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State of the Science of Endocrine-Disrupting Chemicals 2026



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Authors

Chapter 1. Introduction to the state of the science report
Lead authors: Laura N. Vandenberg (University of Massachusetts, United States of America) and R. Thomas Zoeller (University of Massachusetts, United States of America)

Contributing author: Zhanyun Wang (United Nations Environment Programme)

Chapter 2. Evidence for endocrine disruption in humans and animals
Lead authors: Juliette Legler (Utrecht University, Kingdom of the Netherlands) and Henrik Holbech (University of Southern Denmark, Denmark)

Chapter authors: Fela Contreras Berecochea, Sander Lentz, Hana Moreira Farnezi (Utrecht University, Kingdom of the Netherlands), Simone Fibiger Sørensen (University of Southern Denmark, Denmark), Dries Knapen, Lucia Vergauwen (University of Antwerpen, Belgium) and Alice Baynes (Brunel University of London, United Kingdom of Great Britain and Northern Ireland)

Contributing authors: Natalie Aneck-Hahn (University of Pretoria, South Africa), Kyungho Choi (Seoul National University, Republic of Korea), Joëlle Rüegg (Uppsala University, Sweden) and Andrea B. Webster (University of Pretoria, South Africa)

Chapter 3. Testing and assessment of EDCs
Lead authors: Laura N. Vandenberg (University of Massachusetts, United States of America) and R. Thomas Zoeller (University of Massachusetts, United States of America)

Chapter authors: Olwenn V. Martin (University College London, United Kingdom of Great Britain and Northern Ireland), Nicholas Chartres (University of Sydney, Australia), Tracey J. Woodruff (Stanford University, United States of America), Lucia Vergauwen and Dries Knapen (University of Antwerpen, Belgium)

Chapter 4. Exposure to endocrine-disrupting chemicals
Lead author: Martin Scheringer (RECETOX, Masaryk University, Brno, Czech Republic, and ETH Zürich, Zürich, Switzerland)

Chapter authors: Daniel Heidland (ETH Zürich, Zürich, Switzerland) and Fiona Quin Zabel (University of Connecticut, Groton, CT, United States of America)

Contributing authors: Linda Schenk (Karolinska Institute, Stockholm, Sweden), Marlene Ågerstrand (Stockholm University, Stockholm, Sweden), Xanat Flores (Universidad de las Américas Puebla, Mexico), Ipek Imamoglu (Middle East Technical University, Ankara, Türkiye), Asif Qureshi (Indian Institute of Technology Hyderabad, Hyderabad, India) and Hiroshi Yamamoto (National Institute for Environmental Studies, Tsukuba, Japan)

Chapter 5. Socioeconomic and policy analysis for EDCs
Lead authors: Leonardo Trasande (New York University, United States of America) (section 5.1) and Martin Scheringer (RECETOX, Masaryk University, Brno, Czech Republic, and ETH Zürich, Zürich, Switzerland) (section 5.2)

Chapter authors: Brij Mohan Sharma (RECETOX, Masaryk University, Brno, Czech Republic, and ETH Zürich, Zürich, Switzerland) (section 5.1) and Matthis Schäfer (ETH Zürich, Zürich, Switzerland) (section 5.2)

Contributing authors: Marlene Ågerstrand (Stockholm University, Sweden), Alexandra Harrington (Lancaster University, United Kingdom of Great Britain and Northern Ireland), Xanat Flores (Universidad de las Américas Puebla, Mexico), Ipek Imamoglu (Middle East Technical University, Ankara, Türkiye), Asif Qureshi (Indian Institute of Technology Hyderabad, Hyderabad, India) and Hiroshi Yamamoto (National Institute for Environmental Studies, Tsukuba, Japan) (section 5.2)

Chapter 6. Implications for decision makers
Lead authors: Laura N. Vandenberg (University of Massachusetts, United States of America), Henrik Holbech (University of Southern Denmark, Denmark), Juliette Legler (Utrecht University, Kingdom of the Netherlands), Martin Scheringer (RECETOX, Masaryk University, Brno, Czech Republic and ETH Zürich, Zürich, Switzerland), Leonardo Trasande (New York University, United States of America) and R. Thomas Zoeller (University of Massachusetts, United States of America)

UNEP and WHO Expert Group Members

Niklas Andersson (European Chemicals Agency), Jennifer Bruin (Carleton University, Canada), Jingwen Chen (Dalian University of Technology, China, Kyungho Choi (Seoul National University, Republic of Korea), Sofie Christiansen (National Food Institute, Technical University of Denmark, Denmark), Roman Coretchi (Agenția Națională pentru Sănătate Publică, Romania), Marina Olga Fernández (Instituto de Biología y Medicina Experimental, Argentina), Alexandra R. Harrington (Lancaster University, United Kingdom of Great Britain and Northern Ireland), Magali Houde (Environment and Climate Change Canada, Canada), Taisen Iguchi (National Institute for Basic Biology, Japan), Rahel Mesfin Ketema (Hokkaido University, Japan), Jana Klánová (RECETOX Centre, Masaryk University, Czechia), Amalia Laborde (Universidad de la República, Uruguay), Juliette Legler (Utrecht University, Kingdom of the Netherlands), Olwenn Viviane Martin (University College London, United Kingdom of Great Britain and Northern Ireland), Cecile Michel-Caillet (French Agency for Food, Environmental and Occupational Health & Safety, France), Kei Ohno Woodall (Secretariat of the Basel, Rotterdam and Stockholm Conventions), Okechukwu J. Okonkwo (Tshwane University of Technology, South Africa), Heather Patisaul (National Institute of Environmental Health Sciences), United States of America), Caroline Serrano-Nascimento (Universidade Federal de São Paulo, Brazil), Eszter Simon (Swiss Federal Office for the Environment, Switzerland, Leonardo Trasande (New York University, United States of America), Majorie B. Maria van Duursen (Vrije Universiteit Amsterdam, Kingdom of the Netherlands), Andrea B. Webster (University of Pretoria, South Africa), Jordane Wodli (European Commission) and R. Thomas Zoeller (University of Massachusetts Amherst, United States of America).

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Individuals consulted or involved in reviewing the report:

Aseel Abo-Taleb (Children and Youth Major Group to UNEP), David Azoulay (Center for International Environmental Law), Sara Brosché (International Pollutants Elimination Network), Giulia Carlini (Center for International Environmental Law), Linroy Christian (Antigua and Barbuda), Lilian Corra (International Society of Doctors for the Environment), Rikke Donchil Holmberg (Denmark), Magdalena Frydrych (Poland), Mariella Noto (Zero Discharge of Hazardous Chemicals), Rory O'Neill (International Trade Unions Confederation), Cheyenne Rendon (Indigenous Peoples' representative to UNEP), Ninja Reineke (CHEMTrust), Hanna-Andrea Rother (University of Cape Town, South Africa), Chrysanthi Sofokleus (International Council of Chemical Associations), Koki Takaki (Japan), Naveen Thacker (International Pediatric Association), Francesca Trivelloni (International Council of Chemical Associations), Susan Wilburn (Healthcare Without Harm), Somang Yan (CropLife International) and Santos Virgilio (Angola).

UNEP: Sheila Aggarwal-Khan, Dina Abdelhakim, Sandra Averous-Monnery, Ludovic Bernaudat, Andrea Hinwood, Pushpam Kumar, Aphrodite Smagadi, Brij Mohan Sharma, Steven Stone, Malgorzata Alicja Stylo, Kay Williams, Fernando Gaston Iturburu and Michel Rebello; WHO: Marie-Noel Brune Drisse

Secretariat, production, reviewing and coordination:

UNEP: Jacqueline Alvarez, Victor Hugo Estellano Schulze, Stephanie Laruelle and Zhanyun Wang.
WHO: Richard Brown

Editor: John Dawson
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List of abbreviations and acronyms

1-OHP	1-hydroxypyrene
4-MBC	4-Methylbenzylidene Camphor (Enzacamene)
4-NP	4-Nonylphenol
ADH	Antidiuretic Hormone
AF	Attributable Fraction
AFSS	Androgenized Female Stickleback Screen
AOP	Adverse Outcome Pathway
ATGT	Avian Two-Generation Toxicity Test
BBP	Benzyl butyl phthalate
BDE	Brominated diphenyl ether
BP	Bisphenol
BPSIP	4-hydroxy-4'-isopropoxydiphenylsulfone
cAMP	Cyclic adenosine monophosphate
Can$	Canadian Dollar
CAS	Chemical Abstracts Service
CC BY-NC-SA	Creative Commons Attribution-NonCommercial-ShareAlike
CF	Conceptual Framework
CI	Confidence Interval
CIP	Cataloguing-in-Publication
CLARITY-BPA	Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity
CLP	Classification, Labelling and Packaging Regulation
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl phthalate
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DEET	N,N-diethyl-m-toluamide
DEHP	Di-(2-ethylhexyl) phthalate
DINCH	1,2-cyclohexane dicarboxylic acid diisononyl ester
DNA	Deoxyribonucleic acid
E2	17β-Estradiol
EASZY	Estrogen Activity Screening Zebrafish Assay
EATS	Estrogen, Androgen, Thyroid and Steroidogenesis
EC	European Commission / European Community (regulation prefix)
ECHA	European Chemicals Agency
EDC	Endocrine-Disrupting Chemical(s)

EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
ERα	Estrogen Receptor Alpha
EU	European Union
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GESTIS ILV	International Limit Values for Chemical Agents Database
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HBM4EU	Human Biomonitoring for Europe
HPA axis	Hypothalamic-Pituitary-Adrenal axis
ILO	International Labour Organization
IPCS	International Programme on Chemical Safety
IQ	Intelligence Quotient
KC	Key Characteristic
KE	Key Event
K-REACH	Korean Registration and Evaluation of Chemicals
MASLD	Metabolic dysfunction-associated steatotic liver disease
MECPP	Mono-(2-ethyl-5-carboxypentyl) phthalate
MEHHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
mRNA	Messenger Ribonucleic Acid
NAMs	New Approach Methodologies
NP	Nonylphenol
NPnEO	Nonylphenol Ethoxylate
OECD	Organisation for Economic Co-operation and Development
PAH	Polycyclic Aromatic Hydrocarbons
PBDE	Polybrominated diphenyl ethers
PBT	Persistent, Bioaccumulative and Toxic
PCB	Polychlorinated biphenyls
PFAS	Per- and polyfluoroalkyl substances
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PPAR	Peroxisome proliferator-activated receptor
PVC	Polyvinyl chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RXR	Retinoid X Receptor
SAICM	Strategic Approach to International Chemicals Management
StAR	Steroidogenic Acute Regulatory Protein

T3	Triiodothyronine
T4	Tetraiodothyronine (Thyroxine)
TBBPA	Tetrabromobisphenol A
TBT	Tributyltin
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TDCPP	Tris(1,3-dichloro-2-propyl)phosphate
ToxCast	Toxicity Forecaster
TPP	Triphenyl phosphate
UNEP	United Nations Environment Programme
US$	United States Dollar
UV	Ultraviolet
vB	Very Bioaccumulative
vP	Very Persistent
WHO	World Health Organization

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Foreword

The endocrine system is a complex system that releases hormones to regulate growth, brain development, reproductive functions, sleep and more. This system is vital to our health as humans and to the health of the wildlife around us. Yet a growing number of chemicals have been identified as capable of disrupting hormone systems, with humans and wildlife exposed through a variety of pathways.

As the *State of the Science of Endocrine-Disrupting Chemicals 2026* shows, these chemicals are found in food packaging, cookware, cosmetics, toys, textiles and medical equipment – with certain products are key source of exposure. Items in our homes, schools, playgrounds, transport, workplaces, hospitals and the outdoor environment (air, water, soil) can serve as exposure sources. EDCs have been found in human blood and breast milk worldwide. And this is just from the small percentage of chemicals that have been evaluated: many on the market have not been tested for hormone disrupting effects.

The evidence linking EDC exposure to diseases and disorders is strong and continues to grow. Prenatal and early-life exposure affects neurodevelopment, cognition and behaviour. EDCs are linked to cancer, cardiovascular disease, obesity, type-2 diabetes and metabolic liver disease. Reproductive organs, fertility and thyroid functions are also disrupted.

EDC exposure also carries economic costs, conservatively estimated at over US$ 1.1 trillion annually across the globe. There are additional costs associated with damaged ecosystem services (such as safe drinking water), the loss of biodiversity, impacts on food production and even human rights. In laying out these consequences, the report makes a strong case for urgent action on EDCs to protect human health and the environment and points to key areas for policy action.

Actions to protect human and environmental health must be strengthened at all levels, with particular attention to reducing significant sources of exposure and ensuring the safety of chemicals and products throughout their lifecycles. There needs to be an international effort to develop harmonized criteria for EDC identification and regulation – including addressing exposure to mixtures of chemicals and ensuring EDCs are not treated the same as other toxic chemicals. Global legally binding and voluntary instruments, including chemicals and waste multilateral environmental agreements and the Global Framework on Chemicals, have a key role to play in providing effective means to reduce widespread global exposure. Science and surveillance must improve – boosting biomonitoring, expanding testing programmes to focus on the whole endocrine system, and improving transparency so that manufacturers disclose the evidence they are using for purported "safer" substitutions. Together with strong policy and regulatory enforcement, this will be essential to avoiding regrettable substitutions.

Accounting for the costs of EDCs – including their potential impacts on vulnerable and marginalized communities and on ecosystems – is an important step to inform policy and investment actions, while capacity building is needed to boost infrastructure and data sharing in resource-limited countries. Crucially, action must be taken before populations are harmed, not after. Laboratory evidence is already sufficient to support regulatory action to reduce and prevent EDC exposure.

The stakes for innovation and opportunity in the chemical industry are high, with the global green chemistry market projected to surpass US$ 270-328 billion by 2035. The specialised packaging industry alone accounted for 26% of the total market value share of green solutions in 2025, driven by growing regulatory pressure and rising demand for sustainable packaging solutions. This trend extends beyond packaging across the automotive, construction, pharmaceuticals, food and beverages, paints and coatings, and textile industries, where companies aim to improve their sustainability and comply with environmental standards.

This report is an important step towards a safer world, free from exposure to EDCs. Food packaging, cookware, cosmetics, toys, textiles and medical equipment must be free from EDCs given the risk of close human and environment contact. Solutions do exist. Some safer alternatives are available. The task for policymakers is to ensure that these solutions and alternatives are deployed – to protect human, animal and planetary health, and save trillions of dollars each year.



Sheila Aggarwal-Khan
Director
Industry and Economy Division
United Nations Environment Programme



Bruce Gordon
Director a.i.
Department of Environment, Climate Change, One Health and Migration
World Health Organization

Executive Summary

About this report

Scientific concern about chemicals that can interfere with hormone systems has deepened in recent decades. The 1991 Wingspread Conference on Endocrine-Disrupting Chemicals was an early turning point: experts from multiple disciplines reached consensus that "a large number of man-made chemicals released into the environment have the potential to disrupt the endocrine system of animals, including humans". This Conference coined the term "endocrine disruptors". Subsequent works, including the book *Our Stolen Future*, raised public attention and spurred governments and scientists to develop research programmes and testing methods for endocrine-disrupting chemicals (EDCs).

In 2002, the International Programme on Chemical Safety, in a joint venture with the International Labour Organization, the United Nations Environment Programme and the World Health Organization, published the first global assessment of the state of the science of endocrine disruptors. It established a definition that is now widely accepted by governments and stakeholders worldwide: "An ***endocrine disruptor*** is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations."

By 2012, the understanding of EDCs had improved substantially. The second United Nations Environment Programme and World Health Organization assessment documented sharply increased concerns driven by rising rates of endocrine-related diseases in humans, widespread exposure to EDCs, and mounting laboratory evidence linking EDC exposure to disease. The 2012 assessment highlighted the unique characteristics of EDCs that need to be considered when testing, assessing and managing their hazards and risks. Furthermore, it identified critical windows of development, concluded that disease risk from EDCs was likely to be significantly underestimated, and called on governments to reduce human and wildlife EDC exposure.

The current report, the third global assessment of the state of the science of endocrine disrupting chemicals, synthesizes scientific advances during the preceding decade to inform policymakers and decision makers and guide action to protect human health and the environment. Rather than cataloguing all new findings, it provides a high-level analysis of the findings of greatest impact, including critical gaps, and draws out implications for policy- and decision-making.

Key messages

1. Evidence showing that EDC exposure results in serious adverse effects in humans and wildlife is strong across multiple health domains.
2. Widespread and ubiquitous human and wildlife exposure to EDCs is increasingly documented.
3. An increasing number of chemicals have been identified as EDCs as testing programmes have advanced, yet most chemicals registered globally for production and use have not been evaluated for endocrine-disrupting properties and major knowledge gaps persist.
4. The estimated health, environmental and economic burden of EDCs is large and likely underestimated, with global health-related costs alone estimated to exceed US$ 1.1 trillion annually.
5. Policy and governance frameworks have evolved since 2012 but remain fragmented and insufficient to transform products and sectors causing widespread EDC exposure.

What the science shows

1. **Evidence showing that EDC exposure results in serious adverse effects in humans and wildlife is strong across multiple health domains.**

Since 2012, evidence linking EDC exposure to adverse outcomes has continued to strengthen, and the mechanistic evidence is established well enough in many cases to conclude causality. Rates of several endocrine-related disorders, including low semen quality, neurobehavioural disorders, early puberty, obesity, type 2 diabetes and some cancers, have increased worldwide. Because these changes are occurring rapidly, they are unlikely to be explained primarily by genetic change. Human and wildlife studies continue to report associations between chemical exposure and health effects, consistent with evidence from laboratory studies. Many of the mechanisms by which EDCs interfere with hormone systems are well understood, while the endocrine system's complexity means that some effects, mechanisms and pathways remain to be characterized.

Findings also highlight the importance of accounting for critical periods of development (in particular embryonic, fetal and pubertal stages), when EDC-induced hormonal disruptions can be irreversible. Children are especially vulnerable to EDCs not only because of the sensitive developmental processes that occur in early life, but also because they consume more food and water and breathe more air per unit of body weight than adults, resulting in proportionally higher chemical exposure. Early life EDC exposure occurring in utero or during puberty can also have latent effects: outcomes such as cancer, metabolic syndrome and infertility may not manifest until decades after an exposure, consistent with the understanding that early-life exposure can influence health and disease later in life.

Systematic analysis of the literature identifies several health domains in humans and wildlife that are affected by EDC exposure:

- **Developmental and neurobehavioural effects.** There is strong evidence that prenatal and early life exposures to multiple chemical classes – including phthalates, bisphenols, certain pesticides, polychlorinated biphenyls (PCBs) and certain per- and polyfluoroalkyl substances (PFAS) – affect neurodevelopment, cognition and behaviour. Animal mechanistic work reinforces evidence from human epidemiology studies.

- **Reproductive and thyroid outcomes.** There is reliable evidence in humans and across animal species that several EDCs have adverse impacts on development of the male and female reproductive organs, fertility and thyroid function. Wildlife sentinel observations complement human data.

- **Metabolic disorders.** Strengthened epidemiologic and experimental evidence links EDCs (such as bisphenol A, phthalates, certain PFAS and some pesticides) to obesity, insulin resistance, type-2 diabetes and steatotic liver disease.

- **Immune function.** There is increasing evidence that EDCs can perturb immune development and function across animal classes and in humans, with associations reported for asthma, allergy and some autoimmune outcomes.

- **Cancer.** Growing mechanistic understanding (for example, hormone receptor activation, epigenetic reprogramming, deoxyribonucleic acid (DNA) damage pathways) supports the plausibility that EDCs may contribute to cancer development. Early-life EDC exposure, including during fetal development and puberty, may increase later susceptibility to hormone-related cancers (for example, breast, prostate, thyroid and endometrium). Human epidemiological evidence is heterogeneous and limited by study designs, but laboratory animal evidence provides strong support for these findings.

- **Cardiovascular disease.** Emerging epidemiological and experimental evidence links some EDC exposures to hypertension and other cardiovascular outcomes. Associations with cardiovascular mortality have also been reported, but evidence is heterogeneous.

Controlled laboratory studies, including those using animal models, continue to be critical to understand the mode of action and health effects of EDC exposure. These studies can help guide the assessment of outcomes in observational studies of human and wildlife populations.

Evidence revealing adverse effects of EDCs on invertebrate populations (which comprise more than 95% of all animal species) has grown significantly in the past decade. Most of the evidence is based on academic research and environmental observations because few regulatory tests are available for investigating effects of EDCs on invertebrates.

2. **Widespread and ubiquitous human and wildlife exposure to EDCs is increasingly documented.**

Globally, humans and wildlife are exposed to a wide range of chemical classes identified as EDCs, through many pathways of exposure. These include bisphenols, phthalates, polychlorinated and polybrominated biphenyls, certain PFAS, alkylphenols, parabens, many organophosphate pesticides, and others. Human exposure occurs in the everyday environment, including homes, schools, playgrounds, cars, workplaces and specialized settings such as medical environments. EDCs are present in virtually every environmental matrix, including soil, water (including drinking water), air, food and dust and are incorporated in a wide range of products including many plastic items, personal care products, pharmaceuticals, toys, household goods, and electronics as well as pesticides (see Table 1).

Table 1 Examples of EDCs in consumer products and their uses

Product category	Example of EDCs	Example of uses
Food contact materials, packaging and kitchenware	Bisphenols, phthalates, PFAS, nonylphenols, organophosphate additives	Plasticizers, can-lining resins, grease-resistant coatings, non-stick surfaces
Cosmetics and personal care products	Parabens, phthalates, triclosan, UV filters, heavy metals	Preservation, fragrance stabilization, antimicrobial activity, UV protection
Toys and childcare products	Phthalates, bisphenols, PFAS, organophosphate flame retardants	Plasticizers, coatings, flame retardancy, stain resistance
Textiles, furnishing and building materials	Certain PFAS, nonylphenols, phthalates, organophosphate flame retardants	Water repellence, stain resistance, textile processing, flame retardancy
Healthcare and medical devices	DEHP and other phthalates, bisphenols, PFAS	Flexible tubing, blood bags, device components, specialty materials

Note: The above table includes chemical categories associated with endocrine disruption. However, not all substances within these groups have been assessed for endocrine-disrupting properties.

Exposures have been measured in regions where these chemicals are neither manufactured nor used, with some EDCs reaching the Arctic and Antarctic through environmental long-range transport. Some persist in the environment for decades, while others are produced at such high volumes that their levels remain high although the chemicals are degradable.

Human and environmental (bio)monitoring provides three essential pieces of information: the magnitude and distribution of exposure to EDCs within populations and wildlife; spatial patterns that help identify exposure hotspots; and trends over time that allow evaluation of whether regulatory interventions or changes in consumer use patterns are effective. These functions make biomonitoring a cornerstone of EDC management.

Despite progress, monitoring coverage remains uneven globally, with gaps particularly evident in low- and middle-income countries, occupational settings, vulnerable populations, as well as many ecosystems and wildlife populations. As a result, it is difficult to accurately assess exposures, identify populations at risk, and evaluate whether regulatory and risk management measures are effective.

3. An increasing number of chemicals have been identified as EDCs as testing programmes have advanced, yet most chemicals registered globally for production and use have not been evaluated for endocrine-disrupting properties and major knowledge gaps persist.

The number of chemicals identified as EDCs continues to grow, in large part due to the significant investment in the development of assays and testing programmes as well as interest from the scientific community at large. Studies using laboratory animals and lab-based screening assays developed specifically to identify mechanisms and adverse effects, have been especially critical in identifying EDCs and offer promising gains in the speed and cost of EDC evaluations. National and international EDC testing programmes have grown significantly over the past decade, and many new validated and standardized screens, tests, assays and guidance documents are now available.

Despite these advances, human and environmental exposures to EDCs are incompletely documented. And because there are critical gaps in the available assays and implementation of testing programmes has been limited, the total universe of EDCs remains unknown. More than 350,000 chemicals and chemical mixtures have been registered for production and use globally, but the vast majority have never been evaluated for endocrine-disrupting properties. “Regrettable substitution”, whereby one EDC has been replaced with a structurally similar or insufficiently tested chemical, also continues to occur.

Furthermore, while existing testing frameworks provide a foundation for the identification and evaluation of EDCs, they do not provide comprehensive coverage of all relevant elements. The endocrine system is complex, and EDC testing should reflect this complexity. Remaining knowledge gaps include limited testing methods beyond estrogen, androgen, thyroid and steroidogenic pathways, complex dose-response relationships, an insufficient number

of validated assays for invertebrate species, and challenges in accounting for real-world exposures to chemical mixtures and other stressors. The available evidence indicates limitations of single chemical hazard and risk assessments for capturing the cumulative and combined effects of EDC exposure on human health and wildlife.

4. **The estimated health, environmental and economic burden of EDCs is large and likely underestimated, with global health-related costs alone estimated to exceed US$ 1.1 trillion annually.**

Global human health-related costs associated with EDC exposure have been estimated to exceed US$ 1.1 trillion annually. Current estimates of the health and economic burden associated with EDC exposure are however likely conservative and may substantially underestimate the true costs of unabated exposure to EDCs.

Costs associated with damaged ecosystem services include those associated with loss of safe drinking water, impacts on food production (for example, decline of pollinator populations), and inadequate flood control. Additional costs that are harder to quantify include the impact of loss of biodiversity, reduced ecosystem stability and extinction-level events for wildlife. But these costs potentially add another order of magnitude beyond those attributed to impacts on human health. Some of these costs also restrict access to basic and fundamental rights, for example, access to clean water.

To fully account for the costs of EDC exposure, it is critical to understand the costs of inaction, in terms of adverse human health and ecological outcomes associated with EDC exposure. While the total burden of EDC exposure has not yet been fully quantified, existing estimates provide compelling evidence of the high costs of inaction on EDCs.

5. **Policy and governance frameworks have evolved since 2012 but remain fragmented and insufficient to transform products and sectors causing widespread EDC exposure.**

EDCs are addressed through a wide range of binding and non-binding legal instruments as well as voluntary initiatives at the national, regional and international levels. In recent years, the regulatory landscape has strengthened with an increasing number of legal instruments and voluntary initiatives, including non-binding instruments, such as the Global Framework on Chemicals. However, the way in which EDCs are addressed varies between instruments and jurisdictions, which leads to inconsistencies and gaps in the protection of human and environmental health.

Internationally harmonized hazard classes for EDCs within the Globally Harmonized System of Classification and Labelling of Chemicals can support consistent identification, classification and labelling of EDCs worldwide. The growing evidence on EDCs highlights the importance of strengthening and aligning existing binding and non-binding instruments, as well as voluntary initiatives, to support more systematic, comprehensive and effective protection of human health, wildlife and ecosystems.

Evidence is already sufficient to support action, particularly in a number of sectors known to be significant sources of exposure to EDCs. A sector- and value-chain-based perspective can complement traditional chemical-by-chemical approaches and help identify practical opportunities to prevent exposure at source through phase-out, and to promote substitution, innovation and the adoption of safer alternatives. Coordinated international action and related capacity building are particularly important for developing countries.

Moving forward: key areas for action

The scientific evidence is clear: EDCs are a global and growing threat to human and environmental health. The economic costs of EDC exposures, and resulting human health and environmental effects, are large, underestimated and unevenly distributed. Despite advances in science, testing and governance, current approaches to identify EDCs and regulate these chemicals remain uneven and insufficient.

Drawing on the evidence presented in this report, six priority needs or areas for action emerge to address the major scientific findings and challenges associated with EDCs:

- Protect vulnerable populations from EDC exposure, particularly during critical development and life stages, such as pregnancy, infancy and childhood.
- Improve monitoring and understanding of EDC exposure.
- Advance EDC identification, testing and assessment.
- Account for the health, environmental and economic costs of EDC exposure.
- Strengthen governance, partnerships, and regulations and transform products and sectors driving exposures to EDCs.

- Use the One Health approach to characterize the impact of EDCs on understudied species, health outcomes and responses to additional stressors.

The evidence reviewed in this report highlights the importance of immediate, coordinated and equitable action on EDCs, combining international cooperation, national policies and regulations, and strengthened testing, research and science policy. Actions can take place at multiple points across product systems, sectors and value chains. While uptake may differ according to national circumstances and available capacities, there is an expanding body of evidence on practical approaches for reducing exposure, supporting safer alternatives and strengthening EDC management.

The costs of delay – in terms of adverse health effects, lost productivity, ecological damage and economic loss – far exceed the costs of prevention and effective regulation. The evidence is sufficiently strong to support policy action. To protect humans and ecosystems from the harms of EDC exposure, sustained political commitment, adequate resources and international cooperation are required. In the meantime, the effective use and strengthening of already existing policy tools is needed without delay.

