairment of mitochondrial function, while neurodevelopmental impacts are characterized by altered neurotransmitter expression and reduced neurotrophic support. Collectively, these mechanisms demonstrate that EDCs do not merely interfere with isolated hormonal signals but fundamentally alter intracellular signaling, genetic integrity, and structural barriers across multiple organ systems.

Methodological Synthesis and Recommendations

The evidence synthesized across these domains reveals a consistent pattern of methodological constraints that limit the establishment of definitive causal links between endocrine disrupting chemical (EDC) exposure and adverse health outcomes. A primary concern is **exposure misclassification**, arising from a reliance on subjective questionnaires or single "spot-urine" samples, which fail to capture the high kinetic variability and short half-lives of many non-persistent EDCs. Furthermore, analysed publications are predominantly characterized by a **"single-compound" focus**, which neglects the "cocktail effect"—the synergistic and antagonistic interactions of chemical mixtures that more accurately reflect real-world environmental exposure. High levels of **study heterogeneity**, particularly regarding clinical diagnostic criteria (e.g., for ADHD or infertility) and environmental proxies rather than direct biomarkers, further dilute the statistical power of meta-analytical findings.

To overcome these barriers, authors advocate for a fundamental shift toward **standardized, longitudinal prospective studies** that begin in early childhood or the prenatal period. Future research must prioritize **high-frequency bio sampling** and the utilization of tissue-based analysis to improve quantification accuracy. There is a critical need for **multi-component exposure models** that account for chemical mixtures and integrate potential confounders such as socioeconomic status, lifestyle factors, and co-exposure to heavy metals or particulate matter. Finally, researchers emphasize that fertility and metabolic health should be evaluated as shared units—accounting for both partners and both biological and socio-cultural gender factors—to provide a more holistic understanding of the anthropogenic impact on human physiology.

DISCLOSURE

Author Contributions

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During the preparation of this work, the authors used **Gemini 3.0 Flash** for the purpose of **improving the stylistic quality of the text.** After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.
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