1 Introduction to the State of the Science report

Lead authors

Laura N. Vandenberg (University of Massachusetts, United States of America) and R. Thomas Zoeller (University of Massachusetts, United States of America)

Contributing author

Zhanyun Wang (United Nations Environment Programme)

1.1 Why this report, and why now

Anthropogenic chemicals have played a critical role in advancing modern society, yet their use and release into the environment can pose significant risks to humans and ecosystems (Carney Almroth *et al.* 2023). Since the early 1960s, following the publication of *Silent Spring* (Carson *et al.* 1962) and increased public awareness of chemical pollution and its impacts, many national, regional and international efforts have aimed to achieve the goal of global sound management of chemicals. Increasing international attention has focused on the global threat posed by endocrine-disrupting chemicals (EDCs), substances that interfere with the hormone systems of humans and animals and whose health consequences span reproductive and developmental disorders, metabolic disease, cancers and neurodevelopmental conditions.

Scientific concern about chemicals that can interfere with hormone systems has deepened in recent decades (Schug *et al.* 2016; Soto, Schaeberle *et al.* 2021). The first major global scientific synthesis, conducted by the International Programme on Chemical Safety (IPCS) under the aegis of the World Health Organization (WHO) in 2002 (IPCS 2002), established a working definition of EDCs and documented early evidence of their adverse effects on wildlife, while calling for more rigorous studies on their impact on humans (IPCS 2002). A second assessment, completed by United Nations Environment Programme (UNEP) and WHO in 2012, consolidated a decade of new evidence on EDC exposure and health effects, and identified unique features of EDC hazard that demand special consideration in testing, assessment and regulation (UNEP and WHO 2013). Both assessments called explicitly for continued research, improved testing methods and stronger international policy action.

The present report responds to the request of the United Nations Environment Assembly for the Executive Director of UNEP, in cooperation with the World Health Organization, to update the *State of the Science of Endocrine Disrupting Chemicals 2012*.[1] It assesses the most significant scientific advances made since the 2012 assessment, with the explicit goal of informing policymakers and decision makers about what the evidence now shows, where the greatest areas of concern lie and what options exist for action. It builds on the lineage of the 2002 and 2012 assessments while reflecting a field that has advanced substantially in the breadth of health effects documented, in the sophistication of exposure science, in the development of testing and assessment methodologies, and in a growing understanding of the socioeconomic costs of regulatory inaction. A fuller account of the history of EDC research and policy responses is provided in annex I.

1 UNEA resolution 5/7 on the sound management of chemicals and waste.

1.2 Audience for this report

This report is written for policymakers and decision makers working in national and regional regulatory agencies, international bodies, legislative bodies, and the institutions responsible for chemicals management, public health, environmental protection and related domains. It is a high-level synthesis and is not intended as a comprehensive review of the primary scientific literature, or an assessment of every chemical–effect relationship, or as a technical resource for specialist researchers. Rather, it aims to present the state of the science in a form that is accessible, policy relevant and actionable, identifying what is known with confidence, where important uncertainties remain, and what the implications are for those with authority to act.

This audience-centred purpose has shaped decisions about methodology and scope throughout the report, and it is important for readers to understand those decisions clearly, in order both to interpret the report's conclusions appropriately and to guard against misuse of its limitations.

1.3 Structure of the report

In addition to this chapter, which provides essential background on EDCs, the endocrine system, the principles of endocrinology and the One Health approach, the report is organized as follows.

Chapter 2 reviews the evidence on human and animal health effects of EDC exposure, drawing on published systematic reviews and reviews conducted since the 2012 assessment. It identifies the health endpoints for which evidence is strongest and provides readers with a broad evidence-based understanding of the scope of EDC-related health impacts.

Chapter 3 examines current testing and assessment methodologies for EDCs, including the strengths and limitations of existing regulatory frameworks. It identifies key gaps in the global system for identifying and characterizing EDCs and discusses what improvements are needed.

Chapter 4 documents the use of EDCs in different product sectors, the routes and levels of human and environmental EDC exposure, and the challenges of chemical substitution, in particular the recurring problem of replacing known EDCs with chemically related alternatives that carry similar hazard profiles.

Chapter 5 addresses the socioeconomic and policy dimensions of the EDC problem in two parts. The first part (*5.1*) examines estimates of the economic costs of EDC-related disease burdens. It makes the case for why the economics of inaction should motivate policymakers and decision makers to act. The second part *(5.2)* evaluates existing legislative and regulatory frameworks for EDCs across different jurisdictions, assessing their effectiveness and identifying gaps that need to be addressed.

Chapter 6 synthesizes the key findings and messages from the preceding chapters, summarizes current gaps and challenges, and outlines actionable options for policymakers and decision makers working to address the global problem of EDCs.

Box 1.1 WHO/IPCS definition of an endocrine disruptor

An *endocrine disruptor* is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations. A *potential endocrine disruptor* is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.

Source: (IPCS 2002)

1.4 What are endocrine-disrupting chemicals?

Different scientific organizations have posed varying definitions of an EDC, but throughout this state of the science report the WHO/IPCS definition will be used (box 1.1). Simply put, EDCs interfere with the body's hormone systems, leading to harmful effects in humans and wildlife. Based on the WHO/IPCS definition, determining whether a chemical is an EDC requires three elements: (a) demonstration of an adverse effect; (b) demonstration of an endocrine mode of action; and (c) a plausible link between the adverse effect that was observed and the endocrine mode of action. An "endocrine mode of action" can include chemicals that act by mimicking endogenous hormones (hormone receptor agonists); chemicals that block the binding of endogenous hormones (hormone receptor antagonists); and chemicals that alter the synthesis or secretion of endogenous hormones, the transport of hormones in the blood and across cellular barriers, as well as the metabolism and elimination of hormones from the body (Kavlock *et al.* 1996; La Merrill *et al.* 2020).

The interpretation of which endpoints represent an adverse effect relies on expert judgement (Moermond *et al.* 2016; Kase *et al.* 2016; La Merrill *et al.* 2020), and is done on a case-by-case basis. In laboratory animals, outcomes that are overt signs of disease or dysfunction (for example, failure to reproduce or measures of poor fecundity, increased incidence of cancers, the induction of birth defects, and other pathological lesions) are typically considered adverse. Other effects, including significant loss of body weight, alterations in the weight of organs, and measures of disturbed organ function (for example, changes to red and white blood cell counts, serum triglycerides and fasting glucose levels), can be considered adverse. In human studies, outcomes that align with clinical symptoms of human diseases are often considered adverse outcomes, as well as increases in disease burden in human populations (Zoeller *et al.* 2015). When considering adversity in animal populations, many regulations require that effects are observed at the population level. Exposures that are associated with effects on growth, development or reproduction are generally regarded as evidence of adversity because they are relevant to the maintenance of the population or ecosystem (Kortenkamp *et al.* 2011).

Dating back to the 1990s, the earliest studies of EDCs focused on just four general modes of action: estrogen, androgen, thyroid and steroidogenic-related outcomes (referred to as "EATS" outcomes, mediated by alterations in estrogen, androgen and thyroid hormone signalling or disruptions to steroidogenesis). This focus on estrogen, androgen, thyroid and steroidogenic-related outcomes during that time led to significant advances in the identification of numerous estrogen receptor agonists (that is, chemicals that mimic endogenous estrogens), androgen receptor antagonists (that is, chemicals that block the actions of androgens), thyroid hormone system disruptors (that is, chemicals that interfere with thyroid hormone actions through several mechanisms), and chemicals that alter the synthesis of steroidal hormones (for example, by altering the expression of cytochrome P450 enzymes or expression of the steroidogenic acute regulatory [StAR] protein). Although advancements focused on estrogen, androgen, thyroid and steroidogenic modalities have been critical in driving forward knowledge of EDCs, current understanding of the endocrine system acknowledges many more hormones, and thus many more tissues and organ systems that are implicated. For example, and as described in more detail in chapter 2, the effects of EDCs on the immune system, metabolic functions, neurobehaviours and the brain, and the cardiovascular system are becoming better understood with a growing body of evidence generated over the last two decades. So are effects of EDCs on invertebrates that have other types of endocrine systems than vertebrates, such as the ecdysteroid and juvenile hormone systems controlling development, reproduction and moulting in arthropods and insects respectively. Furthermore, while many EDCs identified to date are still within the domain of estrogen, androgen, and thyroid hormone receptor agonists or antagonists, EDCs are also recognized as chemicals that alter hormone synthesis, secretion, transport, metabolism and excretion (La Merrill *et al.* 2020).

1.5 EDCs: an expanding universe of chemicals

An analysis of chemical inventories from 19 countries revealed that more than 350,000 chemicals and chemical mixtures have been registered for production and use globally, and the identities of more than 50,000 have been protected as "confidential" (Wang *et al.* 2020). This assessment also revealed that a large number of common chemicals are shared in inventories across countries, but also that almost every country has a unique set of chemicals that are only registered in that country. Given the scope of the global chemical inventory, it is perhaps not surprising that the vast majority of these chemicals have not been evaluated to determine their endocrine-disrupting properties (Vandenberg *et al.* 2026).

Even with the tremendous challenge posed by the vast number of chemicals in commerce, over the past two decades scientific organizations and governmental authorities have assembled evidence for an increasing number of EDCs. The use, routes of exposure and environmental fates of these chemicals vary, and an increasing body of evidence indicates that both humans and animals, including livestock, across the globe are exposed to many EDCs. Furthermore, exposures can differ significantly between geographical regions based on such vulnerabilities as age, reproductive status and sex; and, for humans specifically, based on occupation. Examples of common EDCs are included in the following categories.

- Non-halogenated substituted phenols: often used as ingredients in plastics and some personal care products, detergents, coatings and polymer stabilizers. Human exposure occurs via food and from dermal exposure via use of cosmetics and household cleaners. Environmental exposures are widespread and mainly occur through water and soil contamination and waste leachates. Examples include bisphenol A (BPA) and its analogues, parabens, alkylphenols (such as nonylphenol and octylphenol) and benzophenones.

- Current-use pesticides (biocides and plant protection products): used in the control of pests both during crop production and in households. Human exposure occurs via residues found on foods and dermal and respiratory exposure, especially for those that apply these chemicals occupationally. Environmental exposure occurs directly in fields due to field run-off and vaporization, as well as production waste. Examples include atrazine, vinclozolin, chlorpyrifos, 2,4-dichlorophenoxyacetic acid, malathion and paraquat.

- Plasticizers: used in production of plastics and other polymers to induce specific properties, including flexibility, durability and workability. Human exposure occurs as these chemicals are released or leach from their product, often because they are not covalently bound, and thus are found in food packaging, medical equipment and other household goods. Examples include phthalates and chlorinated paraffins.

- Halogenated phenols: often used as ingredients in flame retardants, industrial processes and antimicrobial agents. Human exposure occurs as these chemicals are released from electronics, furniture and other household goods; as a result, they are commonly found in dust. Environmental exposure occurs because of their movement in environmental matrices, including water and soil. Examples include hydroxylated polychlorinated biphenyls, hydroxy-polychlorinated biphenyl ethers, triclosan and tetrabromobisphenol A.

- Legacy pesticides: once widely used in the control of pests, many of these chemicals have been replaced with less persistent alternatives, although production and use of some continues. Because these chemicals were typically highly persistent and bioaccumulative, they are still found in human biomonitoring studies, in products derived from domesticated animals, in the bodies of wildlife and in ecosystems. Examples include lindane, dichlorodiphenyltrichloroethane (DDT) and its metabolites, chlordane, endosulfan and tributyltin.

- Other persistent organic pollutants: a number of chemicals listed under the Stockholm Convention have been used in industrial applications, including as flame retardants, plastic additives and processing chemicals. Depending on the chemical, the Convention requires their elimination or restriction, while allowing certain specific exemptions or acceptable purposes. Because of their persistence, potential for bioaccumulation and long-range environmental transport, these substances can remain in the environment and continue to be detected in humans, wildlife and environmental media long after their production or use has ceased. Examples include polychlorinated biphenyls (PCBs), certain polybrominated diphenyl ethers (PBDEs), perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA).

Examples of sectors and value chains where human and environmental exposure is widespread, where there are significant implications for vulnerable populations, where a strong evidence base exists for EDC concerns, and where realistic opportunities to reduce exposure through substitution include consumer-facing sectors such as food contact materials and packaging,

Table 1.1 Overview of consumer product sectors, with examples of key EDCs and possible options for alternatives

Product category	Main exposure pathway	Example of EDCs	Example of function	Possible options for alternatives
Food contact materials, packaging and kitchenware 	Ingestion	Bisphenols, phthalates, PFAS, nonylphenols, organophosphate additives	Plasticizers, can-lining resins, grease-resistant coatings, non-stick surfaces	Glass, stainless steel, biobased packaging, cast iron, ceramic coatings
Cosmetics and personal care 	Dermal absorption, ingestion, inhalation	Parabens, phthalates, triclosan, ultraviolet (UV) filters, heavy metals	Preservation, fragrance stabilization, antimicrobial activity, UV protection	Mineral UV filters, safer formulations
Toys and childcare products 	Mouthing behaviour, hand-to-mouth contact, dust inhalation and ingestion	Phthalates, bisphenols, PFAS, organophosphate flame retardants	Plasticizers, coatings, flame retardancy, stain resistance	Phthalate-free plastics, untreated materials, safer polymers, alternative product designs
Textile, furnishing and building materials 	Ingestion and inhalation of indoor dust, dermal absorption from skin contact	PFAS, nonylphenols, phthalates, organophosphate flame retardants	Water repellence, stain resistance, textile processing, flame retardancy	PFAS-free finishes, safer dyes, alternative flame-retardant approaches, organic textiles
Healthcare and medical devices 	Direct medical contact	Di-(2-ethylhexyl) phthalate (DEHP) and other phthalates, bisphenols, PFAS	Flexible tubing, blood bags, device components, specialty materials	DEHP-free devices, alternative plasticizers, silicone, non-PVC materials

Note: The above table includes chemical categories associated with endocrine disruption. However, not all substances within these groups have been assessed for endocrine-disrupting properties.

cookware and kitchen products, cosmetics and personal care products, toys and childcare products, textiles and furnishings, and selected health care applications (table 1.1).

Importantly, many of these chemicals have other hazardous properties (for example, reproductive toxicity, developmental toxicity, environmental persistence or mutagenic properties) acting through non-EDC mechanisms. Thus, some of the health effects of exposure can be attributed to these other hazards, and these chemicals may be regulated based on those properties.

EDCs have been identified within a range of chemical categories, however, not all chemicals in these categories have been assessed for endocrine-disrupting properties. References to a chemical category should not be interpreted as implying that all chemicals within that category are endocrine disruptors.

As the number of chemicals identified as EDCs continues to increase, there is also increasing concern about the number of "known unknowns", that is, chemicals that are included on publicly available registries that have not been evaluated for endocrine-disrupting properties or have been poorly evaluated. There is also increasing concern over the number of "unknown unknowns", that is, chemicals that have been kept confidential, with the consequence that the scientific community has not had the opportunity to evaluate them for their mode of action or assess exposure in human or animal populations.

1.6 Endocrine-mediated diseases and dysfunctions

Some of the earliest studies of EDCs were stimulated by evidence of the high incidence and increasing trends of many endocrine-related disorders in humans, as well as observations of endocrine-related effects in wildlife populations. These trends, on increasing incidents of endocrine-related disorders, have been summarized elsewhere, but some important examples include:

- Increased global breast cancer incidence and breast cancer mortality rates, especially in women under 50 years of age (Lima, Kehm, and Terry 2021).
- Increased prevalence of overweight and obesity, including in children and in infants under 6 months of age in the United States of America (Kim *et al*. 2006).
- Increased incidence of malformations of the male reproduction tract, including hypospadias (abnormal positioning of the urinary opening on the penis) and cryptorchism (undescended testicles) (Yu *et al*. 2019).
- Earlier timing of puberty, including earlier breast development, in girls (Kay *et al*. 2022).
- Increased incidence of both type 1 and type 2 diabetes, especially in adolescents in the United States of America (Mayer-Davis *et al*. 2017).
- Increasing rates of diagnosis of autism spectrum disorder in children in Japan (Sasayama *et al*. 2021).
- Declining semen quality and sperm count, as well as increasing global prevalence of both male and female infertility (Liang *et al*. 2025; Levine *et al*. 2023).
- Induced imposex in molluscs (Langston 2020).
- Population decline in birds (Mohanty 2024).

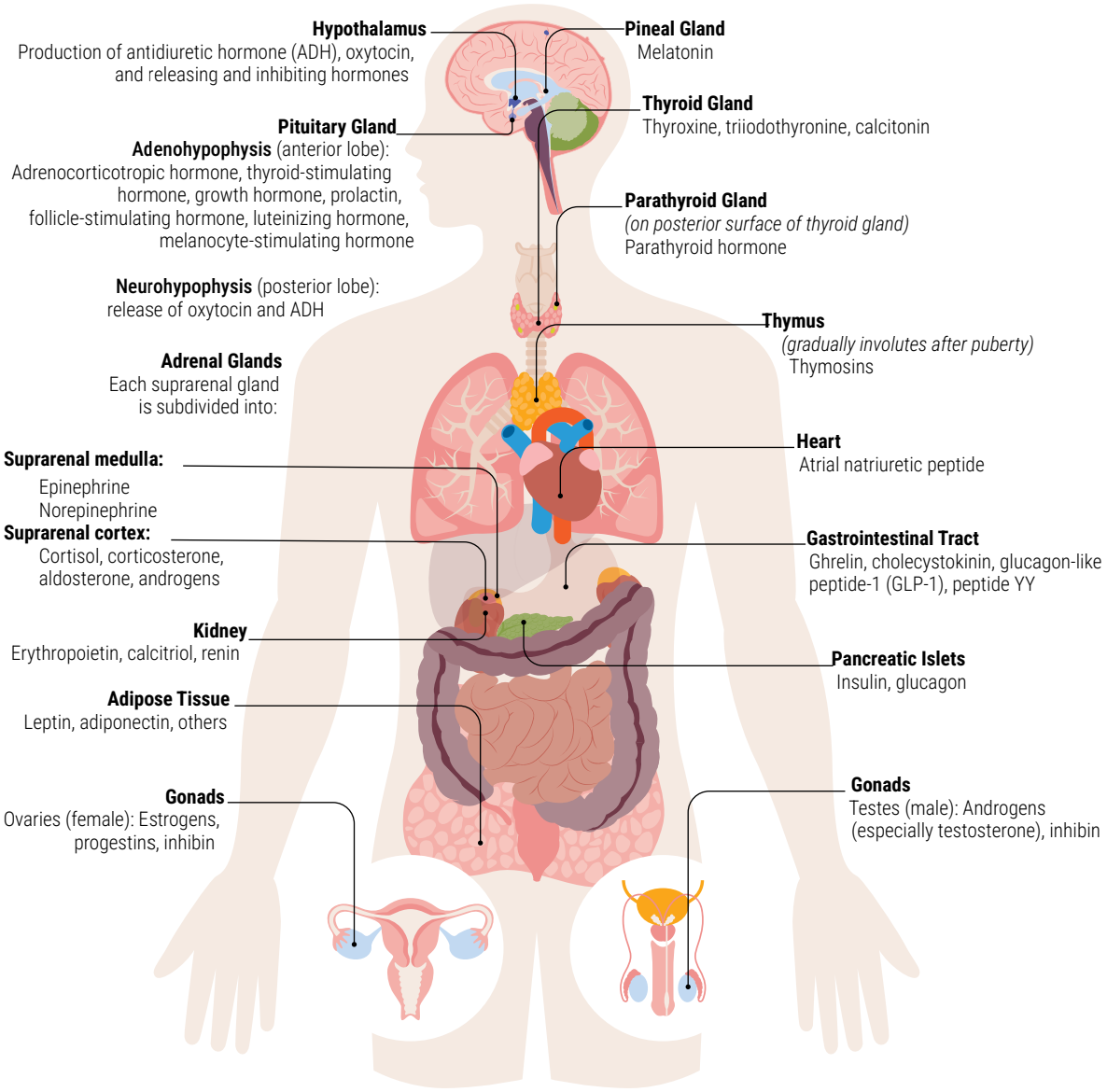
These secular trends, as well as growing evidence from the epidemiology literature showing associations between EDCs and many of the above endocrine-mediated health conditions, confirm the urgency to identify EDCs and mitigate their impacts.

1.7 Understanding the endocrine system

The endocrine system in humans and (vertebrate) animals consists of a series of ductless glands that secrete signalling molecules (hormones) directly into the bloodstream

FIGURE 1.1

HUMAN ENDOCRINE SYSTEM



Source: Adapted from UNEP and WHO (2013)

Box 1.2 What are hormones?

Hormones are signalling molecules produced by specialized cells in a wide range of glands and tissues, from discrete endocrine organs such as the pituitary, thyroid and adrenal glands to tissues not traditionally regarded as endocrine, including adipose tissue, the gastrointestinal tract, heart, kidney and, during pregnancy, the placenta. Many hormones act as classical endocrine signals, travelling through the bloodstream to reach distant target tissues; others act locally, between neighbouring cells (paracrine), on the secreting cell itself (autocrine) or within it (intracrine); and some are released by neurons (neurocrine). Their effects depend not only on the concentration of hormone present but on the timing of exposure, the target tissue and the developmental stage of the organism, factors that are central to how endocrine signalling operates and, as this report examines, how it can be disrupted.

to induce physiological responses and cell, tissue and organ functions (figure 1.1 and box 1.2). Classical hormones include the principal hormones of the female and male reproductive systems such as testosterone and other androgens, estradiol and other estrogens, and progesterone and other progestins. In addition, the endocrine system includes the thyroid hormone system, the adrenal steroids including glucocorticoids and mineralocorticoids, insulin, glucagon and related metabolic hormones, hormones produced by the pituitary gland (for example, growth hormone, prolactin and follicle-stimulating hormone), hormones produced by the hypothalamus (for example, oxytocin, vasopressin, somatostatin, thyrotropin-releasing and gonadotropin-releasing hormones), and many others (Robertson 2023).

The physiological effects of hormones include control of body temperature and blood pressure, reproductive functions including the production of gametes, the storage of nutrients, stimulation of milk production in mammals, and many others. Hormones also act on the brain to integrate behaviours to align with the physiological effects of hormone action. For example, hormones coordinate feelings of hunger and satiety, while also controlling blood sugar levels; and hormones mediate mating behaviours (IPCS 2002), while also controlling ovulation. Based on this classical understanding of the actions of hormones on physiological responses, the endocrine system is sometimes described as being primarily involved in maintaining "homeostasis" (IPCS 2002). However, this view of the endocrine system is understood to be both inadequate and inaccurate. It is inadequate because the endocrine system, and the hormones that are a part of it, also play key roles in embryogenesis and development of the organs of the body, including the reproductive system (Majdic and Tobet 2011) and brain (Zoeller and Rovet 2004; Rovet 2014). It is inaccurate because it presumes that chemicals that interfere with the endocrine system (namely, EDCs) act like natural stressors (similar to other stressors such as changes to temperature or water availability) to which the endocrine system merely responds. Instead, the evidence demonstrates that chemical interference with hormone systems is not equivalent to a perturbation that allows the hormone system to return to a homeostatic set-point. Rather, whether it is the ability of a chemical to cause a hormone receptor to regulate different genes or to deprive the developing organism of hormones during a critical developmental window, the result is disease and dysfunctions (Zoeller *et al.* 2012).

Increasingly, there is an appreciation that virtually all organs of the body respond to hormones, and many more produce hormones than were previously understood. For example, adipose tissue is a producer of hormones (for example, adiponectin, leptin and estrogens) and also responds to hormones (for example, insulin, estrogens and thyroid hormones); the liver produces hormones (for example, angiotensinogen and insulin-like growth factor-1), responds to hormones (for example, growth hormone, estrogens and insulin/glucagon), and is a key player in hormone metabolism; bone produces few hormones (such as osteocalcin), but responds to several to regulate calcium homeostasis and control bone remodelling (for example, parathyroid hormone, calcitonin, estrogens and growth hormone).

The endocrine systems in invertebrate animals are better understood today and represent an important target of chemical exposure. These issues are described in chapter 2.

1.8 General principles of endocrinology and their impact on understanding of EDCs

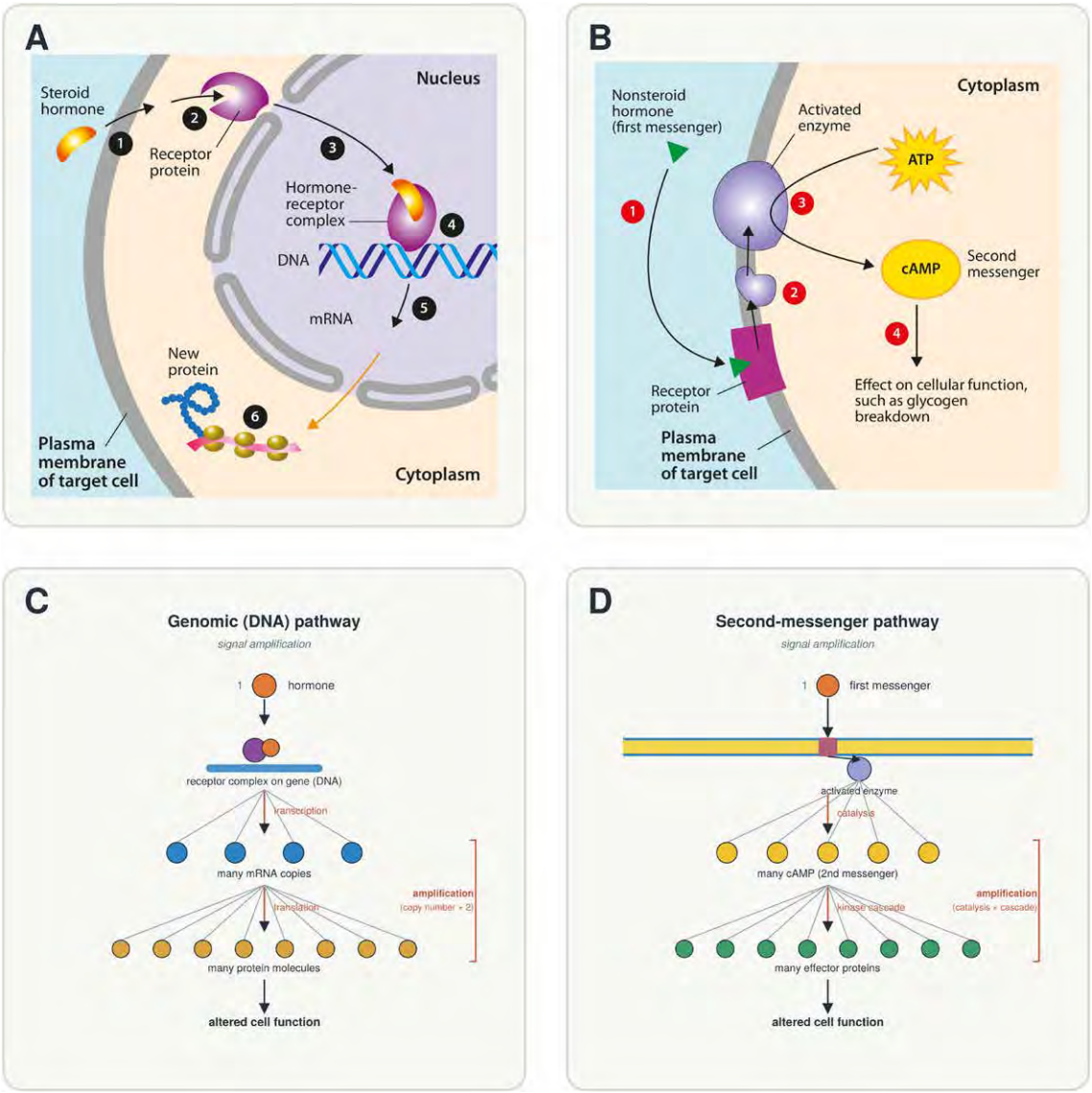
The principles of endocrinology that are relevant to understanding the ways that chemicals can interfere with hormone systems are well established.

- Hormones have critical roles at all life stages, from conception until death. Hormones coordinate virtually every function of the body, and have important functions during development, as well as the regulation of adult functions (Robertson 2023).

- Hormones act by binding to receptors with high specificity normally observed. Increasing the responsiveness of a system can occur by either increasing the available concentration of the hormone (ligand), or by increasing the number of receptors available to be bound by circulating hormones. The location and abundance of receptors are both important features that control the actions of hormones; only cells that express a receptor will respond to its corresponding hormone, and the number of receptors is directly related to the ability of the hormone to execute an effect (Robertson 2023).

FIGURE 1.2

HORMONE SIGNALLING AND SIGNAL AMPLIFICATION

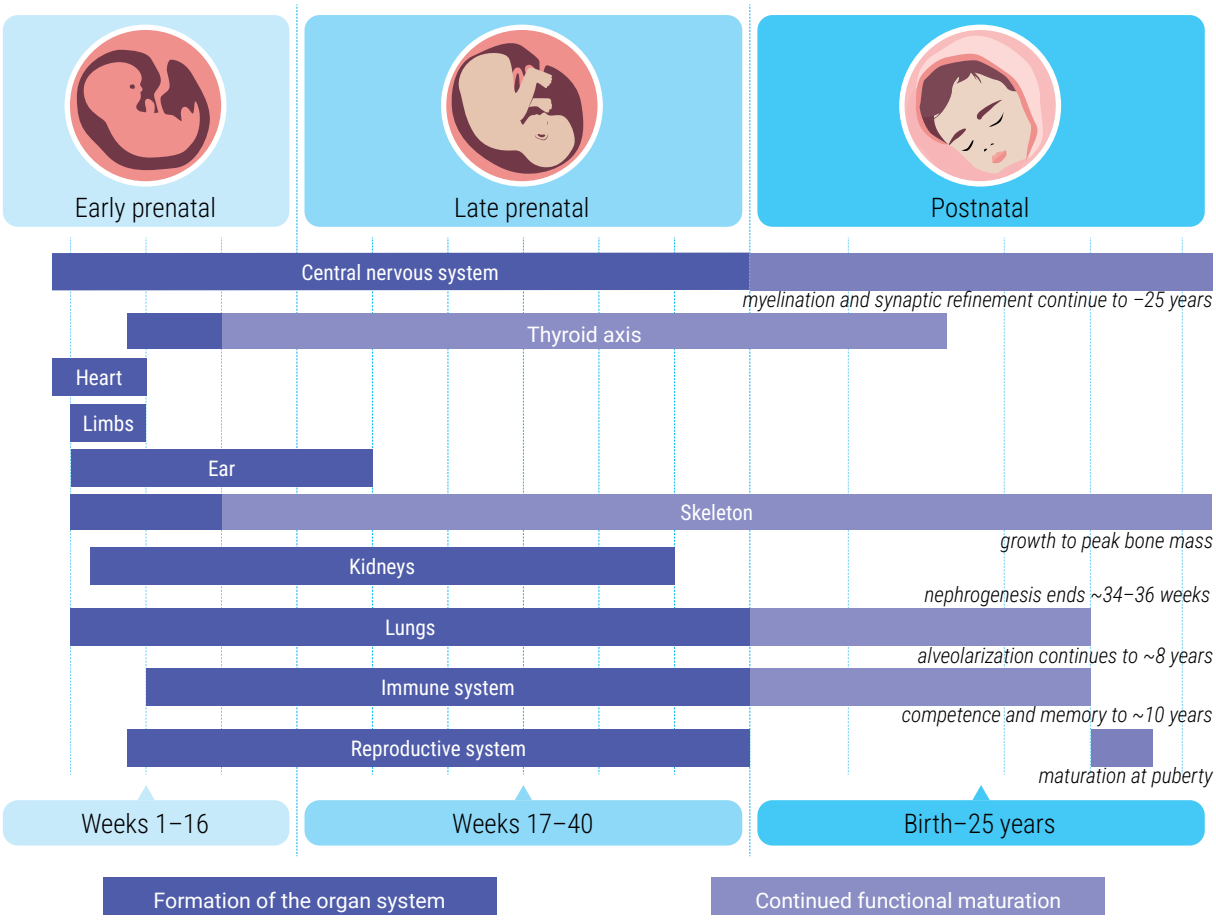


A. Hormone action via a nuclear receptor: the hormone–receptor complex binds DNA and directs transcription and translation (steps 1–6).
B. Hormone signalling via a membrane receptor: the hormone activates an enzyme that generates (e.g.) cAMP, the second messenger, altering cellular function (steps 1–4).
C, D. Signal amplification in each pathway: a single binding event yields many mRNA and protein molecules (C), or many second-messenger and effector molecules (D). Molecule numbers in C and D are illustrative, not quantitative.
Source: Adapted from UNEP and WHO (2013)

- A key feature of hormone action is amplification of the signal induced by receptor binding (figure 1.2). Hormone receptors on membranes trigger a "second messenger" system that dramatically amplifies the hormone signal. Nuclear receptors regulate gene expression where many messenger ribonucleic acid (mRNA) transcripts are derived from a single gene activation sequence, and many individual proteins are made from each transcript. This signal amplification is an important element underpinning the mechanisms of low-dose effects of hormones and EDCs (Robertson 2023).
- Hormones act at low circulating concentrations, often in the part-per-billion or part-per-trillion concentration ranges. Some hormones that are not very soluble in water (such as the steroid hormones and thyroid hormones) are bound to low- and high-affinity proteins when they circulate in blood, which can provide fine-tuning to the amount of hormone that is available to bind to receptors in tissues.
- Physiological responses to hormones are not linear and are often biphasic (that is,

FIGURE 1.3

WINDOWS OF SUSCEPTIBILITY DURING HUMAN DEVELOPMENT



Bar position and length denote the developmental window in weeks post-conception. The prenatal axis is linear; the postnatal segment is compressed to accommodate 25 years. Ranges are approximate and vary between individuals.
Source: Adapted from UNEP and WHO (2013)

non-monotonic). This means that the effects of higher concentrations or doses may not predict the response at lower concentrations or doses.

- The effects of hormones are dependent on life stage, and there are periods of life that are especially dependent on, and sensitive to, hormones. These phases of life are often referred to as "critical windows", "sensitive periods", or "vulnerable life stages" (figure 1.3).

Understanding the *function* of the endocrine system requires an understanding of the *role* of the endocrine system in both health and disease. Therefore, understanding these principles of endocrinology has the following implications for understanding EDCs.

- Because hormones coordinate the functions of the body, EDCs can have effects on virtually every cell, tissue and organ of the body, and it is anticipated that single EDCs can induce multiple diseases and disease syndromes. For example, exposures to di-(2-ethylhexyl) phthalate (DEHP) can induce reproductive tract malformations, altered liver weight and elevated liver enzyme levels in rodents; DEHP exposure is also associated with altered anogenital distance, increased risk of early pregnancy loss and altered neurobehaviours in humans.

- Because hormones act by specific interactions with receptors, EDCs can have effects by altering the concentration of hormones available for binding to receptors, by altering the expression of receptors in target tissues or by altering how the endogenous hormone interacts with its receptor. Exogenous chemicals are typically evaluated for their ability to interact with hormone receptors by biochemical or in vitro assays that limit the number of receptors to force a "competition" between the natural ligand and the chemical under study. However, binding affinity and efficacy are independent properties – a weak competitor in an assay may nonetheless produce a full or enhanced response once bound. Moreover, receptor occupancy is a dynamic equilibrium in which receptor concentration is as important as hormone concentration; tissues with more receptors support a larger pool of hormone receptor complexes. Finally, the assumption that weak xenoestrogens cannot impact the actions of endogenous estrogens is not supported experimentally (Rajapakse, Ong, and Kortenkamp 2001).

- Because hormones act at low circulating concentrations, EDCs also have effects at exceptionally low concentrations, including those that have been measured in human biomonitoring studies and in environmental matrices. The United States Environmental Protection Agency (EPA) defined "low doses" as doses below those typically examined in traditional toxicology studies or doses in the range of typical human exposures (Melnick *et al*. 2002). A very large body of evidence has documented biological responses to EDCs that are observed in the low-dose range (Beausoleil *et al.* 2013) and concluded that many of these responses are adverse. The ability to observe these low-dose effects is dependent on the sensitivity of the outcome being examined. For example, low doses of the estrogenic EDC BPA will alter morphology of the mammary gland and induce diabetes in exposed rodents, whereas much higher doses of BPA are needed to alter the weight of the uterus (Heindel *et al.* 2020).

- Because responses to hormones are non-linear and non-monotonic, EDCs that act via receptors can also have non-linear and non-monotonic responses. This means that effects observed at higher doses cannot be used to predict doses at which no effect will be observed. In many regulatory settings, high dose testing is extrapolated to identify lower doses that are anticipated to be "safe" for population-level exposures, even though these lower levels of exposure are rarely evaluated directly (Vom Saal and Welshons 2026). When non-monotonic dose–responses are observed, the fundamental assumption that high-dose hazards can be used to predict low-dose safety is falsified.

- Because the effects of hormones are dependent on life stage, disruptions in the

function of the same hormone at different periods of life by EDCs can have very different effects. For example, androgen disruptions during fetal development can produce malformations of the penis and permanently alter masculinized regions of the brain, whereas disruptions in adulthood can alter secondary sex characteristics in males.

1.9 One Health and the conservation of the endocrine system

The link between the health of people, animals and the environment has been understood for centuries, and is an entrenched aspect of many indigenous cultures (Riley *et al.* 2021). Yet, it was first articulated in Western sciences under an interdisciplinary concept of "One Health" only in the 21st century. One Health approaches bring together the expertise of human clinicians, veterinarians, ecologists and other public health practitioners to make cross-sectoral, interdisciplinary decisions to detect, control and prevent the risks of global health threats (Atlas 2013). The application of One Health principles and approaches to EDCs is an even more recent development, acknowledging that data from laboratory and domesticated animals can be critically important for understanding the health effects of EDCs on humans and ecosystems, and vice versa. Furthermore, the One Health approach is critical in the management of EDC exposure, as it recognizes the interconnectedness of human, animal and ecosystem exposures to



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environmental pollutants, as well as the shared mechanisms by which EDCs can cause harm (Wang *et al.* 2024; Holbech *et al.* 2020).

It is perhaps unsurprising that EDCs can act similarly across the animal kingdom, as hormones and hormone systems are quite similar among vertebrates despite more than 300 million years of independent evolution among major vertebrate classes (Long *et al.*, 2025; McArdle *et al.*, 2020). Endocrine organs shared by animals and humans include the pituitary, thyroid, adrenal glands and gonads. Other key features of the endocrine system, such as nuclear steroid hormone receptors (Bondesson *et al.* 2015) and enzymes involved in hormone metabolism and function, are structurally and functionally conserved across vertebrates, reflecting the critical evolutionary role of hormonal regulation in processes such as homeostasis and reproduction (Sachs and Buchholz 2017). Furthermore, even though vertebrates diverged from invertebrates more than 500 million years ago, there is also some degree of conservation of the endocrine system between vertebrates and invertebrates (Hartenstein and Mandal 2006). Thus, the effects of EDCs on many endocrine endpoints are conserved across different vertebrate classes, and even between vertebrate and invertebrate animals to a certain extent. Therefore, it is of high relevance for both human health and environmental assessments of chemicals to include all data and evidence, across species, to optimize the assessment of EDCs.

1.10 Building the case: the strength of evidence

As described in the chapters that follow, the body of evidence on EDCs includes epidemiology studies, mechanistic laboratory studies and wildlife observations. There are methods available to integrate and assess evidence from across evidence streams to support determinations about EDCs. Controlled laboratory studies, including those using animal models, continue to be critical to understand the mode of action and health effects of EDC exposure. Animal studies are not only critical for generating evidence about an EDC's mechanism of action; they are also critical for producing evidence of new health effects (Beronius and Vandenberg 2015; Woodruff *et al.* 2008). Controlled laboratory studies can help guide the assessment of outcomes in observational studies of human and wildlife populations. Furthermore, in the last decade, the field of causal inference, which provides helpful tools to establish causal relationships between EDCs and disease outcomes, continues to grow. Causal inference methods evaluate confounding factors, identify potential biases, and draw conclusions while accounting for the limitations of observational data (Engel and Wolff 2013; Gennings *et al.* 2022).

There are strengths and weaknesses to each evidence stream. Laboratory animal studies have controlled exposures but imperfect human concordance; epidemiological studies have human relevance but uncontrolled exposures; and wildlife studies represent real-world exposures but often no truly unexposed comparator. Because the weaknesses of these three evidence streams are largely independent of one another, convergence among them provides a basis for causal inference that no single stream could provide alone. Where the evidence from laboratory, epidemiological and wildlife studies converges, the case that EDC exposure contributes to adverse effects on human health, wildlife populations and ecosystems is compelling.

There has been a substantial expansion of the evidence base since the 2012 assessment. The strength of evidence still varies across chemical–effect outcomes, and research and monitoring capacities are still uneven at global levels. In the chapters that follow, the strength of the evidence is demonstrated across categories of health outcomes. The case is made that while testing to identify EDCs has improved in the past decade, continued improvement of testing strategies is needed; and that while exposures to some EDCs are well documented in some populations, many other chemicals are not well evaluated or monitored, and many populations need to be included in future biomonitoring studies. The economic case is clear that failure to act is costing societies heavy burdens in disease incidence attributed to EDC exposure, as well as the costs of treatment and lost productivity. In many cases, there are already policies to enable regulation of EDCs, if there were sufficient political will to see them through.

2 Evidence for endocrine disruption in humans and animals

Lead authors

Juliette Legler (Utrecht University, Kingdom of the Netherlands) and Henrik Holbech (University of Southern Denmark, Denmark)

Chapter authors

Fela Contreras Berecochea, Sander Lentz, Hana Moreira Farnezi (Utrecht University, Kingdom of the Netherlands), Simone Fibiger Sørensen (University of Southern Denmark, Denmark), Dries Knapen, Lucia Vergauwen (University of Antwerpen, Belgium) and Alice Baynes (Brunel University of London, United Kingdom of Great Britain and Northern Ireland)

Contributing authors

Natalie Aneck-Hahn (University of Pretoria, South Africa), Kyungho Choi (Seoul National University, Republic of Korea), Joëlle Rüegg (Uppsala University, Sweden) and Andrea B. Webster (University of Pretoria, South Africa)

2.1 Introduction

The 2012 report underscored the potential impacts of EDCs on humans and wildlife and showed that wildlife can serve as an essential sentinel for human health risks. The report outlined the urgent need for stricter chemical regulations and further research into the long-term consequences of endocrine disruption across species. Since 2012, EDC identification and safety assessment has moved towards a more collaborative, multi-sectoral "One Health approach" that recognizes the interconnectedness of human, animal and environmental health. The move towards a "One Health approach" is supported, among others, by the large degree to which the endocrine system is conserved, with many of its key structures and functions being shared across species, including all vertebrate animals and to some degree among invertebrates (Hartenstein 2006; McArdle *et al*. 2020). Vertebrates, which diverged from invertebrates over 500 million years ago (Carlisle *et al*. 2024), exhibit a highly conserved endocrine system despite more than 300 million years of independent evolution among major vertebrate classes (Long *et al*. 2025; McArdle *et al*. 2020), encompassing such organs as the pituitary, thyroid, and adrenal glands and gonads. Key components such as nuclear steroid hormone receptors (Bondesson *et al*. 2015) and enzymes involved in hormone metabolism and function are structurally and functionally conserved, reflecting the critical evolutionary role of hormonal regulation in such processes as homeostasis and reproduction (Sachs and Buchholz 2017).

This chapter provides an update of the scientific evidence on EDCs published since the *State of the Science of Endocrine Disputing Chemicals - 2012*. It synthesizes evidence from human epidemiological studies, laboratory animal studies and wildlife studies, reflecting the increasing integration of evidence across human, animal and environmental health research. The chapter reviews evidence relating to reproductive, thyroid, neurobehavioural, developmental, immune, metabolic and cardiovascular disorders, as well as cancer-related outcomes and selected emerging areas, including retinoid signalling disruption and renal disorders. For some health outcomes the evidence has strengthened considerably since 2012, whereas for others it remains limited or emerging. Together, the available evidence provides an updated overview of the current understanding of the health and ecological effects associated with EDC exposure (summarized in Table 2.1)

Table 2.1 **Overview of health outcomes associated with EDC exposure for humans and wildlife since 2012**

Health outcome	Human evidence	Animal evidence	Overall assessment
Female reproductive disorders	Multiple systematic reviews and meta-analyses report associations between EDC exposure and endometriosis, polycystic ovarian syndrome, adverse pregnancy outcomes, hormonal dysregulation and reduced fertility. Evidence for pubertal timing remains mixed.	Strong evidence across mammals, fish, amphibians, birds and invertebrates demonstrates disruption of ovarian development, fertility, fecundity and hormone regulation.	Strengthened evidence that EDC exposure can adversely affect female reproductive health across species
Male reproductive disorders	Evidence has strengthened for associations between EDC exposure and impaired semen quality, altered reproductive hormones, cryptorchidism, hypospadias and infertility.	Extensive experimental evidence demonstrates disruption of spermatogenesis, androgen signalling, reproductive development and fertility across vertebrates and invertebrates.	Strengthened evidence linking EDCs to adverse male reproductive outcomes across species
Thyroid-related disorders	There is consistent evidence for associations between several EDC classes and categories (for example, PCBs, certain PFAS, pesticides) and altered thyroid hormone homeostasis, particularly during development.	Strong mechanistic evidence across vertebrate species shows disruption of thyroid hormone synthesis, transport, metabolism and signalling.	Strengthened evidence that EDCs disrupt thyroid hormone systems in humans and vertebrate wildlife, with emerging evidence in invertebrates
Neurobehavioural disorders	Associations have been reported between prenatal or early-life exposure and adverse cognitive, behavioural and neurodevelopmental outcomes, although consistency varies among outcomes.	Strong experimental evidence demonstrates effects on neurodevelopment, neurotransmitter systems, learning, memory, behaviour and cognition across taxa.	Strengthened evidence across species, particularly for developmental exposures
Developmental disorders (other than neurodevelopmental)	Associations reported with adverse birth outcomes, altered fetal growth, preterm birth and disrupted sexual development.	Extensive experimental evidence demonstrates effects on growth, development, sex differentiation, metamorphosis and developmental programming.	Strengthened evidence that developmental stages are particularly sensitive to endocrine disruption, across species
Immune-related disorders	Increasing evidence links some EDC exposures with allergies, asthma, inflammation and immune dysregulation.	Experimental and wildlife studies demonstrate altered immune function, immune suppression and increased susceptibility to infection across taxa.	Strengthened evidence across species with growing support from mechanistic studies
Metabolic disorders	Evidence links EDC exposure with obesity, insulin resistance, type 2 diabetes and MASLD, a health outcome not assessed in the 2012 report.	Extensive experimental evidence shows disruption of glucose metabolism, lipid homeostasis, adipogenesis and energy regulation.	Strengthened evidence for metabolic disruption across species
Cancer-related outcomes	Associations have been reported for selected cancers, particularly breast, prostate and thyroid cancers, although results remain heterogeneous.	Experimental studies provide biological plausibility through hormonal, epigenetic and cellular mechanisms relevant to carcinogenesis.	Increased evidence that strengthen the plausibility that EDCs contribute with important uncertainties remaining

continued next page

Table 2.1 continued

Health outcome	Human evidence	Animal evidence	Overall assessment
Cardiovascular disorders	Emerging epidemiological evidence links several EDC classes and categories with hypertension, cardiovascular disease and cardiometabolic dysfunction.	Experimental studies show effects on vascular function, cardiac development, inflammation and related pathways.	This is a health outcome not covered in 2012. Evidence suggests associations with cardiovascular disorders, although mechanistic understanding is still evolving
Retinoid signalling disruption	The is limited human evidence.	Strong mechanistic and experimental evidence indicates disruption of retinoid pathways involved in development and reproduction.	This is a health outcome not covered in 2012. Emerging area with strong mechanistic support
Renal disorders	Early evidence links EDC exposure with impaired kidney function.	Experimental studies demonstrate renal injury, fibrosis and oxidative stress.	This is a health outcome not covered in 2012. Further research needed

2.2 Literature review methodology

To summarize the health effects related to EDCs, we performed an umbrella review (a review of systematic reviews, scoping reviews and systematic evidence maps) of the literature since 2012 (Contreras Berecochea *et al*. 2026a). Since systematic reviews are more common in the human health domain, this umbrella review extracted mainly human epidemiological studies. For specific human health outcomes that were not covered in the 2012 review for which few systematic reviews have been performed (i.e. cardiovascular disorders and metabolic dysfunction-associated steatotic liver disease (MASLD) – we also performed a scoping review of the primary human epidemiological literature (Contreras Berecochea *et al*., 2026b). For laboratory animal studies and wildlife studies, we performed a review of reviews, as systematic and scoping reviews are not common in the animal literature. The search methodologies and general overview of the retrieved literature for humans and animals are briefly described in annex II. It should be noted that the term "endocrine-disrupting chemical" refers to the broader class of endocrine-disrupting chemicals. This does not imply that all EDCs are associated with all the reported effects summarized in this chapter. This review methodology also relies on the approaches taken by individual study authors to define the scope and identification of chemicals described as "EDCs". It is also the case that most of the available evidence comes from higher-income settings, and additional evidence from low- and middle-income countries would strengthen the evidence base. It is important to note also that the review methodology using (umbrella) reviews was not designed to provide a comprehensive literature analysis of all primary literature obtained on EDCs since 2012. Instead, (umbrella) reviews of reviews are useful to consolidate vast amounts of evidence for a top-tier overview for decision makers.

2.3 Reproductive disorders

2.3.1 Female reproductive health

Female reproductive health involves the organs of the reproductive tract (that is, the vagina, uterus, oviducts and ovaries) as well as the breast or mammary gland in mammals. Problems affecting female reproductive health include abnormal development of the reproductive tract, decreased fertility and heightened risk of hormone-related cancers (covered in section 2.9). In mammals, these health effects can manifest as ovarian

dysfunction (including polycystic ovarian syndrome – now known as polyendocrine metabolic ovarian syndrome – and premature ovarian failure), disrupted menstrual or estrous cycles, altered timing of puberty, uterine abnormalities (including fibroids), insufficient milk production, and hormonal imbalances affecting estradiol and progesterone. Endometriosis is a chronic estrogen-dependent condition whereby tissue similar to the uterine lining grows outside the uterus, affecting ovaries, fallopian tubes and pelvic tissue. In wildlife, altered female reproductive health can manifest as decreased fertility and fecundity, reproductive organ malformations and altered hormone signalling in all vertebrate classes, including mammals. Effects in invertebrates include decreased egg laying and disrupted ovarian development in bees and imposex – the imposition of male sexual characteristics on females – in marine molluscs. These effects contribute to population declines and ecosystem imbalances, with some species exhibiting shifts in sex ratios and reduced offspring production and survival.

A. Summary of the 2012 assessment

For human health outcomes related to female reproduction, the 2012 assessment reported that adverse pregnancy outcomes – including low birth weight, intrauterine growth restriction and preterm birth – are biologically plausible consequences of endocrine disruption, although epidemiological evidence remained incomplete. The assessment also reported limited and sometimes conflicting evidence from experimental and epidemiological studies linking EDCs to premature breast development; there was also limited evidence for a role of EDCs in the risk of fibroids (phthalates) and endometriosis (PCBs, phthalates and dioxins). Laboratory studies demonstrate that EDCs can interfere with the hormones involved in timing of puberty and menopause and can diminish fecundity and fertility. Wildlife studies related to female reproduction revealed that fibroids and infertility in seals from the Baltic Sea were associated with EDC exposures (particularly PCBs and organochlorine pesticides) and reduced reproductive success in female birds, fish and gastropods were associated with other EDC exposures (PCBs, organochlorine pesticides, tributyltin (TBT) and dioxins).

B. Evidence since the 2012 assessment

Epidemiological studies

The body of research studying EDC exposure and female reproductive health has continued to grow. Our umbrella review revealed three meta-analyses of studies on endometriosis that reported associations with broad classes of EDCs, including dioxins, PCBs, organochlorine pesticides and phthalates (Cano-Sancho *et al*. 2019; Conforti *et al*. 2021; Shirafkan *et al*. 2023). Other systematic reviews on endometriosis also report associations with these classes of EDCs (Caporossi *et al*. 2021; Sirohi, Al Ramadhani and Knibbs 2021), as well as BPA (Sirohi, Al Ramadhani and Knibbs 2021). BPA exposure was associated with polycystic ovarian syndrome in a meta-analysis of multiple studies (Urbanetz *et al*. 2024). However, no consistent pattern of association with phthalates and polycystic ovarian syndrome was reported in another systematic review (Neuvonen *et al*. 2023). Several systematic reviews indicate that EDCs may interfere with female sex hormone regulation. For instance, a meta-analysis reported associations between exposure to specific PFAS (for example, perfluorohexane sulfonic acid or PFHxS) and higher estradiol concentrations in females (Li *et al*. 2024a).

A recent systematic review with a stringent meta-analysis did not find consistent evidence for associations between prenatal or postnatal exposures to a broad range of individual EDCs listed in the European Commission's list of Category 1 EDCs (McCarthy 2011) and changes in pubertal timing in girls and boys (Uldbjerg *et al*. 2022). Similarly, another meta-analysis reported no significant link with BPA and timing of puberty in girls (Lin *et al*. 2023b). In another systematic review, however, several studies suggested that prenatal monoethyl phthalate concentrations are associated with slightly earlier timing of puberty, including age at menarche (Rivera-Núñez *et al*. 2022). A recent systematic evidence map of personal care product exposure and pubertal timing is an example of a useful resource for further detailed evaluation of studies (Taylor *et al*. 2023).

EDC exposure has also been linked with negative fertility outcomes, although findings vary. One systematic review suggested that phthalates


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are associated with reduced success in assisted reproductive technologies (Tian *et al*. 2024). However, no significant link was found between triclosan and infertility in another systematic review (Daza-Rodríguez, Aparicio-Marenco and Márquez-Lázaro 2023). Evidence for other reproductive outcomes (such as time to pregnancy) remains heterogeneous across populations and studies, partly due to cross-sectional designs, non-standardized outcomes and single-point exposure assessments (Hipwell *et al*. 2019; Kahn *et al*. 2021; Kim *et al*. 2019). Individual factors such as nutrition, obesity, socioeconomic status and genetics further complicate interpretation (Lin *et al*. 2023a).

Several systematic reviews reported on maternal EDC exposure and adverse pregnancy and infant health outcomes. For example, Hirke *et al*. (2023) reported higher odds of gestational hypertension with exposure to PFOA, PFHxS and monoethyl phthalate. Meta-analyses of multiple studies by Liu *et al*. (2024a) showed that maternal PFAS and phthalate exposure were associated with elevated risk for preterm birth, small for gestational age, and miscarriage. Maternal PBDE exposure was reported to be associated with lower birth weight and complications such as gestational diabetes and hypertension (Gomes, Begum, and Kumarathasan 2024).

Regarding breastfeeding duration, a review by Timmermann *et al*. (2023) reported that five of six epidemiological studies on exposure to PFAS – for example, PFOS, PFOA and perfluorononanoic acid (PFNA) – showed associations between higher levels of PFAS and shorter total breastfeeding duration, indicating possible impacts of these chemicals on mammary gland function.

Laboratory animal studies

Vertebrates

Mammals. Many rodent laboratory studies confirm the epidemiological effects on female reproduction and furthermore link effects to specific chemicals known to disrupt estrogenic, androgenic or steroidogenic pathways. Bisphenols (such as BPA), benzophenones (such as benzophenone-1 and benzophenone-3), PFAS, persistent organic pollutants, organochlorine pesticides (such as endosulfan and methoxychlor) and non-organochlorine pesticides (such as atrazine and vinclozolin) have been shown to disrupt lactation, affect timing of puberty, and affect mammary gland development and density, among other female reproductive effects (Howdeshell *et al*. 2023; Kam *et al*. 2021; Kass, Gomez and Altamirano 2020; Kay *et al*. 2022; Mustieles *et al*. 2023).

Laboratory studies in rodents show that exposure to PFAS during early life stages negatively affects developing ovaries. Mice exposed to perfluorobutane sulfonic acid (PFBS) had smaller ovaries and bodies, delayed puberty and lower levels of estradiol and thyroid hormones. In utero exposure to PFNA in mice also resulted in smaller ovaries, fewer follicles and delayed puberty in the developing mice. Female rats exposed to PFOA or PFOS had fewer ovarian follicles and corpora lutea (Delbes *et al*. 2022). However, mechanistic evidence for how PFAS affect ovarian development is unclear. PFAS exposure of rodents has also been linked to decreased synapse and spine densities and altered gene expression in relation to neuronal development (Morales-Grahl, Hilz, and Gore 2024). Altered mammary gland morphology in rodents (as a marker of hormone-dependent development and mammalian breast health) has been documented after exposure to low doses of EDCs, including bisphenols (BPA, bisphenol S (BPS) and bisphenol AF (BPAF)), PFOS and phthalates (Matouskova *et al*. 2022).

Fish. Several experimental designs, including Organisation for Economic Co-operation and Development (OECD) test guidelines on fish (mostly zebrafish, fathead minnow and Japanese medaka), investigate how chemicals affect female reproduction (for example, test guidelines 229, 234 and 240). Laboratory experiments using fish have identified many chemicals causing reproductive disorders by disrupting estrogenic, androgenic and steroidogenic pathways. Chemicals include bisphenols, phthalates, phytoestrogens, alkylphenols, PBDEs, and certain fungicides (prochloraz) and pesticides (pyriproxyfen). Effects include altered expression of genes involved in steroidogenesis, changed steroid hormone levels, reduced gonadosomatic index, reduced vitellogenin levels (yolk protein), decreased previtellogenic follicles, delayed pubertal onset, disrupted ovarian maturation, decreased fecundity (egg production) and decreased fertility (Fent 2015; Yu, Han and Liu 2015; Delbes *et al*. 2022; Cabral *et al*. 2024). One study of zebrafish and rare Chinese minnows found that exposure to PBDEs such as 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) and 2,3',4',6-tetrabromodiphenyl ether (BDE-71) cause decreased fecundity and change vitellogenin mRNA expression and vitellogenin protein content (Yu, Han and Liu 2015). Exposure to wastewater and pulp mill effluent, known to contain a mixture of chemicals including EDCs, have also been shown to reduce fecundity in fathead minnow (Marlatt *et al*. 2022).

Amphibians. The estrogenic, androgenic and steroidogenic-mediated effects of chemicals on female reproduction seen in fish are also relevant for amphibians, and – despite the lack of standardized reproductive tests – reproductive effects of chemicals disrupting the estrogenic, androgenic and steroidogenic pathways have been observed in laboratory experiments after exposure to atrazine, PCBs, pentachlorophenol and methoxychlor (Orton and Tyler 2015). In *Xenopus tropicalis* exposure to levonorgestrel (a progestogen) during development of frog tadpoles induced sterility of females when mated with unexposed males during adulthood, highlighting long-term reproductive consequences of early-life exposure (Safholm *et al*. 2014), while aromatase inhibitors fadrozole and flavone induced intersex in females (Safholm *et al*. 2014; Fent 2015).

Birds. In birds, long-term exposure to mercury and persistent organic pollutants such as 2,2',4,4',5-pentabromodiphenyl ether (BDE-99) cause decreased and delayed reproduction (Grace *et al*. 2024; Mohanty 2024). Several types of pesticides (organochlorins, organophosphates and neonicotinoids) perturb the hypothalamic–pituitary–gonadal axis in birds and reduce reproductive output (Mohanty 2024). One example is decreased hatching and brood size in red-legged partridge (*Alectoris rufa*) exposed to the triazol fungicide tebuconazole (Mohanty 2024). Exposure of quail to the phthalate DEHP decreased follicle-stimulating hormone, 17ß-estradiol (E2), and testosterone levels and altered ovarian morphology (Alam, Maowa and Hasan 2025).

Reptiles. Oviparous lacertid lizard (Mongolian racerunner, *Eremias argus*), endemic to eastern Asia, exhibited histological damage in the gonads and changes in gene expression after short-term oral exposure to several pesticides, including a pyrethroid

insecticide (lambda-cyhalothrin), a fungicide (prothioconazole) and a neonicotinoid insecticide (imidacloprid) (Marlatt *et al*. 2022).

Invertebrates

Compared to vertebrates, the effects of EDC on female invertebrates have not been as extensively studied. However, there are reports of female reproductive disorders in a range of invertebrate groups exposed to environmental chemicals or polluted environments. For example, bees (bumblebees and solitary bees) exposed to agricultural chemicals such as imidacloprid and fipronil at sublethal concentrations were shown to have reduced production of eggs and decreased ovary size, a reduced number of brood cells and reduced egg laying (Christen, Kunz and Fent 2018). A range of environmental chemicals have been shown to interact with crustacean neurohormones with knock-on effects observed in gonad development, oocyte number and maturity, and vitellogenin (protein content or mRNA expression) in both marine and freshwater species (Rodriguez 2024). Exposure of earthworms to a range of environmental chemicals (for example, agrochemicals, naphthenic acids, plasticizers and fragrances) disrupted ovarian function and decreased expression of a key peptide (annetocin) involved in triggering egg-laying behaviours (Azevedo *et al*. 2024). Molecular insights have refined understanding of TBT-induced imposex in molluscs. Genomic analyses reveal that molluscs lack nuclear androgen receptors, aromatase (CYP19), and CYP11A1, key enzymes in vertebrate steroidogenesis, suggesting they do not produce or use vertebrate sex steroids endogenously (Scott 2012; Fodor *et al*. 2020; Fodor and Pirger 2022). Instead, TBT probably induces imposex via activation of retinoid X receptor (RXR) and peroxisome proliferator-activated receptor (PPAR) pathways (Beyer *et al*. 2022; Gomes *et al*. 2019).

Wildlife animal studies

Vertebrates

A fish field study on largescale suckers (*Catostomus macrocheilus*) along a contaminant gradient of PBDEs in the United States of America found that vitellogenin was positively correlated with the concentration of BDE-47, 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153) and total PBDE (Yu, Han and Liu 2015). In birds, organochlorine pesticides – including DDT and dichlorodiphenyldichloroethylene (DDE) – sprayed in fruit orchards affect the hatching success of eastern bluebirds (*Sialia sialis*) and American robins (*Turdus migratorius*), and have been positively correlated with population decline in birds of prey (Mohanty 2024). A positive story is that the previously observed population crashes of grey seals in the Baltic Sea area because of female sterility due to exposure to PCBs and DDT have recovered, and reproductive rates have returned to normal. This change correlates with reduced exposure to these persistent organic pollutants after reduction of use and bans in the 1970s in the Baltic Sea region (Sonne *et al*. 2020). In dolphin and killer whale populations in Europe, there are still population declines that are linked to PCB levels far above known toxicity thresholds (Jepson *et al*. 2016). Several studies on birds show that reproductive effects of neonicotinoid pesticides include impairment of egg size, eggshell thickness, embryo viability, hatching rate and offspring survival, although underlying mechanisms are still unclear (Marlatt *et al*. 2022).

Invertebrates

In marine gastropods, imposex is still present in certain hotspots globally, linked to TBT pollution (Langston 2020; Beyer *et al*. 2022). Since TBT has been banned as an antifouling biocide, the frequency and severity of the imposex condition has reduced in many locations (Beyer *et al*. 2022).

C. Key messages

Research since 2012 has significantly strengthened the evidence that exposure to EDCs is associated with adverse female reproductive outcomes in both humans and wildlife. Collectively, the data highlight that female reproductive systems are highly sensitive to environmental EDC exposure, with early-life windows presenting particular vulnerability. Key messages include the following.

- **EDCs are consistently shown to be associated with endometriosis, polycystic ovarian syndrome and hormonal dysregulation in women.** Epidemiological studies and meta-analyses link exposure to dioxins, PCBs, phthalates and BPA with endometriosis.

BPA exposure is also strongly associated with polycystic ovarian syndrome in most studies reviewed, likely via hormonal imbalance. Heavy metals such as mercury and PFAS additionally alter sex hormone profiles.

- **Early-life EDC exposure may alter pubertal timing and mammary gland development.** Human evidence for an effect of early-life EDC exposure on pubertal timing is inconsistent, with limited evidence for earlier puberty following prenatal monoethyl phthalate exposure. However, experimental studies consistently demonstrate that EDCs disrupt pubertal timing, mammary gland development, lactation and ovarian development, supporting that the female reproductive system and mammary glands are sensitive targets of EDCs.

- **Animal studies, including laboratory studies and wildlife studies, show reproductive impairment across species.** In fish, birds, amphibians and mammals, EDCs such as PBDEs, TBT and PFAS reduce fecundity, impair ovarian function and disrupt hormone regulation.

- **Invertebrates show diverse reproductive effects linked to EDCs and neurohormonal interference.** Female reproductive outcomes in bees, crustaceans, gastropods and earthworms are affected by chemicals altering vitellogenin expression, ovary development and neurohormone signalling. TBT-induced imposex remains in hotspots despite bans.


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2.3.2 Male reproductive health

Male reproductive health involves the organs of the reproductive tract, including the external organs (the penis and testes) and the internal organs (the epididymis, vas deferens, ejaculatory ducts, and accessory glands, including the prostate). Problems affecting male reproductive health include malformations of these organs, disruptions to sperm production, altered semen quality and cancers of the reproductive organs. In mammals, including humans, these health effects can manifest as cryptorchidism (undescended testes), hypospadias (a birth defect affecting the urethra), low sperm count, and ultimately infertility. In other vertebrate animals, the effects can manifest as the demasculinization/feminization or phenotypic sex reversal of male fish and amphibians, elevated concentrations of the yolk protein vitellogenin in fish, intersex conditions, disrupted male sex differentiation in fish, amphibians and reptiles, and testicular abnormalities and reduced sperm quality and counts in invertebrates. Collectively, these outcomes can contribute to impaired fertility, leading to diminished reproductive success. Effects on male mating behaviour (for example in birds) are discussed in the neurobehaviour section.

A. Summary of the 2012 assessment

The 2012 assessment examined the potential effects of EDCs on male reproductive health outcomes. Evidence summarized in that report included weak associations between male reproductive tract malformations and maternal exposures to diethylstilbestrol, paracetamol (acetaminophen), mixtures of PBDEs and mixtures of unknown pesticides. Further, accidental exposures to PCBs during fetal development or exposure to dioxins in childhood were associated with an increase in the risk of reduced semen quality in adulthood, and maternal phthalate exposure and reduced

anogenital distance in baby boys (discussed in more depth in section 2.5 below). Laboratory evidence from rodents demonstrated that anti-androgenic pesticides induce malformations of the reproductive tract (including cryptorchidism and hypospadias), reduced semen quality and shortened anogenital distance. In male wildlife, the feminizing effects of EDCs were observed in mammals (deer and bears), fish, amphibians, reptiles and birds, as well as invertebrates. These effects included similar effects as seen in humans as well as intersex and sex reversal, along with reduced testicle size and penis size, lower sperm production and diminished reproductive success.

B. Summary of evidence since 2012

Epidemiological studies

Evidence linking exposure to EDCs and adverse effects on human male reproductive health has grown since the 2012 assessment. Numerous epidemiological studies indicate that EDCs may negatively affect sperm quality, hormone regulation and male reproductive development, with potential long-term consequences for fertility. Associations have been reported in systematic reviews and meta-analyses between exposure to different pesticide classes and impaired semen quality, including reduced sperm motility, concentration and count, with the strongest evidence for organophosphate pesticides (Knapke *et al*. 2022; Hamed *et al*. 2023). BPA exposure in males is associated with reduced sperm count and lowered testosterone levels (Lü *et al*. 2024). Additionally, exposure to polycyclic aromatic hydrocarbon (PAH) metabolites has been linked with reduced semen volume and other markers of male infertility (Kakavandi *et al*. 2023).

Other male reproductive outcomes have also been associated with EDC exposure in humans. A meta-analysis by Bonde *et al*. (2016) reported that early-life exposure to p,p'-DDE was associated with a modest increase in risk for hypospadias, cryptorchidism and testicular cancer. PFAS exposure was linked to reduced testosterone levels (Li *et al*. 2024a). Associations between heavy metals and male sex hormone regulation (such as altered testosterone and sex hormone binding globulin (SHBG) levels) have also been observed (Rami *et al*. 2022).

Laboratory animal studies

Vertebrates

Mammals. Rodent studies consistently demonstrate that EDCs can impair male reproductive development and function. For example, atrazine exposure in rats and mice reduces serum follicle-stimulating hormone, luteinizing hormone, and intratesticular testosterone levels, damages testes and accessory sex organs, and disrupts spermatogenesis (Guimaraes-Ervilha *et al*. 2025; Martins-Santos and Oliveira 2026). Vinclozolin, an androgen receptor antagonist, significantly decreases sperm count, sperm motility and epididymal weight (Feijo *et al*. 2021; Zhu *et al*. 2021). Bisphenols (BPA, TBBPA) disrupt blood–testis barrier-associated proteins and impair sperm morphology, concentration and gene expression in rodents (Wu *et al*. 2021; Peña-Corona *et al*. 2021; Peña-Corona *et al*. 2023). BPA exposure in mice reduces sperm production and motility through oxidative stress and sperm DNA damage, with effects also observed in offspring, indicating transgenerational consequences (Zhang *et al*. 2024). Other EDCs, including finasteride and selected isoflavones, induce oxidative stress in testicular tissue and disrupt spermatogenesis (Lozi *et al*. 2021; Santana *et al*. 2023). Phthalates consistently show antiandrogenic effects, including disruption of fetal testosterone synthesis, oxidative stress and altered sperm physiology (Rapini *et al*. 2024; Zhang *et al*. 2024). Prenatal exposure to phthalate mixtures in mice results in smaller gonads, reduced testosterone levels, and impaired steroidogenesis and spermatogenesis; comparable exposure in rats decreases prostate weight and testosterone levels (Henderson and Colaiacovo 2021). Postnatal EDC exposure further reduces serum testosterone levels and epididymal sperm counts in mice (Gao *et al*. 2021; Faiad *et al*. 2022).

Fish. Laboratory studies in multiple fish species confirm many of the effects observed in mammals. BPA and its analogues (BPS, bisphenol F (BPF), BPAF) increase estrogen levels and suppress androgens in male zebrafish, resulting in reproductive dysfunction (Alavi *et al*. 2021). The phthalate DEHP induces mitotic arrest during spermatogenesis, reduces sperm quality and lowers embryo production (Carnevali *et al*. 2018;

Golshan and Alavi 2019), corroborating conserved endocrine modes of action across vertebrates (Delbes *et al*. 2022).

Amphibians. Although most amphibian studies focus on thyroid hormone system disruption, male reproductive effects have been documented. Exposure to the synthetic progestin levonorgestrel impairs spermatogenesis and reduces fertility in frogs (Safholm *et al*. 2014).

Reptiles. In turtles with temperaturedependent sex determination, BPA exposure disrupts male sexual differentiation, inducing ovarianlike cortical tissue and disorganized testicular tubules (McDonough, Xu and Guo 2021), indicating sensitivity of sex determination pathways to chemical interference.

Birds. Exposure of male birds to mixtures of insecticides and fungicides during gonadal development causes reduced fecundity and disruption of the hypothalamic–pituitary–gonadal axis, including altered gonadotropin-releasing hormone and gonadotropin-inhibiting hormone expression and reduced androgen receptor, testosterone, luteinizing hormone and follicle-stimulating hormone levels (Mohanty 2024). Phthalates similarly impair avian reproduction; quail exposed to dibutyl phthalate (DBP) showed dose-dependent reductions in testicular steroidogenesis (Alam, Maowa and Hasan 2025). Ingestion of microplastics delays sexual maturity and results in increased epididymal lesions in quail, effects probably mediated by leaching EDCs (Wang *et al*. 2021).

Invertebrates

Compared with vertebrates, mechanisms underlying endocrine disruption of male reproduction in invertebrates are less well characterized, though available evidence indicates clear susceptibility (Christen, Kunz and Fent 2018). In bee drones, precise timing and magnitude of juvenile hormone and ecdysteroid signalling are critical for reproductive development. Exposure to agricultural chemicals, including neonicotinoid insecticide (imidacloprid, thiacloprid), fipronil, and juvenile hormone analogues (fenoxycarp, pyriproxyfen), disrupts these pathways and results in reduced sperm concentration, quality and viability, alongside increased sperm mortality (Christen, Kunz and Fent 2018). A metaanalysis of studies in the earthworm *Eisenia fetida* identified significant inhibition of spermatogenesis, disorganized germ cell distribution and reduced numbers of mature sperm bundles following EDC exposure. Methylparaben produced similar effects, coinciding with elevated reactive oxygen species and oxidative damage, with complementary reviews linking EDC exposure to oxidative stress and altered gene expression (Azevedo *et al*. 2024; Chen *et al*. 2025). In arthropods, modulation of the ecdysone receptor by TBT inhibits reproductive capacity, indicating sensitivity of moulting and reproductive endocrine pathways to chemical interference (Rodriguez 2024). Biomarkers originally developed for mammalian sperm toxicology show impaired sperm viability and functionality in echinoderms and molluscs exposed to pesticides under laboratory conditions (Lewis and Ford 2012). Additional studies show that pollutants disrupt sperm morphology during gametogenesis, reduce sperm motility and induce DNA damage in polychaetes and bivalves (Lewis and Ford 2012). At the molecular level, BPA exposure in male *E. fetida* downregulates genes involved in epigenetic regulation (DNA methyltransferase 1, DNA methyltransferase 3B), DNA repair and genomic stability (poly (ADP-ribose) polymerase 1), and hormonal regulation (ecdysone receptor, membrane-associated progesterone receptor and adiponectin receptor), suggesting mechanisms by which fertility and reproductive function may be impaired (Azevedo *et al*. 2024).

Wildlife animal studies

Vertebrates

There is strong evidence of adverse effects on male fish reproduction caused by chemicals in contaminated aquatic systems at the global scale. Decreased testis size (gonadosomatic index), decreased androgen hormone levels (testosterone and 11-ketotestosterone), increased female hormone levels (17β-estradiol (E2)), increased intersex (ovotestis), delayed spermatogenesis and decreased sperm quality have been observed in global fish populations (Alavi *et al*. 2021; Oliveira *et al*. 2023). In a field study on largescale suckers (*Catostomus macrocheilus*) from Columbia River, United States, a negative correlation between total PBDE concentrations and sperm motility was

observed (Yu, Han and Liu 2015). In amphibians, although data are limited, observed effects include lower testicular volume, and a lower numbers of seminiferous tubules, primary spermatogonia and spermatids, and intersex/feminized gonads (Oliveira *et al*. 2023; Orton *et al*. 2023). Effects on male reptiles have mainly been observed in the United States of America, where decreased penis size in alligators has been reported, in some cases accompanied by decreased testosterone levels (Oliveira *et al*. 2023). Male reproduction in birds is also affected by chemicals, especially certain pesticides. Several studies have shown that reproductive effects of neonicotinoid insecticides include impairments of fertilization success, although underlying mechanisms are still unclear (Marlatt *et al*. 2022).

Invertebrates

Testicular abnormalities and reduced sperm count have been reported in amphipods from sites contaminated with PCBs, metals and hydrocarbons (Lewis and Ford 2012). Gammarus held in cages below sewage outfalls showed increased DNA damage (measured using comet assay) in spermatozoa compared to upstream sites (Lewis and Ford 2012).

C. Key messages

EDCs pose a significant and multifaceted threat to male reproductive health across species by disrupting endocrine, developmental and genetic regulatory systems, with consistent and strengthened evidence in humans, model organisms and animals underscoring urgent needs for regulatory action and highlighting the importance of continued research and assessment of exposure pathways and mechanisms. Key messages include the following.

- **Human and laboratory animal evidence has strengthened.** Since 2012, epidemiological and experimental evidence has strengthened the association between EDC exposure and adverse male reproductive health. The strongest human evidence links organophosphate pesticides with impaired semen quality, while experimental studies consistently show that BPA, phthalates, atrazine and vinclozolin disrupt spermatogenesis, steroidogenesis and fertility.
- **EDCs impair male reproductive health by targeting multiple levels of the reproductive system**. Such impairment include direct disruption of androgen receptor signalling, Sertoli and Leydig cell function, steroidogenesis, and the hypothalamic–pituitary–gonadal axis, ultimately affecting sperm production and hormone balance.
- **EDC exposure during critical developmental windows can have lasting effects on male reproduction.** Prenatal and early-life exposure to EDCs can interfere with reproductive tract development, increase the risk of congenital abnormalities (such as cryptorchidism and hypospadias), and induce heritable epigenetic changes that may impact future generations.
- **EDC exposure has widespread impacts on male reproduction in animals.** In vertebrates, EDCs disrupt male reproduction across taxa with effects such as intersex conditions, reduced testis size, altered hormone levels, impaired spermatogenesis and DNA damage, through conserved endocrine pathways such as the hypothalamic–pituitary–gonadal axis. Effects of EDCs on male reproduction in invertebrates, with different endocrine regulations than vertebrates, are well documented in laboratory studies but understudied in the environment.

2.4 Thyroid hormone system-related disorders

In vertebrates, the thyroid gland secretes two forms of thyroid hormone: triiodothyronine (T3) and tetraiodothyronine (thyroxine, T4). The organ is stimulated to synthesize and release thyroid hormones by thyroid-stimulating hormone (also called thyrotropin) from the pituitary gland (Köhrle and Frädrich 2021), which is in turn induced by thyrotropin-releasing hormone released from the hypothalamus (Ortiga-Carvalho *et al*. 2016). In the adult, thyroid hormone is responsible for regulating metabolism and energy expenditure, maintaining body temperature, and regulating mood and cognitive function. Thus, dysregulated thyroid signalling in adult mammals will often manifest as abnormal weight loss or gain, fatigue,



heat or cold intolerance, anxiety, disrupted sleep, and impaired memory or other cognitive functions (Taylor *et al*. 2024). During early development, thyroid hormone is crucial for growth and brain development. Thyroid hormone deficiency during development results in severe brain damage if not corrected. The intellectual deficits observed in individuals diagnosed with congenital hypothyroidism (that is, the thyroid gland of the fetus and newborn does not produce enough thyroid hormone) are typically profound if untreated. The thyroid hormone system is highly conserved among vertebrate classes (Sachs and Buchholz 2017), and there is strong experimental evidence that EDCs can interfere with the hypothalamic–pituitary–thyroid axis in all vertebrates and even in some invertebrates (Morthorst *et al*. 2023). This can lead to disruptions in thyroid hormone homeostasis and downstream developmental processes, including neurodevelopment, metamorphosis, impaired tissue regeneration and disrupted growth patterns.

A. Summary of the 2012 assessment

The 2012 assessment highlighted growing concerns about the role of EDCs as a potential contributing factor in congenital and adult hypothyroidism, autoimmune thyroiditis, hyperthyroidism (Graves disease), thyroid nodules and thyroid cancer. Some epidemiological studies suggested associations between EDC exposures (PCBs, PBDEs, phthalates, BPA and perfluorinated chemicals) and thyroid function. While some studies reported links between EDC exposure and thyroid function in pregnant women, few investigated how these exposures might affect thyroid function in offspring. Laboratory evidence from rodent studies reveals that there are many chemicals that can interfere with thyroid function (for example, by reducing serum thyroid hormone levels). In vertebrate animals, associations between EDC exposures (PBDEs and PCBs) and thyroid hormone system disruptions, including disruptions that contribute to altered development and metamorphosis, were observed.

B. Evidence since the 2012 assessment

Epidemiological studies

PCBs are among the most consistently studied chemicals when it comes to effects on the thyroid hormone system, with both human and animal studies showing altered levels of T3, T4 and thyroid-stimulating hormone related to PCB exposure. A meta-analysis of 11 studies in adults reported significant negative correlations between total sum of PCB congeners and total T3 and free T3 (Little *et al*. 2022), while animal studies confirm thyroid-stimulating hormone and T4 disruptions depending on the congener, dose and exposure duration (Mohammadparast-Tabas *et al*. 2023). A systematic review of mainly cross-sectional studies of occupational exposure to non-persistent pesticides such as organophosphates, dithiocarbamates and pyrethroids suggested that exposures were associated with lower T3 and T4 and higher thyroid-stimulating hormone (Campos and Freire 2016). Meta-analyses of maternal exposure studies to five classes of EDCs showed no effect on neonatal thyroid-stimulating hormone, total T3, free T3, total T4 or free T4 levels. However, prenatal exposure to organochlorines and PFAS was negatively associated with neonatal total T4 levels, while prenatal exposure to 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153) was positively associated with neonatal thyroid-stimulating hormone levels (Sun *et al*. 2022). Studies in humans on triclosan and thyroid hormone were inconclusive (Homburg *et al*. 2022). A systematic review focusing on populations exposed to e-waste suggested that PBDEs may have an adverse effect on thyroid hormone (Singh *et al*. 2022). Studies of heavy metal exposure have also been reviewed, with meta-analysis of occupational exposure to lead associated with increased levels of lead in blood and increased free T3, while another meta-analysis of cross-sectional studies reported a positive

association with cadmium and total T3 levels (Balachandar *et al*. 2023; Chung and Chang 2023). Iodine deficiency, common in some populations, may exacerbate EDC-related thyroid hormone system disruption during pregnancy (Grossklaus *et al*. 2023).

Laboratory animal studies

Vertebrates

Mammals. Studies using mammalian in vitro and in vivo models support the epidemiological studies and specify chemicals interfering with the thyroid hormone system in mammals. The studies identified many pesticides (for example, amitrole, bromide, TBT, mancozeb, dicofol, fenarimol, vinclozolin and pyrethroids such as permethrin) and other chemicals (for example, PCBs, PFAS, triclosan and perchlorate, as well as certain bisphenols and phthalates) that disrupt thyroid hormone signalling and homeostasis via different modes of action, including (in)activation of enzymes involved in thyroid hormone synthesis and metabolism (such as deiodinase, thyroid peroxidase and sodium/iodide symporter), induction of liver enzymes, and interference with thyroid hormone transport proteins (such as monocarboxylate transporter 8 and transthyretin) and with thyroid hormone signalling pathways (Hernandez *et al*. 2020; Graceli *et al*. 2020). Rodent studies also suggest that some pesticides and brominated flame retardants (for example, BDE-71) disrupt thyroid hormone synthesis without a compensatory rise in thyroid-stimulating hormone, indicating that current regulatory endpoints may overlook subtle but relevant changes (Forner-Piquer, Baig and Kortenkamp 2023; Ramhoj *et al*. 2022). Pregnancy and lactation are critical periods of vulnerability, as maternal T4 is essential for fetal neurodevelopment. Disruption during these stages has been linked to lasting cognitive impacts in rodent offspring (Forner-Piquer, Baig, and Kortenkamp 2023; Grossklaus *et al*. 2023).

Fish. Laboratory experiments with model fish species (mainly fathead minnow, Japanese medaka and zebrafish) provide solid evidence that several chemicals (for example, substituted bisphenols; BPA, BPS and tetrabromobisphenol A (TBBPA)), halogenated chemicals (perfluorobutanoic acid, PFOS, tris(1,3-dichloro-2-propyl)phosphate (TDCPP)), and perchlorate disturb thyroid hormone homeostasis and signalling (Peskova and Blahova 2025; Dasmahapatra *et al*. 2023; Kloas *et al*. 2024; Adamovsky *et al*. 2024). Disturbances lead to effects at different organizational levels. Downregulation of gene transcription of proteins involved in thyroid hormone transport, including transthyretin, has been observed in zebrafish exposed to chemicals affecting the thyroid hormone system, such as PFAS, brominated diphenyl ethers (BDEs), pentachlorophenol, TBBPA and triclosan (Spaan *et al*. 2019). The same chemicals caused effects from changes in thyroid hormone levels, transport protein levels and thyroid follicle histopathology to adverse effects such as disrupted development (swim bladder inflation, eye development, neurodevelopment) and changed behaviour (Spaan *et al*. 2019; Couderq, Leemans, and Fini 2020; Gorini *et al*. 2020).

Amphibians. Amphibian metamorphosis is highly dependent on and tightly regulated by thyroid hormone. A substantial body of evidence indicates that EDCs disrupt thyroid hormone homeostasis and signalling to interrupt normal metamorphosis. Studies on *Xenopus laevis* (but also *Rana* spp.) exposed to known "model" thyroid hormone system disrupting chemicals, such as perchlorate, propylthiouracil, and methimazole, as well as PCBs, brominated flame retardants, BPA and BPA alternatives, phthalates and PBDEs, have shown thyroid hormone-mediated effects on metamorphosis (Adamovsky *et al*. 2024; Orton and Tyler 2015; Kloas *et al*. 2024; Thambirajah *et al*. 2019). In one example, the insecticide propiconazole induced faster metamorphosis in *X. tropicalis* (Mohanty 2024). The same effect was seen in common South American toad (*Rhinella arenarum*) tadpoles exposed to atrazine, which were also significantly larger at metamorphosis (Tavalieri *et al*. 2020), and in *X. laevis* after exposure to the pesticide azocyclotin (Trudeau *et al*. 2020). The antibacterial agent triclosan disrupted thyroid hormone-mediated metamorphosis in the Pacific tree frog *Pseudacris regilla* (Kumar and Holt 2014).

Reptiles. Laboratory in vivo studies with reptiles are rare due to ethical concerns and protection

of many threatened species (Savoca *et al*. 2025). The potential of "read-across" of effects for EDC testing between reptiles and other vertebrate classes was discussed in McArdle *et al*. (2020) and showed promising data for (for example) estrogen receptor binding, but data were insufficient to evaluate the thyroid hormone system. Some studies investigated the effects of thyroid hormone on egg hatching in turtles; injection of the antithyroid drug, thiourea, into embryos of the snapping turtle (*Chelydra serpentina*) enlarged the thyroid gland and delayed hatching time. Injection of T3 into eggs of red-eared turtle (*Trachemys scripta elegans*) and short-necked turtle (*Mydura macquarii*) sped up hatching time (Rousseau, Dufour, and Sachs 2021).

Birds. Laboratory studies investigating thyroid hormone system disruption in birds are limited, but read-across to effects in other vertebrate classes is generally relevant due to the conservation of the thyroid hormone system (McArdle *et al*. 2020). Along the same lines, Haigis *et al*. (2023) assessed the cross-species applicability of different molecular initiating events and adverse outcomes of a thyroid hormone system disruption adverse outcome pathway (AOP) network. The evaluation supported plausible applicability of most molecular initiating events to birds based on sequence conservation and found empirical evidence of the link between thyroid hormone system disruption and impaired neurodevelopment, neurosensory development (for example, vision) and reproduction across vertebrate taxa, including birds. A few studies show that avian species are at risk from a variety of ubiquitously present pesticides with thyroid hormone system disrupting properties (Mohanty 2024). In ovo exposure of chickens to Aroclor 1254 caused decreased total T4 and increased total T3, one day after hatch (Mohammadparast-Tabas *et al*. 2023)

Invertebrates

There is increasing evidence that invertebrate classes such as molluscs and tunicates possess a vertebrate-like thyroid hormone system and, therefore, that EDCs also affect invertebrate thyroid-like hormonal processes (Panagiotidis *et al*. 2026). One example is exposure to BDE-47 causing altered thyroid hormone levels and thyroid hormone-regulated gene transcription in Manila clam (*Ruditapes philippinarum*). Another example is exposure of the tunicate (*Ciona intestinalis*) to TBT chloride causing a decrease of T4 and inhibition of T4 synthesis (Morthorst *et al*. 2023).

Wildlife animal studies

Vertebrates

In a meta-analysis, Montaño, Gutleb and Murk (2013) compared measured serum concentrations of halogenated phenolic compounds, such as hydroxylated polychlorobiphenyls, hydroxylated polybromodiphenylethers, pentachlorophenol, and polybromophenols, in birds, fish, whales (cetaceans), and other mammals (for example, polar bears and seals) to known in vitro and in vivo toxicological effect concentrations, including thyroid hormone transport protein binding and thyroid hormone receptor binding. The authors found that serum halogenated phenolic compound concentrations were within the concentration range of observed in vivo and in vitro developmental, endocrine and neuronal effects. It was found that polar bears hold halogenated phenolic compound concentrations comparable to total thyroid hormone transport protein capacity (Montaño, Gutleb and Murk 2013). The specific thyroid hormone system disrupting mechanisms of halogenated phenolic compounds has been further outlined by Gutleb, Cambier and Serchi (2016), including decreased synthesis of T3 and T4, decreased serum levels of T3 and T4, and altered activation of thyroid hormone-dependent gene transcription. Perchlorate is one of the few other chemicals where there is field evidence for adverse thyroid-related disruption of amphibian metamorphosis: tadpoles of two frog species (*Rana catesbeiana* and *Pseudacris triseriata*) in perchlorate-contaminated sites in the United States exhibited delayed metamorphosis and enlarged thyroid glands. A lower ratio of hind limb length to snout–vent length was observed in adults (Orton and Tyler 2015). A meta-analysis by Egea-Serrano *et al*. (2012) found that pollution (nitrogenous and phosphorous compounds, pesticides, road deicers, heavy metals, and other wastewater contaminants) is a major threat to amphibians, with large effects observed on abnormality frequency and moderate effects on survival and mass, but less effect on time

to metamorphosis. The authors did not outline thyroid-specific effects or chemicals. A summary of the evidence of effects of EDCs on wildlife, including thyroid hormone system disruption, has been published by Godfrey *et al*. (2019). A meta-analysis of endocrine-disrupting effects of mercury in wild birds identified a significant negative association with T4 and a significant positive association with T3 across sex and life stages, suggesting thyroid hormone system disruption (Hernandez-Gonzalez *et al*. 2025).

Invertebrates

No reviews of thyroid hormone system disruption in wild invertebrate populations have been identified.

C. Key messages

Evidence since 2012 shows that EDCs disrupt thyroid signalling across taxa through multiple conserved and divergent mechanisms, with strong evidence in humans and vertebrate wildlife and emerging relevance in invertebrates, raising concerns for both public health and ecosystem health. Key messages include the following.

- **EDCs disrupt the thyroid hormone system in humans through multiple mechanisms**. These include inhibition of synthesis, interference with hormone transport, receptor signalling, and deiodinase-mediated metabolism, leading to altered T3/T4/thyroid-stimulating hormone levels and potential health consequences.

- **Evidence of EDC effects on the thyroid hormone system in humans varies by chemical class, life stage and study design.** The strongest data are for PCBs, perchlorate, and BPA, and the greatest concern is during pregnancy and early development due to neurodevelopmental vulnerability.

- **The vertebrate thyroid hormone system is evolutionarily conserved.** Similar disruptions by EDCs occur across vertebrate taxa, with strong experimental and some field evidence of disrupted development, metamorphosis and neurogenesis in fish and amphibians.

- **There is partial conservation of a thyroid-like hormone system in invertebrates.** Thyroid-like signalling exists in select phyla such as molluscs and echinoderms, and while some key genes (for example, thyroid hormone receptor, thyroid peroxidase and deiodinases) are present, ligand binding and transcriptional activation are less understood and diverge from vertebrates.

2.5 Neurobehavioural disorders

Multiple hormones are responsible for the growth, development and function of the brain, including thyroid hormones, estrogens and androgens. The role of the thyroid hormone in cognitive development and brain function is described in the first part of the section 2.4 above; the role of estrogens and androgens in the development of sexually dimorphic brain regions, and associated behaviours, is also well established. In mammals, problems affecting the brain and neurobehaviour can manifest as general cognitive deficits, including lower intelligence quotient (IQ) scores, memory deficit, learning disabilities and impaired executive functioning; and behavioural outcomes, including anxiety, hyperactivity and aggression. In humans, these neurobehavioural outcomes can be diagnosed as autism spectrum disorder, attention-deficit/hyperactivity disorder and other neuropsychiatric conditions. Neurotransmitter systems in the brain – such as dopamine, serotonin and noradrenaline – are conserved between animal wildlife and humans and are involved in the modulation of many endocrine functions, including behaviour (Thompson and Vijayan 2022). At the individual organism level, neurotransmitter concentrations can be affected via, for example, selective serotonin reuptake inhibition (Leon-Olea *et al*. 2014) during development, causing impaired neurodevelopment. In animal wildlife, EDCs affecting neurobehaviour can manifest as disruption to social behaviour and courtship behaviour, disruption to feeding behaviour, decreased ability to avoid predators, and other learning deficits. Collectively, these effects can reduce reproductive success and impact population survival.


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A. Summary of the 2012 assessment

The 2012 assessment highlighted growing concerns about the rising prevalence of neurodevelopmental disorders in children and the potential role of environmental pollutants in these trends. In human studies, developmental exposures to EDCs (PCBs, lead and methylmercury) were associated with cognitive and behavioural deficits and increased risk of hyperactivity and aggression. Evidence supported the involvement of altered thyroid hormone signalling in some of these outcomes. In experimental animals, in utero exposure to EDCs altered cognition, disrupted sexually dimorphic behaviour and induced memory deficit. Finally, there was evidence that EDCs induce neurotoxicity in animal wildlife, with some EDCs (PCBs, mercury) associated with altered behavioural outcomes in birds relevant to reproductive success, including courtship and mating behaviours and song patterns.

B. Evidence since the 2012 assessment

Epidemiological studies

Epidemiological studies published since the 2012 assessment provide new evidence that other EDCs are associated with neurodevelopmental disorders, particularly when exposure occurs during critical periods for brain development, such as during gestation and other early life stages. A systematic review of 17 studies indicated that pyrethroid pesticides may be human developmental neurotoxicants, with effects observed including poorer cognitive and language development, as well as problems with behaviour and attention and executive function, associated with prenatal exposure at exposure levels occurring in the general population (Andersen *et al*. 2022). Two systematic reviews link prenatal phthalate exposure to adverse cognitive and behavioural outcomes in children, especially in boys (Zhang *et al*. 2019; Ejaredar *et al*. 2015). In a systematic review that combined animal (see below) and human literature, BPA exposure was linked to hyperactive behaviour in humans (Rochester, Bolden and Kwiatkowski 2018). Prenatal BPA and BPA exposure in childhood was related to adverse behaviour outcomes in children, including higher levels of anxiety, depression, aggression and hyperactivity (Ejaredar *et al*. 2017). Some systematic reviews, however, did not report an association between EDC exposure and neurological disorders, for example for EDCs and autism spectrum disorder (Cunha *et al*. 2023; Jeddi *et al*. 2016; Marí-Bauset *et al*. 2022). A systematic review of early-life PFAS exposure reported no association with language and communication development in children, though these inconclusive findings may partly be explained by the limited validity of the tests used (Stübner *et al*. 2023).

Laboratory animal studies

Vertebrates

Mammals. Experimental studies with rodents suggest that EDCs can alter neurotransmitter systems (such as dopamine and glutamate) and interfere with sex hormone signalling in the developing brain (Howdeshell *et al*. 2023; Suresh, Singh and Vellapandian 2022). Findings from the large-scale study by the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA) show that BPA exposure can affect estrogen receptor gene expression in fetal and neonatal brains. Bisphenols, including BPA, BPS and BPF, have demonstrated cross-species neuroendocrine effects. In developing rodents, exposure to BPA and BPF have been shown to induce long-term behavioural changes indicative of anxiety and depression, which has been linked to dopamine transport and receptor binding (Leon-Olea *et al*. 2014; Pelch *et al*. 2019). BPA has also been shown to increase hyperactive behaviour in male rodents, according to a systematic review

and meta-analysis (Rochester, Bolden and Kwiatkowski 2018). BPA and phthalates disrupt sexual behaviour in rats – possibly via disruption of the neuroendocrine system (Maxon and Mahoney 2024). Notably, adult exposure can also result in persistent anxiety-like behaviours (Dias *et al*. 2025; McDonough, Xu and Guo 2021). In other studies with developing rats and mice, exposure to phthalates (for example, DEHP, DBP and benzyl butyl phthalate (BBP)) and vinclozolin induce long-term behavioural changes indicative of anxiety and depression and, in many of the studies, sex differences in effects were observed (Wiersielis, Samuels and Roepke 2020; Bakoyiannis, Kitraki and Stamatakis 2021; Dias *et al*. 2025). There is increasing evidence that microplastic and nanoplastic exposure during gestation can induce autism spectrum disorder-like phenotypes in rodent offspring. This is classified by stereotyped behaviours, reduced sociality and altered cognition, and is linked to decreased hormone levels (for example, follicle-stimulating hormone, luteinizing hormone, testosterone and thyroid hormone), disruption of the neuroendocrine system, and inflammation (Fowler *et al*. 2025).

Fish. Neurotoxic effects of neonicotinoid pesticides have been demonstrated in aquatic species. In zebrafish, the neonicotinoid insecticide thiamethoxam causes brain tissue necrosis and red blood cell infiltration, indicative of blood–brain barrier damage. Additionally, thiamethoxam caused changes in cortisol and acetylcholinesterase, consistent with neurotoxicity (Mandal *et al*. 2025). In zebrafish, BPA, BPS and BPF cause behavioural changes indicating neurotoxicity (dos Santos *et al*. 2022; Leon-Olea *et al*. 2014; McDonough, Xu and Guo 2021; Liu *et al*. 2024b). Microplastics and nanoplastics may contribute to similar effects by leaching chemicals such as bisphenols and phthalates, which can interfere with hormone signalling pathways and neurotransmitter signalling. In zebrafish, these leachates can ultimately cause hyperactivity and hypoactivity as well as altered aggression, which impacts social dynamics in the fish population (Hasan *et al*. 2024; Wu *et al*. 2024a). One proposed mechanism that might contribute to these effects is disruption of the dopaminergic system, supported by laboratory studies showing reduced movement in zebrafish exposed to exogenous dopamine (Wu *et al*. 2024a). In zebrafish, PFOS exposure impairs dopaminergic pathways, causing hyperactivity, altered swimming behaviour, and learning deficits consistent with attention-deficit/hyperactivity disorder-like phenotypes (Hamed *et al*. 2026).

Amphibians. A few studies investigated behavioural effects of chemicals in amphibians. In red-spotted newts, the insecticide endosulfan disrupts pheromone production, impairing reproductive behaviours (Saaristo *et al*. 2018). In studies with exposure of northern leopard frogs (*Lithobates pipiens*) to PFOS and PFOA, outcomes included reduced dopamine concentrations and reduced dopaminergic neuron numbers. The authors state that these findings are parallel to pathophysiological mechanisms relevant to Parkinson disease (Hamed *et al*. 2026).

Birds. European starlings exposed to a PCB mixture had reduced activity and showed incorrect orientation for migration (Saaristo *et al*. 2018). Exposure to BDE-99 exerted long-term effects on mating behaviour in zebra finches; furthermore, exposure to environmental levels of the organophosphate flame retardant triphenyl phosphate is associated with increased aggression in Japanese quail (Grace *et al*. 2024).

Reptiles. No reviews investigating neurobehavioural outcomes in reptilian laboratory studies were identified. However, due to the conserved neuroendocrine systems among vertebrates, it is expected that chemicals affecting neurobehaviour in other vertebrate classes also affect reptiles.

Invertebrates

As with vertebrates, in invertebrates, the developing nervous system is sensitive to interference by exogenous agents, with critical windows of susceptibility to chemicals (Gomes *et al*. 2019), and a range of neurobehavioural and neurodevelopmental disorders have been reported. For example, chemical exposures to PCBs, cadmium, naphthalene and fluoxetine have been linked to altered neurohormonal regulation of colour change and behavioural change in crustaceans such as crabs and shrimps (Fong and Ford 2014;

Knigge, LeBlanc and Ford 2021; Knigge 2024). EDCs (such as BPA) have been shown to affect neurodevelopment in marine invertebrate chordates called ascidians (tunicates or sea squirts), including disruption of the development of a gravity-sensing organ (Dumollard *et al*. 2017; Gomes *et al*. 2019). Agricultural insect growth regulators, which act as juvenile hormone analogues, have been shown to induce the switch to becoming a forager bee earlier than controls (Christen, Kunz and Fent 2018). Studies investigating the effects of EDCs on earthworms found significant effects on behaviour concurrent with increases in reactive oxygen species, elevated oxidative damage, genotoxicity and altered gene expression profiles (for example, in acetylcholinesterase) (Azevedo *et al*. 2024; Chen *et al*. 2025). Increase in reactive oxygen species and elevated oxidative damage have also been reported in studies with *Caenorhabditis elegans* exposed to BPA or BPS in association with reductions in body bends, head thrashing and feeding behaviour (McDonough, Xu and Guo 2021).

Wildlife animal studies

Vertebrates

Linking neurobehavioural disruption to chemical exposure in wildlife is a challenge in most animal classes, because such field studies need to investigate associations between changes in complex behavioural patterns and chemical (mixture) exposure. Even field studies of basic behavioural neuroscience are challenging and need to "become more experimental, mechanistic, and causally informative" (Beehner and Flagel 2026).

A few studies have found clear associations between EDC exposure and changes in neurobehaviour in birds and fish. Environmental exposure to organochlorine pesticides has been linked to reduced parental care behaviour in predatory birds (Saaristo *et al*. 2018). Fish living downstream from pulp mill effluents (often shown to have androgenic or anti-androgenic activity) change mating behaviour (Godfray *et al*. 2019). Neonicotinoid pesticides, the most widely used insecticides globally, pose a risk of neurobehavioural disruption in birds. Birds are particularly vulnerable through ingestion of neonicotinoid insecticide-coated seeds, and multiple studies have linked neonicotinoid insecticide exposure to declines in bird biodiversity in North America, England and the Kingdom of the Netherlands. Neonicotinoid insecticides act by binding to nicotinic acetylcholine receptors, creating a plausible mechanism by which neonicotinoid insecticides disrupt sexual behaviour (Marlatt *et al*. 2022; Terayama *et al*. 2022).

Invertebrates

No reviews on invertebrate field studies investigating neurobehavioural disorders were identified, but based on the effects seen in laboratory studies, and the demonstrated ability of many insecticides to target juvenile hormone receptors, it is expected that chemicals affecting neurobehaviour in laboratory studies will also affect invertebrate wildlife – adding to the decline in invertebrate populations.

C. Key messages

Emerging evidence since 2012 reinforces the links between early-life exposure to EDCs and neurodevelopmental disorders in humans and neurotoxic effects across wildlife, mediated by disrupted hormone signalling and neurotransmitter systems. Although findings vary in strength and consistency, the convergence of epidemiological, experimental and ecological data underscores the vulnerability of developing nervous systems to EDC exposure. Key messages include the following.

- **Early-life exposure to EDCs is associated with adverse neurodevelopmental and behavioural outcomes in humans.** Epidemiological studies link prenatal and childhood exposure to phthalates, BPA, pyrethroid pesticides, and other EDCs with hyperactivity, anxiety, aggression, depression and impaired cognitive development. While evidence for autism spectrum disorder and some other neurological disorders remains inconsistent, the developing brain appears particularly vulnerable to disruption by EDCs.

- **Cross-species neurobehavioural effects have been demonstrated for bisphenols.** Exposure affects learning, memory, anxiety, and synaptic function via interactions with estrogen receptors and dopaminergic signalling.

- **Experimental studies demonstrate that EDCs disrupt neuroendocrine and neurotransmitter systems across vertebrate species.** Rodent, fish, amphibian and bird studies show that BPA, phthalates, PFAS, neonicotinoids, and other EDCs alter dopamine, glutamate, acetylcholine and hormone signalling pathways, leading to anxiety-like behaviours, hyperactivity, learning deficits, impaired cognition, and altered social and reproductive behaviours.

- **Neurobehavioural effects of EDCs can impair fitness and population sustainability in wildlife.** Across wildlife species, EDC exposure has been linked to altered courtship, mating, migration, parental care, feeding and predator avoidance behaviours. Such behavioural disruptions may reduce reproductive success and contribute to population decline, particularly in birds, fish and other environmentally exposed species.


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2.6 Other disorders of development

Developmental disorders span a range of outcomes, including the development of congenital birth defects (including those involving the reproductive tract, see section 2.2 above), cognitive and neurodevelopmental issues (see section 2.4 above) and pubertal timing (see section 2.2 above). This section will focus on other disorders that are specific to early development. Mammalian development progresses from fertilization through the early embryonic period, organogenesis and the fetal growth period. Each of these stages involves complex controls by hormone signalling and other morphogens. For example, implantation of the developing embryo requires progesterone (to induce uterine receptivity), and organogenesis of the reproductive organs and sexually dimorphic structures involves numerous hormones. Mammalian fetal development is also influenced through altered placental vascularization, which can impair hormone production and disrupt nutrient transport (Seymore *et al*. 2022). Collectively, in mammals, disruptions to embryonic and fetal development can manifest in the outcomes described below, such as abnormal measures of fetal size (for example, length of the baby at birth, birth weight and neonatal head circumference) and in utero measures of sexually dimorphic development (for example, anogenital distance). Effects can also be measured based on maternal outcomes (for example, length of pregnancy or risk of preterm birth). In wildlife, effects can manifest as abnormal size at time of birth or hatching, disrupted sexual development and altered sex ratios, abnormal shell thickening (molluscs), disrupted metamorphosis in amphibians, disruptions to temperature-dependent sex development in reptiles and abnormal moulting (arthropods).

A. Summary of the 2012 assessment

The 2012 assessment emphasized that fetal and embryonic development are the most sensitive life stages for endocrine disruption, noting that EDC exposure can alter fetal growth, reproductive tract development and sexually dimorphic endpoints such as anogenital distance. In wildlife, the 2012 assessment reported that EDCs were strongly linked to disrupted sexual development, altered sex ratios, reproductive failure, developmental abnormalities and population declines, with particularly well-supported evidence in fish, molluscs, birds and mammals.

B. Evidence since the 2012 assessment

Epidemiological studies

Several systematic reviews have studied the association between EDCs and adverse anthropometric birth outcomes in humans, such as low birth weight, shortened body length at birth, decreased head circumference and preterm birth. These outcomes are risk factors for developmental delays or increased risk of

chronic diseases later in life. BPA is one of the most studied EDCs in this area. BPA is associated with an increased risk of preterm birth (Lin *et al*. 2023a), fetal growth restriction (Vrachnis *et al*. 2021), low birth weight (Liu *et al*. 2024a) and negative effects on health outcomes in neonates (Guo *et al*. 2023a). Some systematic reviews have also reported negative associations between PBDEs and birth outcomes. Gomes, Begum, and Kumarathasan (2024) found that maternal PBDE exposure was associated with low birth weight and reduced birth length and head circumference in offspring. Singh *et al*. (2022) reported mixed findings, including both increased and decreased birth length associated with PBDEs, as well as lower Apgar scores and body mass index, consistent with reduced growth and delayed development. PAH exposure, assessed as 1-hydroxypyrene (1-OHP) metabolites in urine, has also been implicated in altered birth outcomes. A meta-analysis of eight epidemiological studies by Moghaddam Hosseini *et al*. (2023) reported that higher maternal urinary 1-OHP levels were associated with reductions in birth weight, length and head circumference, although the associations were not statistically significant. Benzophenone-3, a chemical found in personal care products, showed sex-specific effects (Ghazipura *et al*. 2017), with higher birth weight associated with exposures in males but lower in females following prenatal exposure. Two systematic reviews of prenatal phthalate exposure report associations with adverse birth outcomes, including low birth weight (Golestanzadeh, Riahi and Kelishadi 2019) and increased risk of preterm birth (Lin *et al*. 2023a; Y. Wu *et al*. 2022). Several systematic reviews report that other chemicals, including triclosan, and some metals, are also associated with preterm birth (Kek, Geršak and Virant-Klun 2024; Khanam *et al*. 2021). However, evidence remains heterogeneous, particularly for triclosan, which shows mixed or null associations in meta-analyses (Khoshhali *et al*. 2020). A meta-analysis of 21 epidemiological studies by Liu *et al*. (2024a) concluded that exposure to some PFAS increased the risk of preterm birth and small for gestational age.

Some EDCs have estrogenic or anti-androgenic properties that may interfere with normal fetal sexual differentiation. A frequently used biomarker of disrupted androgen signalling in humans and other mammals is anogenital distance, a physical measure that closely reflects fetal androgen activity. Prenatal exposure to phthalates has been associated with shorter anogenital distance in male infants, indicating that androgen action is inhibited by these chemicals. A meta-analysis of 10 studies by Zarean *et al*. (2019) found significant reduction in anogenital distance in male offspring exposed to the sum of DEHP metabolites, monobutyl phthalate, monoethyl phthalate and monoisobutyl phthalate. Although most studies examining anogenital distance have focused on male offspring, Zarean *et al*. (2019) also reported a significant association between monobenzyl phthalate and anogenital distance in girls. A meta-analysis of three studies by Nelson *et al*. (2020) reported a small but significant reduction in anogenital distance among female offspring prenatally exposed to BPA.

Laboratory animal studies

Vertebrates

Laboratory studies with animals have demonstrated that endocrine-mediated disruption of developmental processes can be induced by chemicals via many different modes of action, leading to adverse effects on individuals and populations. The phenotypic sexual development in several non-mammalian vertebrate classes is more plastic than in mammals (including humans) and some chemicals can affect the development via interference with estrogenic, androgenic and steroidogenic pathways, but also the thyroid pathway, which is involved in vertebrate development, including sexual development (Duarte-Guterman, Navarro-Martin and Trudeau 2014; Robaire *et al*. 2022; Safholm *et al*. 2014).

Mammals. Anogenital distance is a biomarker used to evaluate fetal androgen action in rodent studies. A short male anogenital distance, regarded as feminization due to anti-androgenic activity, is associated with genital malformation at birth and reproductive disorders in adulthood (Schwartz *et al*. 2019). Chemicals decreasing male rat anogenital distance include phthalates (for example, DBP, DEHP, dicyclohexyl phthalate (DCHP) and BBP), parabens (including butylparaben), analgesics (for example, paracetamol) and pesticides

(for example, vinclozolin, procymidone and linuron). Female rat anogenital distance can also be affected; for example, the aromatase-inhibiting, anti-estrogenic fungicide prochloraz increases female rat anogenital distance (Schwartz *et al*. 2019; Pulcastro and Ziv-Gal 2024). Male rat nipple retention is an additional sensitive and specific biomarker of disrupted androgen signalling that complements anogenital distance measurements and is associated with a high likelihood of permanent nipple retention into adulthood. Male rat nipple retention has been observed following exposure to EDCs, particularly those with anti-androgenic activity, such as selected phthalates, androgen receptor antagonists (especially flutamide, vinclozolin and procymidone) and several anti-androgenic pesticides (Schwartz *et al*. 2021).

Fish. In Fish, developmental toxicity has been extensively studied under controlled laboratory conditions. Many chemicals, including parabens, phthalates, bisphenols, benzophenones, alkylphenols and PCBs, affect development (Dasmahapatra, Chatterjee and Tchounwou 2024; Dasmahapatra *et al*. 2023). PFAS exposure induces broader developmental impairments, such as negative effects on weight and length in aquatic species (Banyoi *et al*. 2022). Exposure to some chemicals can activate estrogen receptors or interfere with steroidogenic enzyme expression, causing feminization of genetic males, which leads to intersex (Abdel-moneim *et al*. 2015) or phenotypic sex reversal (Carnevali *et al*. 2018). In laboratory experiments with fish, EDCs change sex ratios due to estrogen receptor agonism, estrogen receptor antagonism, androgen receptor agonism, androgen receptor antagonism, aromatase (Cyp19) inhibition, and also via the hypothalamic–pituitary–thyroid axis through sodium/iodide symporter inhibition (Dang and Kienzler 2019; Dasmahapatra *et al*. 2023; Huang *et al*. 2015; Mastromonaco, Houck and Bergfelt 2012).

Amphibians. Laboratory experiments with amphibians exposed to different agrochemicals interfering with the estrogen, androgen, thyroid and steroidogenic pathways disturb sexual development and cause skewed sex ratios. The fungicide prochloraz causes male-biased sex ratio (in *Rana temporaria*); intersex was observed after exposure to atrazine and the anti-androgenic herbicide linuron caused female-biased sex ratio (Trudeau *et al*. 2020). Generally, both feminizing and masculinizing developmental effects in amphibians have been observed after exposure to pharmaceuticals, persistent pollutants (PCBs, PBDEs, BPA, and PFOS) and pesticides (Orton and Tyler 2015; Slaby *et al*. 2019). Amphibian metamorphosis is highly susceptible to chemicals that disturb the thyroid hormone system, as described in section 2.4.

Birds. Developmental effects in birds, such as beak and feet deformities, have been documented for persistent organic pollutants, including DDT and its metabolites, PCBs and PBDEs (Hao *et al*. 2021). The endocrine-mediated eggshell thinning caused by the DDT metabolite DDE is one of the most well-described effects in both controlled experiments and field observations of wild bird populations (Godfray *et al*. 2019). Laboratory studies have shown developmental effects of both pre- and post-hatch exposure to EDCs (dioxin, PCBs, PBDEs and lead) as well as microplastics, including beak deformities and developmental abnormalities (Grace *et al*. 2024).

Reptiles. In reptiles, EDCs can interfere with temperature-dependent sex determination. For example, PCB exposure in pond sliders (semiaquatic turtles) causes sex reversal (from male to female). In sex-reversed animals, the ovaries are less functional than in normal females, due to ovarian gene expression being delayed, and regulation of aromatase, the enzyme that converts testosterone to estrogen, still resembles male patterns. Similarly, in sea turtles, exposure to estrogenic EDCs has been linked to underdeveloped gonads and disrupted expression of genes involved in sexual development (Smaga *et al*. 2022). As mentioned under chapter 2.2.1 Female reproductive health and 2.2.2 Male reproductive health under "Wildlife animal studies", estrogenic EDCs can cause partial or complete sex reversal of turtles that mature under male-determining temperatures, causing a skewed sex ratio in the population. Apart from sex determination, estrogenic EDCs also affect the development of turtles (Ford 2017); in turtles from the Great Lakes region, persistent organic

pollutant concentrations were associated with decreased reproductive success and development (Marlatt *et al*. 2022).

Invertebrates

Exposure to EDCs can cause developmental and population-level effects in invertebrates by targeting specific (non-vertebrate) hormone-regulated pathways. In crustaceans such as *Daphnia* spp., chemicals mimicking juvenile hormones, such as specific pesticides, interfere with synthesis and receptor signalling, promoting the production of male offspring and reducing yolk protein (vitellogenin) expression and reproductive output (Toyota *et al*. 2022; Miyakawa and Iguchi 2023; Guo *et al*. 2023b), which contributes to population decline. Moulting disruption is a critical effect observed across arthropods and is regulated by ecdysteroids. A broad suite of chemicals (for example, plasticizers, pharmaceuticals, biocides and metals) disrupt ecdysteroid signalling by acting as agonists of the ecdysone receptor, or by inhibiting steroidogenic and chitin-degrading enzymes. These disruptions lead to premature, incomplete or failed moulting, often resulting in death due to feeding cessation or cuticle retention (Song *et al*. 2017; Zou 2020; Knigge, LeBlanc and Ford 2021). Neuroendocrine regulators, especially serotonin, modulate both ecdysteroid synthesis and larval development in crustaceans, and larval, reproductive and shell development in molluscs, yet pollutant effects on these pathways remain understudied (Knigge, LeBlanc and Ford 2021; Imiuwa, Baynes and Routledge 2025; Imiuwa, Baynes and Routledge 2023). In molluscs, organotin compounds such as TBT and triphenyltin disrupt RXR-mediated signalling, inducing imposex and abnormal shell thickening (Beyer *et al*. 2022), while pharmaceutical inhibitors of steroidogenesis induce severe shell deformities (Imiuwa, Baynes and Routledge 2023). These findings underscore the vulnerability of invertebrate endocrine systems to EDCs across multiple taxa.

Wildlife animal studies

Vertebrates

A significant inverse correlation between the proportion of male individuals and estrogenic activity has been confirmed in populations of the common toad (*Bufo bufo*) collected in contaminated ponds in the United Kingdom of Great Britain and Northern Ireland (Orton *et al*. 2023). The presence of intersex gonads in frogs has been documented in agricultural areas, though the link to specific EDCs is not solid (Trudeau *et al*. 2020). In avian species, developmental abnormalities have also been observed. For instance, beak deformities in birds have been linked to EDC contamination (Chen *et al*. 2024).

Invertebrates

In molluscs, compounds such as TBT disrupt RXR-mediated pathways and impair shell development. Historic TBT contamination was linked to mass oyster mortality in France (Langston 2020).

C. Key messages

The scientific evidence has been consolidated since 2012, showing that EDCs can disrupt development via pathways that are shared across species (conserved) as well as through species-specific pathways, with documented impacts on birth outcomes, neurodevelopment, sexual differentiation and metamorphosis. These effects span multiple taxa from humans to molluscs. In particular, the following key messages are formulated.

- **Developmental stages such as embryonic, fetal, neonatal and early postnatal life are particularly sensitive to endocrine disruption.** Exposure during these windows can alter organogenesis, neurodevelopment, sexual differentiation, placental function, growth and reproductive development, with effects that may persist into later life.

- **Human epidemiological studies report associations between prenatal exposure to several EDCs (including BPA, PBDEs, phthalates, PAHs, and PFAS) and adverse birth outcomes.** Impacts include low birth weight, reduced birth length and head circumference, fetal growth restriction, small for gestational age and preterm birth. These outcomes may increase the risk of later developmental and health impairments.

- **In vertebrates, EDCs disrupt sex differentiation by acting on estrogen,**

androgen and thyroid axes. This includes feminization, masculinization and sex reversal in fish, amphibians, reptiles, and turtles via estrogen receptor and androgen receptor modulation or aromatase inhibition. EDCs also disrupt sex differentiation in invertebrates via retinoid or invertebrate-specific axes.

- **EDC-mediated disruption of thyroid signalling can impair developmental processes across vertebrates.** In fish and amphibians, thyroid disruption affects developmental endpoints, including metamorphosis, neurodevelopment, swim bladder inflation, eye development and sex differentiation.

2.7 Immune-related disorders

Hormones are critical regulators of immune system development and function, with fundamental roles for sex hormones, thyroid hormones, progestins and glucocorticoids in vertebrate immune cell maturation and immune system function (De Vito *et al*. 2012; Hoffmann *et al*. 2023). Estrogens typically enhance immune responses, while androgens typically suppress adaptive immunity (the "learned" immunity involving B and T cells) and support innate immunity (the rapid, non-specific defences involving macrophages, neutrophils and natural killer cells). Sex steroid receptors directly regulate immune responses at the transcriptional level to alter disease outcomes (Hoffmann *et al*. 2023). Glucocorticoids also suppress adaptive immune responses and play a critical role in the maturation of the haematopoietic stem cells, which serve as the body's source of immune cells (including the myeloid macrophages and neutrophils, as well as the lymphoid cells, including T, B and natural killer cells). Sex hormones also play a key role in modulating the development and signalling of T and B cells. Autoimmune conditions can arise when this hormonal balance is disrupted. In humans and other mammals, autoimmune conditions include lupus, rheumatoid arthritis, type 1 diabetes, coeliac disease, Graves disease and Hashimoto disease. Hormones also play a critical role in the development of allergic responses, with estrogens increasing the production and release of histamine from immune cells, and progesterone stabilizing histamine-releasing immune cells. In animal wildlife, immune system functions and diseases are quite divergent but also highly hormone dependent. Amphibians, for example, rely heavily on innate immunity until the adaptive immune system is developed after metamorphosis; adaptive immune responses remain heavily influenced by the environment (for example, temperature). In fish, the steroid and thyroid hormone systems are involved in regulation of many immune-related processes (Hasani and Baumann 2025). Insects have a robust innate immune system that allows them to engulf and encapsulate pathogens, and develop humoral responses (whereby the fat body produces antimicrobial peptides into the lymphatic circulation) (Hillyer 2016). Common immune-related conditions in wildlife involve infections with viruses, bacteria and fungi.

A. Summary of the 2012 assessment

The 2012 assessment underscored increasing concerns about the impact of EDCs on immune function, noting rising rates of immune-related disorders, including allergies, autoimmune diseases and certain immune cancers in mammals. Epidemiological studies reported associations between exposure to some EDCs (PAHs, PCBs and other persistent organic pollutants) and autoimmune thyroid disease; other studies revealed associations between EDCs (phthalates, dioxins) and asthma, allergies and endometriosis. Furthermore, systemic inflammation, immune dysfunction and immune cancers, such as lymphoma and leukaemia, were associated with EDC exposure in humans. Evidence from laboratory animal studies found that developmental exposures to the synthetic estrogen diethylstilbestrol or the phytoestrogen genistein induced immune disorders in postnatal life, other estrogens induced prostate inflammation, and exposure to BPA caused allergic sensitization, antibody production and type 2 helper T cell immune responses. Fish, amphibian and bird studies demonstrated that exposure to PCBs increased susceptibility to parasitic infections and infectious diseases, and studies in marine mammals fed EDC-contaminated fish showed significant immunosuppression, including reduced natural killer cell activity and impaired hypersensitivity responses.


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B. Evidence since the 2012 assessment

Epidemiological studies

Since the 2012 assessment, a number of new epidemiological studies have been carried out, as mapped in a comprehensive systematic evidence map developed to catalogue and characterize the PFAS evidence base (Shirke *et al*. 2024). In two meta-analyses of multiple epidemiological studies, prenatal BPA exposure is associated with an increased risk of childhood allergic diseases, including wheezing and asthma, probably through atopic or allergic immune mechanisms (Lin *et al*. 2023a; Tang *et al*. 2022). BPA is also associated with systemic inflammation, as evidence also highlighted associations between BPA exposure and elevated pro-inflammatory biomarkers such as C-reactive protein and interleukin-6 (Peinado, Iribarne-Durán and Artacho-Cordón 2023). For some EDCs, such as triclosan, no associations were found with childhood allergic diseases (Tang *et al*. 2022), and for parabens and benzophenones, too few studies exploring the associations with inflammation are available (Peinado, Iribarne-Durán and Artacho-Cordón 2023).

Laboratory animal studies

Vertebrates

Immune dysfunction in animals is increasingly recognized as a consequence of exposure to chemicals, with evidence pointing to both direct effects of EDCs on immune cells and organs, and broader impacts on immune regulation across species. Thyroid hormone system disrupting chemicals (including Aroclor 1248 and PBDEs) may cause weakened immune response, making affected organisms more susceptible to bacterial, viral and parasitic infections, ultimately affecting the survival of species at both individual and population levels (Hasani and Baumann 2025). Another molecular target for chemicals such as PFAS is the recombination-activating gene (RAG) proteins RAG1 and RAG2, which act together as a heterodimer to regulate the assembly of immune system lymphocytes in all vertebrates (Kreychman *et al*. 2024; Campbell, Dixon and Whitehouse 2021).

Mammals. A systematic review of animal studies supports associations between BPA and outcomes such as respiratory allergy, airway inflammation and altered oral tolerance to food allergens. Mechanistic data from the CLARITY-BPA programmes show that BPA affects cytokine production, nitric oxide release and phagocytic activity in macrophages of exposed rats, with evidence suggesting an epigenetic basis for these immune disruptions (Howdeshell *et al*. 2023). A laboratory study examining mice exposed to BPA found that it affects Th17 cells in mice, which are important for cellular immune regulation and play a role in autoimmunity and lung inflammation (Molina-Lopez *et al*. 2023). Mouse pups exposed to BPS from gestational day 15 to weaning responded with an increase in the faecal level of lipocalin, an inflammatory marker, and BPA, BPS and BPF altered the expression of cytokines and chemokines (McDonough, Xu and Guo 2021). Other EDCs, such as phthalates, have also been implicated in immunotoxicity. DEHP, in particular, has been shown to upregulate tumour necrosis factor-alpha (TNF-α) secretion in both in vitro and in vivo models, pointing to the activation of inflammatory pathways (Hansen *et al*. 2015). Associations between autoimmune diseases and EDCs has been observed after subchronic exposure of rats to nonylphenol for over 180 days leading to immunotoxicity and inflammatory effects, as well as alteration of the activity of transcription factors such as activator protein-1, nuclear factor of activated T cells, and nuclear factor kappa-B, as well as inflammatory cytokine expression (Xu *et al*. 2025).

Fish. In teleost fishes, estrogens regulate both the innate and adaptive immune system responses. Several estrogen receptors are present in immune organs and tissues such as the head kidney (Burgos-Aceves *et al*. 2016; Chuphal *et al*. 2023; Sinha and Mandal 2025; Wojnarowski *et al*. 2022). During development, estradiol (E2) modulates the expression of estrogen receptors in leukocytes, thereby affecting long-term immune function via modulation of estrogen receptor-controlled gene transcription (Burgos-Aceves *et al*. 2016). In zebrafish, exposure to environmentally relevant concentrations of the pharmaceutical ethinyl estradiol caused sex-specific changes in thymus morphology. In male zebrafish, early-life exposure to ethinyl estradiol induced persistent long-term changes to the thymus size, whereas the effects in female zebrafish were reversible, indicating that male fish are more sensitive to estrogen-mediated immune disruption (Braga *et al*. 2024; Campbell, Dixon and Whitehouse 2021; Li *et al*. 2024b). Additional immunotoxic effects have been observed in zebrafish exposed to the pyrethroid insecticides cypermethrin and deltamethrin, including altered gene expression related to cell death and immune toxicity; graphene oxide, which caused increased levels of certain cytokines; and the herbicides atrazine and butachlor, which affected cytokine expression and immune genes in embryos (Braga *et al*. 2024).

Amphibians. Limited studies are available on EDCs causing immune-related disorders in amphibians. In *Xenopus laevis*, immune modulatory effects were observed in both tadpoles and adult frogs after exposure to a mixture of 23 chemicals commonly found in wastewater from drilling and hydraulic fracturing activities in the United States. The mixture included several EDCs, including nonylphenol and octylphenol, and had anti-estrogenic, anti-androgenic and anti-progesterone activity. Effects included decreased numbers of leukocytes and lymphocytes and impaired defence against a *Rana* virus (FV3), including increased viral load (Nagel *et al*. 2020). Exposure of *X. laevis* to atrazine (herbicide) and carbaryl (pesticide) as tadpoles and during development caused increased FV3 viral loads and decreased gene expression responses of TNF-α and type I interferons, which are central cytokines in immune responses (McGuire and Robert 2023).

Birds. The spleen and bursa somatic indices were smaller in American kestrel nestlings exposed to PBDE from egg for 29 days while phytohaemagglutinin response increased, which are signs of immunomodulation (Hao *et al*. 2021). Glaucous gull chicks fed a diet containing DDT, hexachlorobenzene and PCB, mimicking natural contaminant content in the north Atlantic area, had negative effects on many immune parameters, including immunoglobulin G and M concentrations, and higher peripheral blood lymphocyte response to phytohaemagglutinin (Hao *et al*. 2021).

Reptiles. Reptile immune functions are influenced by environmental temperatures and steroid hormone concentrations and, unlike mammals, the reptilian thymus (site of T cell maturation) and spleen exhibit seasonal involution. PCB exposure suppressed innate immunity while enhancing adaptive responses in loggerhead sea turtles (*Caretta caretta*). Similar immune dysregulation occurs in lizards: estradiol (E2) induces thymic atrophy and reduces thymocyte proliferation in yellow-bellied gecko *Hemidactylus flaviviridis*, while ethinyl estradiol decreases leukocyte and splenocyte counts in western fence lizard *Sceloporus occidentalis* (Finger and Gogal 2013).

Invertebrates

Immune dysfunction or modulation by EDCs has also been reported in invertebrates. Bees exposed experimentally to a range of agricultural chemicals exhibited disrupted immune responses, such as decreased haemocyte density, reduced encapsulation response, reduced phenoloxidase activity (enzyme involved in invertebrate immune system) and higher virus titres compared to controls (Christen, Kunz and Fent 2018). In molluscs and crustaceans, the neuroendocrine system is involved in immunity. In bivalves, serotonin has been shown to be of vital importance in neuroendocrine immune regulation, protecting the host from pathogen infection (Canesi *et al*. 2022). Many antidepressants are targeted to affect serotonin re-uptake. Molluscs exposed to antidepressant drugs

displayed reduced haemocyte viability, proliferation and phagocytotic activity (Imiuwa, Baynes and Routledge 2025). Dopamine has been shown to be a key modulator of immune parameters in crustaceans (Fong and Ford 2014). MicroRNAs have also been postulated as a route of estrogenic activated immunomodulation in bivalves (Burgos-Aceves and Faggio 2017), and phthalate exposure has been reported to alter immune-related genes and proteins in molluscs (Savoca *et al*. 2025).

Wildlife animal studies

Vertebrates

Exposure to persistent organic pollutants leads to immunosuppression across marine mammal species and may explain the colonic alterations and chronic infections continuously observed in Baltic grey seals (Sonne *et al*. 2020). Effects related to the immune system have also been seen in wild fish species. A field study in Sweden found that wild perch from PFAS-polluted areas had a reduced number of lymphocytes and granulocytes compared to fish from clean areas (McGuire and Robert 2023), making PFAS-exposed fish more vulnerable to infection. A study comparing concentrations of whole blood persistent organic pollutants to concentrations of basophils, eosinophils, heterophils, lymphocytes and monocytes, as well as alterations in mature and immature red blood cells, in wild populations of Antarctic chinstrap penguins (*Pygoscelis antarctica*) showed that contaminants, such as DDT and its metabolites (ΣDDT), as well as PCBs (ΣPCB), had significant correlations to eosinophils, lymphocytes and heterophils. This indicates possible immunohaematological alterations derived from exposure to such EDC contaminants (Hao *et al*. 2021). A review by Ellwanger, Ziliotto, and Chies (2025) outlined associations between metal concentrations (including metals with endocrine-disrupting potential such as cadmium, lead and mercury) and pathogen infections in vertebrates and invertebrates where increased exposure to these metals impairs the immune system of different animal classes and species (mammals, fish, birds, reptiles, molluscs and insects), facilitating infectious processes.

Invertebrates

No reviews linking environmental exposure of EDCs to effects on invertebrate immune systems were identified. The laboratory studies of invertebrates mentioned above, however, do provide a warning for effects in the environment. This is further supported by in vitro studies on effects of chemicals, including BPA, DDE and chlorpyrifos, on immune cells in molluscs (called haemocytes) showing reduced haemocyte motility, phagocytosis and parasite encapsulation (Leão *et al*. 2024).

C. Key messages

The updated evidence base shows that EDCs can compromise immune integrity across taxa by interfering with conserved developmental, receptor-mediated and neuroendocrine mechanisms. These disruptions have measurable outcomes in terms of disease susceptibility, immunoregulation and ecological fitness. Key messages include the following.

- **Immune impairment due to EDCs is a conserved phenomenon observed in humans, other vertebrate species and invertebrates.** Impacts range from altered cytokine profiles and immune cell development to increased susceptibility to infection and inflammation-driven pathology, confirming immunotoxicity as a cross-phylum concern.

- **EDC exposure is linked to autoimmunity and allergic disease in humans.** Post-2012 evidence strengthens associations between early-life exposure to BPA, phthalates and PFAS and elevated risk for allergic disease, as well as systemic inflammation and immune intolerance.

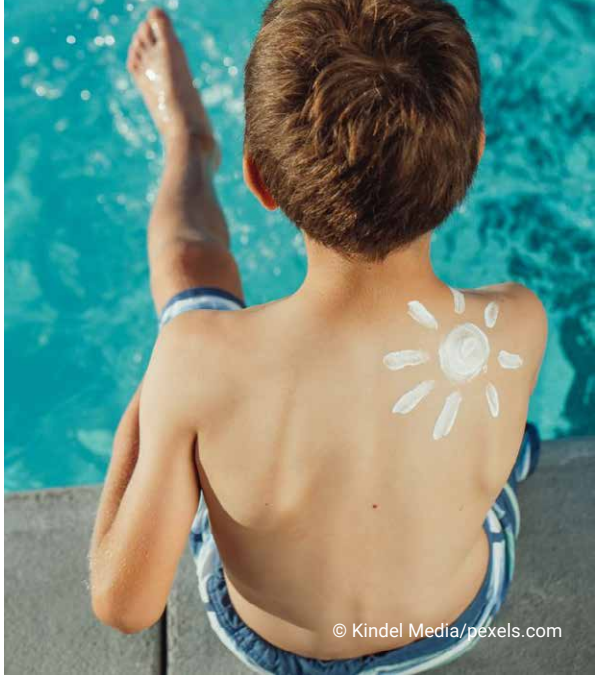
- **EDC exposure is also associated with functional and morphological immune disruption.** Marine mammals, fish, birds and amphibians exposed to PCBs, DDT, PBDEs and PFAS exhibit lymphoid organ atrophy, reduced leukocyte counts, suppressed natural killer and T cell activity and increased infection rates.

2.8 Metabolic disorders

Metabolic tissues and organs are responsible for energy storage and utilization. They include the liver, skeletal muscle, adipose tissue, brain and digestive organs, including the pancreas. These organs are responsive to a number of hormones that coordinate energy usage and homeostasis, including the thyroid hormones (discussed in section 2.3 above), insulin and glucagon (regulating blood sugar), leptin (appetite control) and adiponectin (managing energy use in adipocytes). In humans, common metabolic disorders include disruptions to glucose metabolism and homeostasis (for example, insulin resistance and type 2 diabetes mellitus), increased body weight and obesity (with accompanying inflammation and dysfunctional adipocytes), and non-alcoholic fatty liver disease (currently referred to as metabolic dysfunction-associated steatotic liver disease, or MASLD). Metabolic syndrome represents a group of interrelated disorders in humans, including central obesity, impaired glucose tolerance, dyslipidaemia and elevated blood pressure, that together substantially increase the risk of type 2 diabetes, cardiovascular disease and other serious health problems (Neeland *et al*. 2024). In laboratory animals and wildlife animals, metabolic disorders may manifest as effects such as increased body fat accumulation, altered lipid and glucose metabolism, and altered resting metabolic rates. Importantly, a recent review indicates that EDCs might differently affect metabolic health in women and men across various stages of the life course, stressing the importance of sex and gender when considering the effects of EDCs (D'Archivio *et al*. 2024).

A. Summary of the 2012 assessment

The 2012 assessment reported on the role of EDCs in metabolic disorders, particularly obesity, type 2 diabetes and metabolic syndrome. Some epidemiological studies reported associations between exposure to EDCs (persistent organic pollutants, BPA and arsenic) and altered glucose metabolism, increased fat accumulation and insulin resistance. In rodents, developmental exposures resulted in long-term metabolic disturbances, including weight gain, disrupted cholesterol metabolism and impaired glucose


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tolerance. Prenatal and early-life exposure to EDCs altered the (epigenetic) programming of endocrine pathways involved in energy balance, leading to metabolic dysfunction later in life.

Wildlife studies provided additional evidence that EDCs disrupt metabolic regulation across species. Fish and amphibians exposed to TBT and some persistent EDCs, such as PBDEs, PCBs and DDT, exhibited increased fat accumulation, disruptions in fat metabolism and lipid homeostasis, and changes in gene expression related to obesity and insulin signalling.

B. Evidence since the 2012 assessment

Epidemiological studies

The role of EDCs is being increasingly studied in the development of metabolic disorders in humans, including obesity and type 2 diabetes, with the first epidemiological studies with MASLD appearing. Relevant evidence from systematic reviews of human epidemiological studies for these three main subcategories of this broader health outcome are synthesized below.

Obesity

Both epidemiological and experimental studies (described below) provide evidence that EDCs may promote adiposity and obesity. Systematic reviews with meta-analyses of multiple epidemiological studies reported associations between phthalate exposure and increased body mass index, waist circumference and obesity risk in children and adults (Golestanzadeh, Riahi and Kelishadi 2019; Mérida *et al*. 2023; Wu *et al*. 2023), as well as higher risk for metabolic syndrome

(Mérida *et al*. 2023). However, another systematic review with meta-analysis reported that prenatal exposure to DEHP was associated with decreased body mass index Z-score in children, and not associated with body fat percentage (Lee *et al*. 2022). BPA exposure has also been associated with higher odds of overweight and obesity, with increased prevalence of overweight and obesity associated with BPA exposure across diverse populations reported in two independent meta-analyses of primary epidemiological studies (Ribeiro *et al*. 2020; Lin *et al*. 2023a). In addition, exposure to 2,5-dichlorophenol has been associated with obesity in children (Ribeiro *et al*. 2020).

For PFAS, findings appear heterogeneous, with a systematic review reporting positive associations between PFNA and PFOA exposure and higher body mass index in older children, while null or negative associations were observed in younger children or for other PFAS congeners (Frigerio, Ferrari and Fustinoni 2023). Studies examining pesticide exposures also show heterogeneity across populations. A systematic review reported associations between some organochlorine and organophosphate pesticides and increased body mass index or waist circumference (Duque-Cartagena *et al*. 2023), while others showed no clear association with increased adiposity or body weight (Duque-Cartagena *et al*. 2023; Pinos *et al*. 2021).

Type 2 diabetes mellitus

Evidence in humans suggests that EDCs may disrupt glucose homeostasis and contribute to type 2 diabetes mellitus. Meta-analysis of observational cohort studies suggests that PFAS exposure may increase the risk of type 2 diabetes mellitus, and that PFOA may exert a non-monotonic dose–response effect on type 2 diabetes mellitus risk (Gui *et al*. 2022). Recent meta-analyses found strong associations between organochlorine pesticides and type 2 diabetes mellitus risk, specifically for oxychlordane, trans-nonachlor and heptachlor epoxide (Mendes *et al*. 2021), as well as DDT (Tian *et al*. 2025). BPA exposure was also linked to increased type 2 diabetes mellitus odds (Lin *et al*. 2023a). Meta-analyses have found that exposure to phthalates, such as DBP, butylbenzyl phthalate, and DEHP, was associated with insulin resistance and diabetes risk (Shoshtari-Yeganeh *et al*. 2019; Zhang *et al*. 2022). Vulnerable populations include pregnant women, as prenatal exposure to PCBs, PBDEs, phthalates and PFAS has been linked to higher risk of gestational diabetes mellitus (Yao *et al*. 2023; Yan *et al*. 2022).

Metabolic dysfunction-associated steatotic liver disease

MASLD, a condition not covered in the 2012 assessment, is becoming increasingly prevalent in humans worldwide. Scientific evidence suggests that EDCs may contribute to hepatic steatosis and related metabolic dysfunction, through (for example) interactions with nuclear receptors, disturbance of hormone signalling and mitochondrial function, and alteration of epigenetic regulation (Nikolaou *et al*. 2024). A systematic review and meta-analysis by Pan *et al*. (2024) found that exposure to phthalates, BPA and cadmium was positively associated with increased MASLD risk, indicating modest yet statistically significant associations between EDC exposure and MASLD prevalence. Suggested mechanisms of EDC exposure leading to MASLD include interaction with nuclear receptors, disturbance of hormone signalling and mitochondrial function, and alteration of epigenetic regulation (Nikolaou *et al*. 2024).

Our scoping review of primary human epidemiological data (Contreras Berecochea *et al*. 2026b) found that phenolic chemicals, mainly BPA but also the structurally related analogue BPS, were associated with MASLD (Dallio *et al*. 2018; Peng, Du and Ma 2023; Verstraete *et al*. 2018; Zhang *et al*. 2025). Phthalate metabolites, particularly mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) (MECPP), mono(2-ethylhexyl) phthalate (MEHP) and mono-carboxy-isooctyl phthalate (MCiOP), were associated with MASLD, adverse lipid profiles, insulin resistance and liver enzyme elevations (Cai *et al*. 2021; Milošević *et al*. 2020; J. Zou, Gu and Gu 2024). The one PFAS study retrieved reported an inverse association between a mixed PFAS index and MASLD (Wu *et al*. 2024b). Organochlorine pesticides, including p,p'DDE, oxychlordane and transnonachlor,

were also associated with MASLD (Sang *et al*. 2022). The parabens propylparaben and butylparaben, and the UV filter benzophenone-1, were linked to increased odds of steatotic liver disease (Zhang *et al*. 2025).

Laboratory animal studies

Vertebrates

Key molecular components involved in lipid homeostasis have likely appeared early in animal evolution and are partly conserved across vertebrates and even invertebrates (Capitão *et al*. 2017). Metabolic disorders, commonly associated with obesity, insulin resistance and dysregulated insulin secretion in humans, have also been observed across various animal taxa and species exposed to EDCs, often manifesting as disrupted glucose and lipid homeostasis, disrupted pancreatic beta cell function, altered body composition and impaired energy regulation, leading to hyperglycaemia and disrupted lipid metabolism resulting from dysregulated insulin action (White, Wewer Albrechtsen and Campbell 2025).

Mammals. Key hormones related to metabolism are shared across the mammalian taxa, including insulin, glucagon, glucocorticoids, growth hormones, adrenaline, thyroid hormones, and leptin and ghrelin. The functions of the hormones are also conserved, such as glucagon's involvement in glucose production (Yang *et al*. 2023; Goldberg and Goldstein 2026). Therefore, effects of EDCs on mammals are often relevant to humans and vice versa. However, it is important to recognize that small mammals such as rodents have a high metabolic rate per kilogram body weight and large mammals have a low metabolic rate, affecting EDC metabolism and energy turnover. In laboratory studies with rodents several pesticides, including organophosphorus insecticides (chlorpyrifos), pyrethroids (permethrin, bifenthrin), and neonicotinoids (imidacloprid), were found to increase body weight, disrupt lipid homeostasis, impair glucose tolerance and induce insulin resistance. One proposed mechanism behind some of these effects is suppression of adenosine monophosphate-activated protein kinase, important in regulating lipid metabolism (Gutgesell *et al*. 2020). Changes in the balance between brown and white adipose tissue development, along with impaired thermogenesis due to reduced uncoupling protein activity, contribute to decreased energy expenditure and increased fat accumulation in rats and mice exposed to EDCs such as phthalates (DEHP, DBP), dioxin, phytoestrogens and BPA (Francis *et al*. 2021). Another bisphenol, BPS, impaired glucose absorption and promoted hepatic gluconeogenesis in mice, leading to insulin resistance (McDonough, Xu and Guo 2021). Paternal BPS exposure produced sex-specific metabolic effects in rat offspring, with males showing increased body weight and impaired glucose tolerance (Zhang *et al*. 2024). In other studies with rats and mice, exposure to PFAS, DEHP, DBP and monoethyl phthalate, as well as BPA and BPS, caused metabolic disruption, including decreased insulin sensitivity and glucose tolerance, disruption of glucose and lipid metabolism, pancreatic beta cell disruption and apoptosis, and changed serum levels of insulin, leptin and adiponectin (Quan *et al*. 2026; Ramalho *et al*. 2025; Martinez-Pinna *et al*. 2023). Persistent organic pollutants (POPs) are a group of diverse chemicals (dioxins, organochlorine and organophosphate pesticides, PCBs, PFAS, halogenated and organophosphorus flame retardants) causing metabolic disruption in mammals, including affected glucose homeostasis and beta cell dysfunction (Hoyeck *et al*. 2022).

Fish. Recent laboratory studies using zebrafish show that certain chemicals can exert transgenerational effects related to metabolic dysregulation through epigenetic changes that alter gene expression of genes related to receptor function and hormone metabolism. Zebrafish exposed to TBT exhibited increased hepatic triglycerides and altered hepatosomatic index, indicative of metabolic toxicity (Maradonna and Carnevali 2018). Triazole fungicides disrupted lipid and energy metabolism in zebrafish, affecting genes involved in lipogenesis, glycolysis and fatty acid metabolism (Huang *et al*. 2022). In zebrafish and other fish species (gilthead seabream, salmon), EDCs – for example, TBT, benzophenone-3, alkyl phenols, phthalates, PFOS, PFOA and the chlorinated organophosphate tris(1,3-dichloro-2-propyl)phosphate – act as metabolic disruptors via interference with hormone receptors or the molecular clock,

causing altered lipid metabolism (Bottalico and Weljie 2021; Mukherjee and Maitra 2024; Hamed *et al*. 2026). The role of the circadian clock in energy balance is further supported by evidence in mice, where core circadian gene knockouts caused obesity and diabetic conditions (Bottalico and Weljie 2021; Mukherjee and Maitra 2024; Liu *et al*. 2024b). Metabolic dysregulation has also been linked to chemical disruption of the fish microbiome, with impaired intestinal glucose absorption and glucose metabolism caused by bisphenols (Mukherjee and Maitra 2024; Erradhouani *et al*. 2024).

Amphibians. In amphibians, TBT exposure induced ectopic gonadal fat, probably via RXR/PPAR activation (Maradonna and Carnevali 2018; Capitão *et al*. 2017). Other studies showed that exposure of frogs (*Xenopus* spp.) to benzo(a) pyrene and triclosan induces a prediabetes state whereby a marked insulin secretory defect results in glucose intolerance. Effects were still present one year after exposure (Kloas *et al*. 2024; Gao *et al*. 2021; Thambirajah *et al*. 2019; de Lacerda Valverde, Carvalho and de Oliveira 2026). Energy homeostasis has been disrupted by EDCs such as atrazine in *Xenopus* spp. and grey tree frog, and exposure of African toad to endosulfan showed an increase in serum glucose levels and reduction in liver glycogen, indicating disorders in carbohydrate metabolism (Trudeau *et al*. 2020).

Birds. In birds, early-life exposure to contaminants such as PAHs, triphenyl phosphate and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters metabolic function, including reduced metabolic rates in juveniles, which consequently increases parental energetic demands due to a prolonged juvenile incubation period (Grace *et al*. 2024). DEHP induced lipid metabolic disorders in quail via nuclear factor kappa-B and PPAR pathways (Alam, Maowa and Hasan 2025), while tebuconazole lowered resting metabolic rate in sparrows (Dong 2024).

Reptiles. Toxicity testing with reptiles is not common and no reviews dedicated to metabolic disruption in reptilians were identified. Due to their phylogenetic proximity to birds, avian hazard data are often used as a surrogate for reptilian data (McArdle *et al*. 2020).

Invertebrates

Various studies have investigated fat accumulation in the nematode *Caenorhabditis elegans* after exposure to BPA or BPS (McDonough, Xu and Guo 2021; Rodriguez 2024). Results vary depending on the concentration tested, with a decrease in fat accumulation observed after exposure to low concentrations and an increase in fat accumulation at high concentrations, or non-monotonic U-shaped responses in accumulation of triglycerides. Mechanisms involved insulin signalling pathways (McDonough, Xu and Guo 2021; Rodriguez 2024). Exposure of crabs to fluoxetine increases haemolymph glucose levels (Knigge 2024). Serotonin plays a key role in *C. elegans* lipid metabolism and can be modulated for example by fluoxetine exposure, reducing body fat accumulation (Rodriguez 2024). In crustaceans such as daphnia and crabs, TBT can disrupt carbohydrate and lipid homeostasis and induce obesity by interacting with RXR and PPAR pathways and crustacean hyperglycaemic hormone signalling (Vogt, Model and Vinagre 2018; Gomes *et al*. 2019). Vertebrate obesogens, such as BPA and pyriproxyfen, increased lipid levels in daphnia, while others – such as fenarimol, fluoxetine, emamectin benzoate, nonylphenol, methoprene and di-2-ethylhexyl phthalate – decreased lipid levels at concentrations that did not affect feeding (Capitão *et al*. 2017).

Wildlife animal studies

Vertebrates

Emerging evidence from laboratory studies suggests that metabolic impairments caused by EDCs may have ecological relevance across vertebrate classes as they can influence growth, survival and other traits linked to population-level adversity. Environmental studies of metabolic disruption are very limited because of the unique challenges compared to controlled clinical or laboratory settings, including the need to establish baseline lipid profiles across environmental, biological and temporal variability to distinguish natural variation from environmentally induced changes (Koelmel *et al*. 2020). A few studies in polar bears and grey seals have, however, reported associations between contaminant burdens and metabolic disruption (Karaer and Snoj 2026).

Invertebrates

Environmental studies of metabolic disruption in invertebrates are very limited for the same reasons as mentioned above for wildlife vertebrates. Two studies did report changes in fatty acid profiles of freshwater molluscs from polluted sites compared to reference sites, but a direct link to EDC exposure was not made (Koelmel *et al*. 2020). A study on clams (*Scrobicularia plana*) in French estuaries found increased total lipids and glycolipids in estuaries with higher estrogenic activity and PAH concentrations and a study on queen conch (*Aliger gigas*) could link alteration in the expression of lipid metabolism-related genes to TBT concentrations (Capitão *et al*. 2017).

C. Key messages

EDCs can disrupt metabolic regulation across taxa by targeting conserved endocrine and metabolic pathways, particularly during sensitive developmental windows. Evidence from human epidemiological studies, supported by mechanistic findings from animal models, links EDC exposure to obesity, type 2 diabetes mellitus and MASLD, a health outcome not assessed in the 2012 report. Key messages include the following.

- **Evidence in humans links several EDC classes to obesity, type 2 diabetes mellitus and MASLD.**
    - **Obesity.** BPA, phthalates, PFAS and some pesticides are associated with increased adiposity, body mass index or waist circumference, though findings are heterogeneous for some chemical groups.
    - **Type 2 diabetes mellitus.** PFAS, BPA, phthalates and organochlorine pesticides are associated with insulin resistance, gestational diabetes and increased type 2 diabetes mellitus risk.
    - **MASLD.** Recent evidence links BPA, phthalates, cadmium and some other contaminants to hepatic steatosis and metabolic liver dysfunction, a health outcome not assessed in the 2012 report.
- **Experimental studies provide mechanistic support for the observed effect.** Experimental studies indicate that EDCs can disrupt receptor signalling, insulin and glucose regulation, mitochondrial function, epigenetic programming and lipid metabolism, particularly following developmental exposure.
- **Metabolic disruption is observed across vertebrate and invertebrate taxa.** Exposure to BPA, BPS, TBT, PFAS, pesticides and other EDCs alters glucose and lipid homeostasis, body fat accumulation, energy balance and hepatic lipid storage, with evidence for transgenerational and sex-specific effects.
- **Circadian rhythm disruption is an emerging mechanism.** EDCs such as TBT and TDCPP can interfere with molecular clock pathways, linking circadian dysregulation to altered lipid metabolism, glucose homeostasis and metabolic health.

2.9 Cancer-related disorders

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. Under normal conditions, cell division and death are tightly regulated to maintain healthy tissues. Cancer develops when genetic and molecular changes disrupt these controls, allowing cells to proliferate uncontrollably, evade programmed cell death, invade surrounding tissues and sometimes spread to distant organs through metastasis. The development of cancer typically occurs in several stages: initiation, promotion, progression and metastasis.

EDCs can contribute to each of these stages by interfering with hormonal and cellular signalling pathways (Macedo *et al*. 2023). During the initiation stage, EDCs may induce DNA damage directly or indirectly through oxidative stress, increasing the likelihood of mutations in critical genes involved in cell cycle regulation and DNA repair. Some EDCs can also alter epigenetic mechanisms, modifying gene expression without changing the DNA sequence and potentially predisposing cells to malignant transformation. In the promotion stage, EDCs may mimic or block natural hormones such as estrogen and androgen hormones, stimulating excessive cell proliferation in hormone-sensitive tissues. Increased cell



division raises the probability that mutated cells will survive and expand into larger populations. Chronic inflammation and immune dysregulation triggered by certain EDCs can further support tumour growth by creating a cellular environment favourable to survival and proliferation. During progression, cancer cells acquire additional genetic and molecular alterations that enhance their aggressiveness. EDC exposure may promote angiogenesis, resistance to apoptosis and changes in cellular communication that facilitate tumour expansion. In advanced stages, EDCs may also influence metastasis by altering tissue structure, cell adhesion and migratory behaviour, enabling cancer cells to invade other organs. Together, these mechanisms suggest that endocrine disruption can play a significant role in both the development and advancement of cancer.

A. Summary of the 2012 assessment

The 2012 assessment highlighted concerns about the increasing incidence of hormone-related cancers, including breast, endometrial, ovarian, prostate and thyroid cancers. While genetic and lifestyle factors contribute to cancer risk, the assessment emphasized that environmental exposures may also play a role. Research into hormonal cancers has long recognized the role of endogenous and therapeutic estrogens and androgens in cancer development, making it biologically plausible that EDCs could also contribute to cancer risk. However, chemicals such as dioxins and PCBs have been associated with breast and prostate cancer in some studies, and these substances do not necessarily have strong estrogenic activity, suggesting that multiple mechanisms may be involved. For thyroid cancer, weak associations were reported with certain pesticides and dioxins, but no clear evidence linked these effects to hormonal disruption. Additionally, the assessment underscored a major challenge in identifying hormonal carcinogens, as no standardized models for regulatory testing exist, making it difficult to assess risks before disease onset.

Laboratory animal studies highlighted in the 2012 assessment provided experimental evidence supporting a potential link between EDC exposure and hormone-related cancers. Research in rodents demonstrated that exposure to estrogenic and anti-androgenic chemicals could increase tumour formation in hormone-sensitive tissues. Experimental models suggest that EDCs may contribute to carcinogenesis by interfering with normal hormone signalling, disrupting gene regulation and altering tissue differentiation. Studies also indicate that early-life exposure to EDCs, particularly during fetal development and puberty, may increase susceptibility to hormone-related cancers later in life. The 2012 assessment emphasized that establishing direct causal links in humans remains challenging due to the complexity of exposure patterns, interspecies differences and the long latency period of cancer development.

B. Summary of evidence since 2012

Epidemiological studies

Since the 2012 assessment, research on EDCs and cancer risk has expanded, particularly regarding hormonally sensitive cancers. Findings depend on chemical class, cancer type and study design. Evidence is strongest for organochlorine pesticides, selected PCBs and some phthalate metabolites in hormone-sensitive cancers, especially breast cancer (Liu *et al*. 2023; Meng *et al*. 2024). For breast cancer, organochlorine pesticides showed the clearest positive associations. A meta-analysis of 36 studies by Liu *et al*. (2023) reported that exposure to p,p'-DDT and its metabolite p,p'-DDE was associated with increased breast cancer risk, particularly when measured in blood serum rather than adipose tissue. Hexachlorocyclohexane and chlordane exposure were also associated with elevated breast cancer risk. In contrast, hexachlorobenzene

showed no significant association (Liu *et al*. 2023). In a systematic review of studies on pesticides and prostate cancer, most studies (32 articles) reported a positive association between prostate cancer and certain pesticides or agricultural occupations (Silva *et al*. 2016).

Among PCB congeners, PCB 99, PCB 105, PCB 118, PCB 138 and PCB 183 were positively associated with breast cancer risk, although heterogeneity between studies was substantial for some congeners. PCB 187 showed little or no significant association (Liu *et al*. 2023).

The evidence for dioxins and PFAS was weaker and less consistent. Meta-analysis by Cong *et al*. reported no overall significant association between breast cancer and exposure to TCDD, PFOA, PFOS, PFNA or PFHxS. However, subgroup analyses suggested that internal TCDD exposure measured in serum was associated with increased breast cancer risk (Cong *et al*. 2023).

Phthalates and their metabolites demonstrated mixed associations across cancers. Meng *et al*. found significant overall associations between urinary MEHHP, MECPP, DBP and monobenzyl phthalate metabolites and cancer risk in a meta-analysis of 11 studies (Meng *et al*. 2024). However, when analysed by cancer type, results differed. Breast cancer was negatively associated with monobenzyl phthalate and showed little or no association with monoethyl phthalate, mono-n-butyl phthalate or MEHP. In contrast, stronger positive associations were observed for thyroid and prostate cancers with certain metabolites, particularly MEHP-related compounds (Meng *et al*. 2024).

Laboratory animal studies

Vertebrates

Mammals. Experimental studies suggest that EDCs such as BPA and nonylphenol may promote breast tumour progression by stimulating estrogen receptor activity and metastatic signalling pathways, such as epithelial–mesenchymal transition (Howdeshell *et al*. 2023; Koual *et al*. 2020). Several laboratory studies with rats and mice have shown associations between BPA exposure and increased prostate cell proliferation and enhanced tumour progression (Magnifico *et al*. 2025; Lacouture *et al*. 2022). The UV filter benzophenone-3 and its major metabolite benzophenone-1 show estrogenic and anti-androgenic activity in vitro and in adult mice who were fed a high fat diet. Benzophenone-3 exposure increased mammary tumour cell proliferation, decreased tumour cell apoptosis and increased tumour vascularity (Mustieles *et al*. 2023). More than 200 chemicals have been shown to induce mammary tumours in rodents, including PCBs, PAHs, PFOA, BPA, BPS, BPAF and phthalate mixtures (Kay *et al*. 2022). Nonylphenol, an estrogenic alkylphenol, enhanced mammary gland cancer in mice and rats (Noorimotlagh *et al*. 2020).

Non-mammalian vertebrates

Cancer is rarely investigated in non-mammalian vertebrate laboratory studies in relation to chemical exposure. This is mainly because cancer in individuals is not regarded as a population-relevant effect and therefore not included in tests investigating endocrine disruption.

Wildlife animal studies

It is difficult to link increased cancer incidences in animal wildlife to specific EDCs due to mixture exposure, but also because pathogens are often linked to the induction of cancers in wild mammals and fish (Pesavento *et al*. 2018). A few studies have, however, associated contamination with PAHs and PCBs in estuaries to liver tumour prevalence of 15–25% in fish (white sucker) and marine mammals such as sea lions and beluga whales (Pesavento *et al*. 2018; Mataragka 2025).

C. Key messages

Since 2012, accumulating evidence has strengthened the plausibility that EDCs contribute to hormone-sensitive cancers through multiple endocrine, molecular, epigenetic and cellular signalling mechanisms, though epidemiological findings remain heterogeneous and causal relationships are difficult to establish.

- **Epidemiological evidence linking EDCs to cancer has expanded.** This is particularly the case for breast, prostate and thyroid cancers. The strongest associations have been reported for organochlorine pesticides, selected PCB

congeners and some phthalate metabolites, though findings vary by compound, exposure assessment and study design.

- **Mechanistic understanding has advanced substantially.** EDCs can contribute to multiple stages of carcinogenesis through hormone receptor signalling, oxidative stress and DNA damage, epigenetic reprogramming, immune and inflammatory pathways, resistance to apoptosis, angiogenesis, and altered cell migration and invasion.

- **Early-life exposure remains a critical window of susceptibility.** Developmental exposures during fetal life and puberty may increase long-term cancer risk, supported by animal studies and limited human evidence.

- **Important knowledge gaps remain.** These include prospective human studies, critical windows of exposure, mixture effects and approaches for establishing causality in environmentally driven cancers.

2.10 Cardiovascular disorders

Cardiovascular health extends beyond the heart and includes the blood vessels and their functions throughout the body. Thus, cardiovascular disorders include heart disease and atherosclerosis, but also hypertension and altered vascular function, including risk of stroke and vascular dementia.

A. Summary of the 2012 assessment

Cardiovascular outcomes were not covered in the 2012 assessment.

B. Evidence since the 2012 assessment

Epidemiological studies

Emerging evidence since 2012 suggests that EDCs may adversely impact cardiovascular health. A growing number of epidemiological and experimental studies (described below) link various EDC classes to increased risk of hypertension, altered vascular function and broader cardiometabolic outcomes. Two systematic reviews with meta-analyses of primary epidemiological studies reported associations between phthalate exposure and elevated blood pressure, dyslipidaemia and cardiometabolic risk in children and adolescents (Golestanzadeh, Riahi and Kelishadi 2019; Mérida *et al*. 2023). Low-molecular-weight phthalates, in particular, have been tied to increases in both systolic and diastolic blood pressure. Several studies have also highlighted associations between PFAS exposure and hypertension. A meta-analysis reported that PFOA, PFOS and PFNA were linked to higher odds of hypertension, especially among men (Chang, Chung and Kwak 2023; Pan *et al*. 2023). However, evidence for stroke and other cardiovascular events is heterogeneous, with some findings suggesting neutral or inverse associations (e.g., PFHxS). BPA has also been associated with adverse cardiovascular outcomes. One meta-analysis reported associations between BPA and both hypertension and overall cardiovascular disease (Lin *et al*. 2023a). PCBs may contribute to cardiovascular-specific mortality, even when not associated with all-cause or cancer mortality (Fiolet *et al*. 2021), pointing to a possible pathway linking background exposure to long-term cardiovascular outcomes.

Our scoping review of primary epidemiological literature (Contreras Berecochea *et al*., 2026b) revealed that phenols, including BPA and its analogues, were consistently associated with increased cardiovascular disease risk, hypertension, arterial stiffness and inflammatory markers (Jiang *et al*. 2020; Tsen *et al*. 2021; Wang *et al*. 2015). Some phthalates exhibited mixed effects, with some compounds linked to increased cardiometabolic risk, blood pressure and cardiovascular disease mortality (Mansouri *et al*. 2019; Trasande, Liu and Bao 2022; Wang *et al*. 2024; Wiberg, Lind and Lind 2014), while other compounds were negatively associated with blood pressure and cardiovascular disease risk-related factors, such as body mass index and waist circumference (Guil-Oumrait *et al*. 2022; Sol *et al*. 2020; Wang *et al*. 2024). Specific PFAS compounds were predominantly associated with coronary artery disease and vascular calcification (Arredondo Eve *et al*. 2024; Osorio-Yanez *et al*. 2021). Persistent organic pollutants, such as PCBs and dioxins, showed strong associations with stroke, glucose metabolism disruptions and lipid profile alterations (Berghuis *et al*. 2022; Lim *et al*.


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2018). Specific PAHs and heavy metals, including arsenic, cadmium and lead, were also linked to cardiovascular disease mortality and metabolic disturbances (Di *et al*. 2023; Ettinger *et al*. 2014; Fan *et al*. 2023).

Laboratory animal studies

Vertebrates

Many of the effects observed in humans are also relevant for animals, especially mammals but also other vertebrate classes and even invertebrates. This is because the mechanisms of cardiovascular disruption are conserved among most animals, including nuclear receptors that regulate gene expression of lipid metabolism and inflammation regulators.

Mammals. Mice exposed prenatally to polystyrene nanoplastics showed sex-specific cardiac injury in adult offspring via oxidative stress and dysregulated estrogen receptor signalling in one study and cardiotoxicity through metabolic, immune and fibrotic-apoptotic disruption in another study. Rats exposed prenatally to polystyrene showed maternal and fetal cardiovascular dysfunction and fetal growth restriction (He 2026). In rabbits, BPA exposure increase atherosclerosis, probably via pregnane X receptor activation (Lin and Zhou 2025), and in rhesus monkeys, BPA exposure of pregnant females altered fetal transcription of genes involved in cardiac pathologies such as cardiac isoform alpha (MYH6) and myosin heavy chain (Robaire *et al*. 2022). Other chemicals inducing cardiovascular disease in rodents include the phthalates DEHP and DCHP (Lin and Zhou 2025).

Exposure to the herbicide atrazine induces cardiovascular effects in mice, rats and dogs, including disrupted myocardial structure and cardiac fibrosis. The mechanism is suggested to be potentiated responses to stimulation of the adrenal gland, and cultured adrenocortical cells have been shown to produce elevated and prolonged aldosterone concentrations when exposed to atrazine (Holliman *et al*. 2025).

Fish. Many studies show effects of chemicals on the cardiovascular system in fish, but direct links to endocrine-mediated effects are rarely established, and most of the effects observed can also be caused by non-endocrine-mediated toxicity. The anti-epileptic drug gabapentin led to abnormal vessel development in zebrafish embryos by inhibiting the expression of relevant genes (flk1, vegfr-3, gata1, vegfα and vegfr-2) (Hesova, Svobodova and Lakdawala 2025). Zebrafish embryos exposed to acetochlor showed thrombosis, pericardial oedema, and haemorrhage and downregulation of the genes nkx2.5 and gata4, which are relevant for cardiac function (Lu, Ivantsova and Martyniuk 2023). Also in zebrafish embryos, exposure to BPA and PFAS caused cardiovascular effects, including pericardial oedema and decreased red blood cell density, tissue vascularization, heart rate and cardiac output (Hamed *et al*. 2026; Thakkar *et al*. 2022).

Amphibians. No direct evidence of endocrine-mediated cardiovascular effects of chemical exposure of amphibians has been identified. As for fish, there are known EDCs causing effects on the cardiovascular system, but the mechanistic link is often not known, or effects are occurring at chemical concentrations causing effects at different organizational levels from gene expression changes, through developmental and morphological disturbances to behavioural changes. In one example, tadpoles of the American ground frog (*Odontophrynus americanus*) exposed to the insecticide pyriproxyfen showed significantly decreased average heart rate (Cabral *et al*. 2024), but the mechanism is not understood. Another study exposed *Xenopus laevis*, during embryonic development, to PFAS and observed changes in blood vessels and smaller embryos (Gonkowski

and Ochoa-Herrera 2024). It is, however, well known that EDCs can affect cardiovascular physiology in amphibians indirectly through disruption of thyroid hormone signalling, which regulates cardiac function, metabolism and developmental remodelling during metamorphosis (Thambirajah *et al*. 2019; Kloas *et al*. 2024).

Birds. No reviews specifically on cardiovascular toxicity in birds have been identified, but it is plausible that EDCs can affect cardiovascular function in birds indirectly through disruption of conserved endocrine pathways (such as thyroid and steroid systems) that regulate metabolism, circadian physiology and systemic organ function (McArdle *et al*. 2020; Mohanty 2024).

Reptiles. EDCs can affect physiological processes in reptiles through disruption of conserved endocrine pathways (such as thyroid and steroid systems) that regulate metabolism and systemic function, with likely downstream consequences for cardiovascular regulation (McArdle *et al*. 2020).

Invertebrates

EDCs can affect cardiovascular-like functions in invertebrates by disrupting endocrine pathways that regulate haemolymph circulation, cardiac activity and systemic energy balance, thereby impairing organismal physiology (Knigge, LeBlanc and Ford 2021; Ford and LeBlanc 2020). Specific EDCs, including TBT, heavy metals (for example, copper and cadmium), and juvenile hormone analogues, disrupt endocrine regulation of haemolymph circulation and cardiaclike activity in invertebrates by altering neuroendocrine signalling and metabolic homeostasis (Knigge, LeBlanc and Ford 2021; Ford and LeBlanc 2020; Jordão *et al*. 2015).

Wildlife animal studies

Vertebrates

There are almost no studies measuring cardiovascular endpoints directly in wild animals exposed to EDCs, though a few studies links EDCs to cardiovascular effects. A study investigating effects of PFAS in American alligators (*Alligator mississippiensis*) observed a positive correlation between animals exposed to high levels of PFAS and a high number of abnormal red blood cells, including schistocytes (Gonkowski and Ochoa-Herrera 2024). In other taxa, EDCs such as methylmercury and estrogenic contaminants have been linked to cardiovascular-relevant effects primarily through indirect pathways, including circulatory performance and endocrine-mediated physiological disruption in birds, fish and amphibians inhabiting contaminated environments (Windsor, Ormerod and Tyler 2018; Kloas *et al*. 2024; Hazlerigg *et al*. 2025).

Invertebrates

As for vertebrates, there are almost no studies measuring cardiac-like endpoints directly in wild invertebrate populations. This said, EDCs such as TBT and pesticides affect invertebrate taxa, including gastropod molluscs (for example, *Nucella* spp.) and crustaceans, interfering with hormonal control of haemolymph dynamics, cardiaclike activity and energy allocation, thereby disrupting circulatory transport processes that underpin organismal performance and homeostasis (Knigge, LeBlanc and Ford 2021; Langston 2020; Fernandez 2019).

C. Key messages

This is a new health outcome not covered in 2012. Growing evidence suggests that EDCs may adversely affect cardiovascular health by disrupting endocrine pathways involved in blood pressure regulation, vascular function, inflammation and cardiac development. Epidemiological and experimental studies support associations with hypertension and other cardiovascular outcomes, although evidence remains heterogeneous and mechanistic understanding is still evolving. Key messages are as follows.

- **Human studies provide extensive evidence.** Human studies link phthalates, PFAS, BPA, PCBs, dioxins, PAHs and some metals to hypertension, cardiovascular disease, dyslipidaemia and cardiometabolic dysfunction.

- **Experimental studies provide mechanistic support for the cardiovascular effects of EDCs.** Such studies implicate oxidative stress, inflammation, endocrine signalling, vascular dysfunction, fibrosis, and altered lipid metabolism in cardiovascular toxicity.

- **Developmental exposures represent an important window of vulnerability.** Prenatal exposure is linked to long-term alterations in cardiac and vascular function in animal models.

- **Significant knowledge gaps remain.** These include causality, endocrine-specific mechanisms, mixture effects and cardiovascular impacts in wildlife populations.

2.11 Other disorders

A. Summary of the 2012 assessment

In the 2012 assessment, additional health outcomes connected to EDC exposure included adrenal and bone disorders. However, no eligible reviews emerged from the human health umbrella review conducted for the period 2012–2024 and few literature reviews were found on adrenal and bone disorders in the wildlife literature. The lack of recent literature reviews may indicate that these disorders are understudied in humans and wildlife; however, to confirm this, further examination of the primary literature is needed.

B. Evidence since the 2012 assessment

Retinoid signalling disruption

In vertebrates the enzymes involved in retinoid conversion and metabolism seem to be highly conserved and represented throughout mammals, birds, reptiles, amphibians and fish. Retinoid signalling is involved in development (especially embryogenesis), metabolism (lipid metabolism and adipogenesis), immune function and reproduction in all vertebrates and some invertebrates via retinoic acid receptor (RAR) and retinoid X receptor (RXR) induction or repression of genes (OECD 2021). All-trans-retinoic acid binds the RAR component of RAR–RXR heterodimers; 9-cis-retinoic acid can bind both RARs and RXRs. The binding is triggering a conformational change that promotes dissociation of corepressors, recruitment of coactivators, and activation of retinoic acid response elements. In the absence of ligand, RAR and RXR remain associated with corepressors that repress transcription by recruiting histone deacetylase and methyltransferase complexes, thereby maintaining chromatin in a repressed state (Ghyselinck and Duester 2019). The 2012 *State of the science of endocrine disrupting chemicals* report stated that TBT causing imposex in molluscs has very strong affinity for the RXR and the peroxisome proliferator-activating receptor subtype gamma (PPARγ). It was later confirmed that this was indeed the main mode of action of TBT-induced imposex. RXR can heterodimerize with other nuclear receptors – such as PPAR (α, β and γ), thyroid hormone receptor, vitamin D receptor and farnesoid X receptor – and activate gene expression relevant for the above-mentioned processes. The involvement of RXR and RAR in human and animal metabolic disorders has been discussed under that health outcome, so here, the effects of retinoid signalling disruption are discussed in relation to other outcomes in animals. For a detailed review of the retinoid system functions and effects of EDCs see the OECD detailed review paper on the retinoid system (OECD 2021), and for a developmental neurotoxicology focused review see (Cediel-Ulloa *et al*. 2022). Another recent review summarizes the impacts of retinoic acid signalling effects on morphology, phenotype and development across vertebrate taxa (Kubickova *et al*. 2021).

Laboratory evidence for retinoid signalling disorders

Vertebrates

Mammals. The OECD detailed review paper (OECD 2021) summarized effects of chemicals disturbing male or female reproduction, neurodevelopment and skeletal development via retinoid signalling disruption in rodent in vitro and in vivo models (rats and mice). BPA, phthalates and organotins affected both male and female reproductive parameters, while other chemicals only affected one sex (for example, acetaminophen (paracetamol), indomethacin and lindane). Several AOPs were developed to support the mechanistic links to the observed effects (OECD 2021).

Fish. In zebrafish, developmental exposure to the RXR/PPARγ agonist triphenyltin caused abnormal eye development and severe skeletal and morphological malformations in larvae (He 2026). Several studies investigated the effects of BDEs, such as BDE-47, in developing zebrafish and found disruption of the developing eye, including ocular pathologies such as retinal degeneration,



cataracts and retinoblastoma, leading to changes in neurobehaviour and vision. The effects were linked to retinoid pathway disruption (Louzon *et al*. 2026).

Amphibians. In *Xenopus laevis* embryos, exposure to TPT caused teratogenic effects such as enlarged proctodeum (developing anus) and narrow fins (He, Li and Li 2021). Exposure of *X. laevis* embryos to the herbicide glyphosate and a glyphosate-based herbicide caused disrupted cephalic and neural crest development and shortened anterior–posterior axis. Effects were correlated with deformities in the cranial cartilages at later tadpole stages. The mechanism behind the effects was probably an increase in retinoic acid, demonstrated by rescued teratogenic effects after co-treatment with an RAR antagonist (OECD 2021; Hoy, Haas and Hallock 2024). Triadimefon, a triazole fungicide, induced craniofacial malformations in *X. laevis* embryos; the developmental effects were reduced by co-treatment with the all-trans retinoic acid synthesis inhibitor, citral (OECD 2021).

Birds. As other vertebrates, birds possess nuclear retinoid receptors (RAR, RXR) and transport proteins and enzymes involved in retinoid synthesis, transport and metabolism. Chicken embryos have been used as models for investigating teratogenic effects of all trans retinoic acids.

Reptiles. As other vertebrates, reptiles possess nuclear retinoid receptors (RAR, RXR) and transport proteins and enzymes involved in retinoid synthesis, transport and metabolism (OECD 2021). It is therefore expected that chemicals disrupting retinoid signalling can induce effects such as those observed in the other vertebrate classes, such as developmental and teratogenic effects. However, no laboratory experiments with reptiles explore the connection between such effects and retinoids.

Invertebrates

Genomic and biochemical evidence suggests that retinoid metabolic and signalling pathways originated in the last common ancestor of bilaterians. Although these pathways are not yet fully characterized in many nonchordate invertebrates, data indicate the presence of biologically active retinoid signalling. While some features appear evolutionarily conserved, the underlying enzymatic mechanisms may differ from those in vertebrates. This evolutionary conservation implies that a wide range of metazoans may be susceptible to disruption of retinoid pathways by EDCs (Andre *et al*. 2014). The effect of TBT and triphenyltin on induction of imposex in marine molluscs is weak, with RXR interference as the main component. In crustaceans, TBT also seems to interact with RXR and negatively affect ecdysteroid receptor and RXR-dependent gene expression. In *Daphnia magna*, RXR is also activated by TBT (Andre *et al*. 2014).

Wildlife animal studies

Vertebrates

The OECD detailed review paper (OECD 2021) states that "dysmorphogenesis of various tissues associated with altered retinoid transport, metabolism and signalling is reported in wild populations of fish, birds, amphibians and mammals", but does not refer to specific studies. As described previously, the induction of imposex in female marine molluscs is very well described, with population declines and local extinction of some gastropod species (Fernandez 2019; Langston 2020).

Renal disorders

The 2012 assessment did not address the potential association between EDCs and chronic kidney disease. For the past decade, studies have reported links between EDC exposure and

kidney disease, suggesting various mechanisms. The kidney is one of the primary excretion routes for environmental chemicals following concentration and filtration, and therefore may serve as a site of accumulation for EDCs. Exposure to EDCs, such as phthalates, PFAS, dioxins and metals, has been associated with adverse renal outcomes, including reduced glomerular filtration rates and albuminuria in general populations, although such associations between prenatal exposure and kidney function remain inconclusive (Hsu and Tain 2021). Experimental animal studies have shown that EDCs, including dioxins, BPA and phthalates, can cause oxidative damage, tubular injury, epithelial–mesenchymal transition and fibrosis (Zhang *et al*. 2023). This is a health outcome that warrants further scientific research in the future to elucidate endocrine mechanisms.

C. Key messages

Since 2012, evidence has emerged indicating that EDCs may disrupt health outcomes that were not mentioned in the 2012 assessment, including retinoid signalling and renal dysfunction.

- **Retinoid signalling is a highly conserved pathway and an important target of EDCs.** Experimental evidence across vertebrates and invertebrates shows that disruption of retinoic acid receptors (RARs) and retinoid X receptors (RXRs) signalling can cause developmental and reproductive defects, with strong mechanistic support for compounds such as organotins, BPA, phthalates and certain pesticides.

- **The association of EDC exposure with adverse kidney outcomes warrants further investigation.**

3 Testing and assessment of EDCs

Lead authors

Laura N. Vandenberg (University of Massachusetts, United States of America) and R. Thomas Zoeller (University of Massachusetts, United States of America)

Chapter authors

Olwenn V. Martin (University College London, United Kingdom of Great Britain and Northern Ireland), Nicholas Chartres (University of Sydney, Australia), Tracey J. Woodruff (Stanford University, United States of America), Lucia Vergauwen and Dries Knapen (University of Antwerpen, Belgium)

3.1 Introduction

The evidence provided in chapter 2 demonstrates that EDC exposure is associated with adverse health effects in human and wildlife populations, and that mechanistic studies strongly support the conclusion that many of these associations are causal. These associations between EDC exposure and adverse health effects have been identified in human and wildlife populations despite the existence of regulatory testing and assessment strategies, suggesting those strategies are inadequate to protect human and wildlife health. Testing paradigms developed by various agencies have not expanded at the same rate as the introduction of new chemicals with potential endocrine-disrupting properties or their use across commercial sectors (Maffini and Vandenberg 2022). Yet, identification of EDCs through regulatory testing programmes informed by current scientific knowledge could support efforts to reduce exposure in human and wildlife populations. In addition, scientific understanding of the mechanisms by which EDCs interact with endocrine systems and contribute to adverse effects has continued to evolve. In recognition of these challenges, several agencies and organizations have launched efforts to improve EDC testing programmes.

Regulatory testing programmes depend on operational definitions. The 2002 Global assessment of the state-of-the-science of endocrine disruptors (IPCS 2002) defined an EDC as an "exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub) populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations." The European Union and OECD have adopted the WHO 2002 definition for the purpose of chemical regulation (European Food Safety Authority [EFSA] 2013). Thus, identification of EDC properties of a chemical or mixture requires three elements: (a) the evaluation of endpoints that inform regulators of adversity; (b) the identification of an endocrine mode of action; and (c) a plausible link between the two.

The *State of the Science of Endocrine Disrupting Chemicals – 2012* (UNEP and WHO 2013) did not have a specific section on testing and assessment of EDCs, but it made some general comments (box 3.1). These comments describe challenges associated with applying testing systems developed primarily for the identification of acute toxicity to the evaluation of endocrine-disrupting properties. Since publication of that report, updates to testing programmes have been introduced to address some of the limitations identified.

Box 3.1 Testing and identification of EDCs from the 2012 assessment on EDCs

- "These insights from endocrine disruptor research in animals have an impact on current practice in toxicological testing and screening. Instead of solely studying effects of exposures in adulthood, the effects of exposures during critical windows in fetal development, perinatal life, childhood and puberty require careful scrutiny."
- "Testing for endocrine disruption must encompass the developmental period and include lifelong follow-up to assess latent effects."
- "Chemical testing strategies do not routinely require evaluation of the ability of a chemical to produce developmental neurotoxic effects in a pre-market setting."
- "Models of hormonal cancers are not available for regulatory testing. This makes the identification of hormonal carcinogens very difficult and forces researchers to rely on epidemiological studies. However, epidemiological studies cannot easily pinpoint specific chemicals and can identify carcinogenic risks only after the disease has occurred."

This chapter describes current methods for testing EDCs, with an emphasis on OECD test guidelines (OECD 2018b). It reviews tests that establish an endocrine mode of action alongside those that evaluate adverse effects induced by chemical exposure. It covers the ongoing work to revise and update EDC testing approaches, including efforts to incorporate new scientific methods and reduce reliance on animal testing.

Much of this work traces back to a landmark 2007 United States of America National Research Council report on toxicity testing in the 21st century (Council 2007) and has continued to evolve through more recent authoritative frameworks, including the OECD test guideline 150 toolbox for evaluating chemicals with endocrine-disrupting properties (OECD 2018b). This chapter will also provide an overview of approaches that can be used to organize the data derived from standardized tests and academic research, including the key characteristics of EDCs as a basis for hazard identification, and the use of adverse outcome pathways (AOPs).

Finally, the chapter reviews the literature on key topics that influenced both the testing of EDCs and interpretation of testing results. These topics include dose–response interpretation with an emphasis on non-monotonic responses, the concepts of thresholds and potency, approaches to evaluate chemical mixtures, and the importance of considering vulnerable periods of development. The chapter also examines new approach methodologies and their known strengths and limitations, and the challenges they present for EDC regulation.

3.2 Endocrine-disrupting chemicals: definition and key terms

The chapter presents definitions for key terms that are relevant to testing and assessment of EDCs. These terms are also briefly summarized in chapter 1.

3.2.1 Endocrine system

This document uses the definition of the endocrine system as described in the 2012 assessment (UNEP and WHO 2013), which went beyond a description of the hormones and organs that are included in the endocrine system; it also provided an extensive description of the role that hormones play in the control of major physiological processes during development and throughout adulthood. The term "development" includes embryonic, fetal and neonatal development, childhood and puberty in humans, and the equivalent states in wildlife. But it also refers to larval and juvenile stages of invertebrates, where progression through these stages is governed by hormones and are frequently the target of biocides. The principles of endocrinology have been described in depth elsewhere (Vandenberg *et al*. 2013; Vandenberg *et al*. 2012; Zoeller *et al*. 2012), and their relevance to understanding and identifying EDCs is described in chapter 1.


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3.2.2 Functions of the endocrine system

The endocrine system comprises the "synthesis, secretion, transport, metabolism, binding, action, [and] elimination of natural blood-borne hormones" (Kavlock *et al*. 1996). Therefore, in this chapter, the phrase "disrupt the function(s) of the endocrine system" is interpreted to include any chemical-induced perturbation that interferes with any of these aspects of the endocrine system (La Merrill *et al*. 2020). This could include abnormal changes in blood concentrations of hormones but also includes chemicals that mimic endogenous hormones, those that prevent the binding of endogenous hormones to their receptors, and those that alter hormone synthesis, transport, metabolism or excretion. This definition is consistent with the European Chemicals Agency and European Food Safety Authority 2018 guidance document (ECHA and EFSA 2018).

3.2.3 Adverse effect

IPCS defines an adverse effect as a "change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences" (IPCS 2004). Although some groups have interpreted the term to mean "toxicity, pathology, or functional impairment" (Nohynek *et al*. 2013), there are no clear and transparent ways to determine which endpoints in a test guideline (or other evaluation approach) represent adverse outcomes. Some authors have proposed that outcomes that align with clinical symptoms of human diseases may be considered adverse outcomes; similarly, it has been proposed that observed increases in disease burden within a study population be considered an adverse effect (Zoeller *et al*. 2015). Importantly, when considering adversity for wildlife, the regulatory protection goal is the maintenance of populations. Effects on growth, development or reproduction observed in individual organisms are generally regarded in regulatory assessments as indicators of adversity, because they are considered relevant to population maintenance unless shown otherwise (ECHA and EFSA 2018).

Disease is often the visible end of a longer process. Expert panels proposed tracing recognized adverse effects back to the measurable biological changes that appear first before illness is evident (Woodruff *et al*. 2008). This concept represents the origins of the adverse outcome pathway (AOP), which is discussed in more depth in section 3.4.2 of this chapter.

Overt measures of functional capacity to compensate for additional stressors are not captured in any standardized test protocol. Examples in protocols that have not been validated, however, include evaluations of whether an early-life EDC exposure alters the sensitivity of a hormone-responsive organ to a subsequent administration of a carcinogenic agent (Weber Lozada and Keri 2011), or whether EDC exposure alters the response of an individual to an immune challenge such as a vaccine (Timmermann *et al*. 2024) or allergen (O'Dell *et al*. 2021). One example reported in the research literature involves mice in which the alpha thyroid hormone receptor was deleted. The animals had only subtle abnormalities when kept at a normal temperature for laboratory animals (22°C), but when transferred to 4°C, they completely lost their ability to maintain temperature and died within a day (Pelletier *et al*. 2008). This and similar examples illustrate how effects on an organism's capacity to compensate for additional stressors may not be captured in standardized guideline studies.

3.2.4 Intact organism

The OECD Guidance Document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption states: The term "intact organism" is understood to mean that the effect would occur in vivo, either observable in a test animal system, epidemiologically, or clinically. However, it does not necessarily mean that the adverse effect has to be demonstrated in an intact test animal but may be shown in adequately validated alternative test systems predictive of adverse effects in humans and/or wildlife. The importance of mechanistic data derived from experimental systems (in vitro or in vivo in which the animals have been surgically or genetically altered as part of a focused experiment) [is] also recognized" (OECD 2018b). This text originally comes from Solecki *et al*. (2017).

3.2.5 Validated test systems

The text above (defining an intact organism) contains several terms that warrant further explanation. The term validated is a core element of the OECD system of mutual acceptance of data (Koeter 2003), which allows data from OECD adopted test guidelines to be recognized across jurisdictions, reducing redundant testing. The validation of a test involves demonstrating that the methods utilized are accurate, precise, sensitive and specific. OECD Guidance Document 34 describes the approaches needed for the validation and international acceptance of new or updated tests (OECD 2005).

The term alternative test systems is often used to mean in silico, in chemico and in vitro approaches, as well as in vivo approaches using non-protected life stages or species (for example, fish and amphibian embryos or invertebrates) (Serafini *et al*. 2024). These are discussed in further detail in section 3.3.5 and section 3.4 of this chapter as "new approach methods".

Finally, mechanistic data can be generated from numerous experimental approaches, including in silico, in vitro or in vivo tests (OECD 2017; Sakuratani *et al*. 2018). The term is normally used to describe the sequence of events from when an exposure occurs through to when a biological response is observed. These data are often summarized in AOPs using terms such as molecular initiating events, key events and adverse outcomes (see also section 3.4.2).

3.3 Standardized testing to identify EDCs

The OECD has developed a framework for the standard testing of all chemicals except pharmaceuticals. The framework examines five key areas: (a) the physical and chemical properties of the compound; (b) the effects on biotic systems; (c) the chemical's environmental fate and behaviour; (d) the health effects induced by exposure; and (e) other features of the chemical. Addressing each of these five areas relies on the use of test guidelines, which are internationally agreed-upon methods used in the context of regulatory testing (OECD 2024a). Test guidelines are developed on the basis of scientific evidence and are intended to address the biological effects being assessed.

3.3.1 Test guideline development and validation

The process of developing and validating test guidelines is time consuming and resource intensive. The scale of this effort is illustrated by the validation of the uterotrophic assay, which was conducted across three phases involving up to 19 participating laboratories and the testing of multiple doses of test chemicals and controls using four different procedures (Kanno *et al*. 2001; Kanno *et al*. 2003). While this represents a particularly extensive validation exercise, it illustrates the resources that may be required to achieve regulatory acceptance of a test guideline and highlights considerations relating to the time, cost and effort associated with assay validation.

Indeed, even animal-free assays are anticipated to require significant time and funding for round robin validations involving multiple laboratories. The Toxicity Forecaster (ToxCast) programme provides an example: high-throughput assays developed by the United States EPA for chemical screening were described by the agency as "unique, proprietary assays developed by

companies supporting the pharmaceutical industry", with intellectual property considerations restricting their commercial use to those who have licensed them or paid for testing services from the assay owner or licensee (Judson *et al*. 2013). Because of these constraints, the EPA planned to use ToxCast assays in their largely non-validated form as a screening tool to prioritize chemicals for further testing with validated approaches. Subsequent work has focused more on determining whether the data generated by the individual assays can be applied in a scientifically defensible manner; for example, by assessing whether patterns across multiple assays reliably predict chemical hazards (Richard *et al*. 2016).

Independent comparative evaluations of assays are also an important part of the broader validation landscape, helping to compare new screening tools to other accepted measures of the same outcomes. Such evaluations of the ToxCast assays have reported varying levels of performance depending on the endpoint examined. In the domain of ecotoxicology, the predictive value of ToxCast data was generally poor, and risk conclusions differed substantially when high-throughput screening data were used in place of traditional in vivo data (Rodea-Palomares and Bone 2024). These differences in predictability of assays may influence both hazard identification and risk assessment outcomes. A recent study identified a pesticide, buprofezin, as a previously unrecognized environmental obesogen through experimental validation in human stem cells, despite the chemical being classified as inactive in ToxCast assays, a finding the authors attributed to the inability of current high-throughput screening data to capture partial agonist activity (Hwang *et al*. 2025). Collectively, these evaluations indicate that assay performance varies across endpoints and that comparative validation studies continue to be needed to determine the circumstances under which high-throughput screening data can be applied to decision-making, especially in the absence of data from validated methods.

Significant efforts have also been made to phase out the use of animals in toxicity testing (see also section 3.3.5), but many authoritative organizations and researchers have stated that replacement of animal testing across all areas of toxicity testing is not currently feasible using alternative methods. The OECD has stated that "there are currently too few methods and approaches that have passed the stage of validation and reached regulatory acceptance for phasing out of animal testing: only topical hazards such as skin sensitization and eye irritation can be evaluated without animal tests" (OECD n.d.a). The OECD further cautions that efforts to accelerate or reduce the costs of validation must not compromise the credibility and quality of the work, or the reliability of the resulting test guideline.

It is equally important that newly developed assays reflect current understanding of endocrinology, both in design and in application. Extensive efforts have focused, for example, on identifying cell-based assays predictive of a uterotrophic response and capable of identifying estrogen receptor agonists (Corton *et al*. 2022). Montevil *et al*. (2020) reported that the uterotrophic assay is insensitive compared to other downstream tissue endpoints for detecting estrogen action. Consequently, cell-based assays developed to predict uterotrophic responses may exhibit limitations similar to those associated with the uterotrophic endpoint itself.

A related but distinct limitation arises from the concentration ranges used in high-throughput screening assays. For example, the United States EPA has noted that chemicals of low potency will only be detected in the most sensitive assays and only when tested at sufficiently high concentrations, because typical screening assays limit testing to micromolar concentrations (Judson *et al*. 2019). This limitation is not confined to the estrogen receptor pathway. Kleinstreuer *et al*. (2018) reported that false negatives in the ToxCast androgen receptor model were predominantly "low potency" chemicals whose lowest effect levels in vivo fell above the concentrations tested in the screening assays. Importantly, these are limitations of how high-throughput screening tools are currently deployed, not inherent features of the validation framework itself. Established regulatory test guidelines specify concentration ranges adequate for detecting lower-potency compounds. OECD test guidelines 455 and 493 both provide guidance on extending concentration ranges

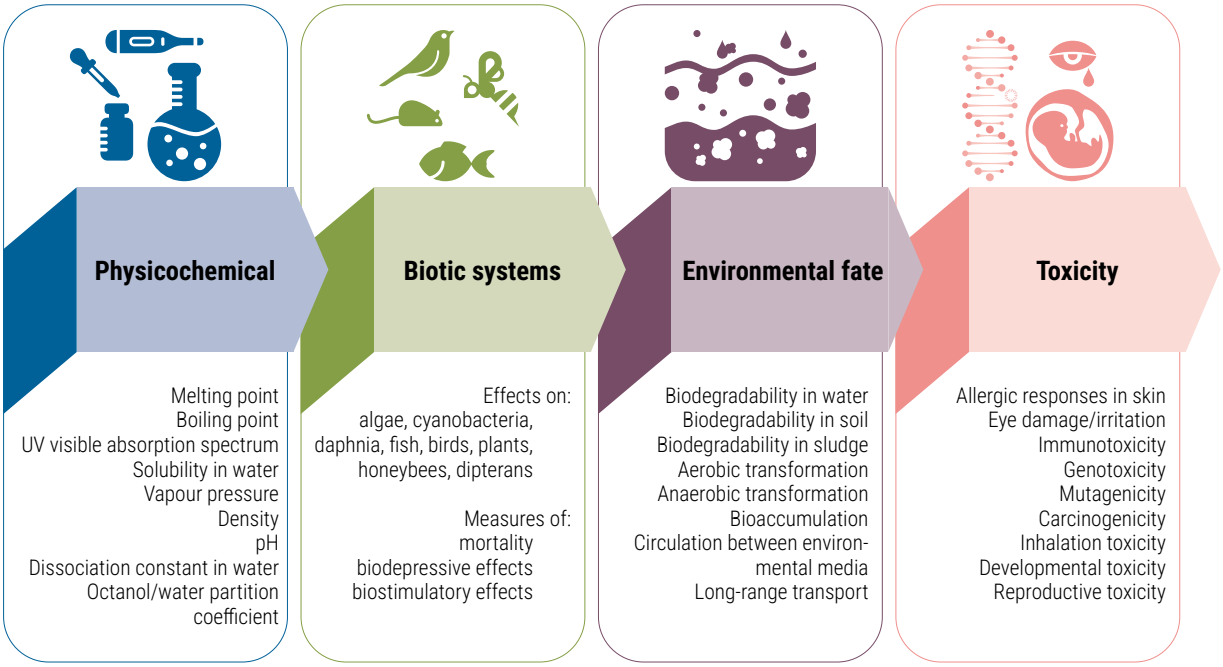
where weak activity is suspected. Assessment frameworks may consider not only whether an assay has been formally validated, but whether the biological endpoint it is designed to capture and the concentration ranges used are appropriate for the regulatory purpose at hand. Consideration of low-potency chemicals is discussed in section 3.5.3, indicating that EDCs that have only modest effects on some of the endpoints in screening assays (such as the uterotrophic and Hershberger assays) can have significant effects in endpoints that are more sensitive than those included in some screening assays. Studies have reported as well that lower-potency chemicals contribute to mixture effects (Silva *et al*. 2002; Sprong *et al*. 2023).

3.3.2 Test guidelines provide a structured approach to testing and assessment of EDCs

Using standardized testing approaches to evaluate toxicity focuses on characterizing a chemical's physicochemical properties, followed by the effects of a chemical on biotic systems, and the chemical's fate in the environment (figure 3.1). These features are relevant for EDCs and non-EDCs alike, because they describe properties of chemicals that influence their degradation in the environment, mobility, accumulation in environmental matrices and other hazards. The results of these studies can inform later evaluations (for example, chemicals with low water solubility may not be suitable to test in aquatic systems). They also provide information about whether a chemical bioaccumulates and biomagnifies in the food chain (Amézqueta *et al*. 2020). PCBs, for example, are EDCs that are also persistent organic pollutants. These characteristics can contribute to prolonged exposure and associated effects because persistent compounds can remain in environmental media and biological systems for extended periods. The United States EPA and the Stockholm Convention on Persistent

FIGURE 3.1

CHEMICAL FEATURES USED TO EVALUATE TOXICITY



The assays described enable the characterization of a chemical's physicochemical properties, the effects of a chemical on biotic systems, and the chemical's fate in the environment. These features are not specific to endocrine disruption, but can influence other aspects of endocrine toxicity (for example, by increasing bioaccumulation).

Organic Pollutants report that PCBs and their breakdown products can also induce adverse outcomes, including cancers, disruption of the immune system and altered reproductive function. Importantly, the test battery that is selected is dependent upon the statutory requirements of the jurisdiction that governs the tested chemical (Secretariat of the Stockholm Convention n.d.).

3.3.3 Endpoints relevant to endocrine disruption

Endpoints in standard test guidelines for EDCs are described on the OECD website and summarized in table 3.1 (OECD n.d.b.). These endpoints are organized in five levels, as described in OECD Guidance Document 150 (OECD 2018b). Aligned with the IPCS definition of an EDC, guideline endpoints are designed to provide information about an endocrine mode of action and/or the adverse outcomes induced by exposure. Lower levels of the conceptual framework (CF1) focus on identifying pre-existing data, plus existing or new non-test information. CF2 includes in vitro data relevant to an EDC mode of action for mammals or non-mammalian vertebrates. The middle levels of the conceptual framework (CF3 and CF4) include in vivo assays that can inform single or multiple endocrine pathways and adversity within the domain of estrogen, androgen, thyroid and steroidogenesis modalities, with tests that are relevant to both human and wildlife populations. The final level of the conceptual framework (CF5) includes assays that can be used to provide information on adverse effects that arise from endocrine or other mechanisms.

The in vivo assays included in CF level 3 largely focus on classical hormone-sensitive tissues to evaluate whether test chemicals have an endocrine mode of action. For example, one test of a chemical's anti-androgenic potential is based on the ability of the chemical to interfere with the action of androgens that increase the weight of male reproductive organs, such as the seminal vesicles (see Hershberger assay, CF3 in table 3.1). Another example is the amphibian metamorphosis assay (see CF3 in table 3.1), where pre-metamorphic frog tadpoles are administered test chemicals and thyroid hormone-dependent metamorphic outcomes, such as hind limb length, are monitored over a three-week period, followed by thyroid gland histopathology at the end of the assay. These endpoints are used to both identify and

Table 3.1 OECD conceptual framework for the testing and assessment of EDCs

CF level	Endpoints
CF level 1 Existing data and existing or new non-test information	Mammalian and non-mammalian toxicology • Physical and chemical properties, e.g. Molecular Weight, reactivity, volatility, biodegradability • All available (eco)toxicological data from standardized or non-standardized tests • Read-across chemical categories, quantitative structure–activity relationship and other in silico predictions, and absorption, distribution, metabolism and excretion model predictions
CF level 2 In vitro assays providing data about selected endocrine mechanisms or pathways (mammalian and non-mammalian methods)	Mammalian and non-mammalian toxicology • Estrogen (OECD TG 493) or androgen receptor binding affinity (United States EPA TG OPPTS 890.1150) • Estrogen receptor transactivation (OECD TG 455, ISO 19040-3), yeast estrogen screen (ISO 19040-1 and 2) (OECD TG 457) • Androgen receptor transactivation (OECD TG 458) • Steroidogenesis in vitro (OECD TG 456) • Aromatase assay (United States EPA TG OPPTS 890.1200) • Thyroid disruption assays (e.g. thyroperoxidase inhibition, transthyretin binding) • Retinoid receptor transactivation assays • Other hormone receptor assays, as appropriate • High-throughput screens

continued next page

Table 3.1 continued

CF level	Endpoints
CF level 3 In vivo assays providing data about selected endocrine mechanisms or pathways	Mammalian toxicology • Uterotrophic assay (OECD TG 440) • Hershberger assay (OECD TG 441) • Non-mammalian toxicology • Fish short-term reproduction assay (OECD TG 229) • 21-day fish assay (OECD TG 230) • Amphibian metamorphosis assay (OECD TG 231) • *Xenopus* embryonic thyroid signalling assay (OECD TG 248) • EASZY assay; detection of substances acting through estrogen receptors using transgenic CYP19a1b GFP zebrafish embryos (OECD TG 250) • Rapid androgen disruption activity reporter (RADAR) assay (OECD TG 251) • Rapid estrogen activity in vivo (REACTIV) assay (OECD TG 252) • Short-term juvenile hormone activity screening assay using *Daphnia magna* (JHASA) (OECD TG 253) • Androgenized female stickleback screen (AFSS) (OECD GD 148) • Juvenile medaka anti-androgen screening assay (JMASA) (OECD GD 379)
CF level 4 In vivo assays providing data on adverse effects on endocrine-relevant endpoints	Mammalian toxicology • Repeated dose 28-day study (OECD TG 407) • Repeated dose 90-day study (OECD TG 408) • Pubertal development and thyroid function assay in peripubertal male rats (PP male assay) (United States EPA TG OPPTS 890.1500) • Pubertal development and thyroid function assay in peripubertal female rats (PP female assay) (United States EPA TG OPPTS 890.1450) • Prenatal developmental toxicity study (OECD TG 414) • Carcinogenicity (OECD TG 451), chronic toxicity (OECD TG 452), and combined chronic toxicity and carcinogenicity studies (OECD TG 453) • Reproduction/developmental toxicity screening test (OECD TG 421) • Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) • Developmental neurotoxicity (OECD TG 426) • Repeated dose dermal toxicity: 21/28-day study (OECD TG 410) • Subchronic dermal toxicity: 90-day study (OECD TG 411) • 28-day (subacute) inhalation toxicity study (OECD TG 412) • Subchronic inhalation toxicity: 90-day study (OECD TG 413) • Repeated dose 90-day oral toxicity study in non-rodents (OECD TG 409) • Non-mammalian toxicology • Fish sexual development test (FSDT) (OECD TG 234) • Larval amphibian growth and development assay (LAGDA) (OECD TG 241) • Avian reproduction assay (OECD TG 206) • Fish early life stage (FELS) toxicity test (OECD TG 210) • *Potamopyrgus antipodarum* reproduction test (OECD TG 242) • *Lymnaea stagnalis* reproduction test (OECD TG 243) • Chironomid toxicity test (OECD TG 218 and TG 219) • *Daphnia magna* reproduction test (with male induction) (OECD TG 211) • Earthworm reproduction test (OECD TG 222) • Enchytraeid reproduction test (OECD TG 220) • Sediment water *Lumbriculus* toxicity test using spiked sediment (OECD TG 225) • Predatory mite reproduction test in soil (OECD TG 226) • Collembolan reproduction test in soil (OECD TG 232) • New guidance document on harpacticoid copepod development and reproduction test with *Amphiascus* (OECD GD 201)

continued next page

Table 3.1 continued

CF level	Endpoints
CF level 5 In vivo assays proving more comprehensive data on adverse effects on endocrine-relevant endpoints over more extensive parts of the life cycle of the organism	Mammalian toxicology • Extended one-generation reproductive toxicity study (EOGRTS) (OECD TG 443) • Two-generation reproduction toxicity study (OECD TG 416, most recent update) • Non-mammalian toxicology • Fish life cycle toxicity test (FLCTT) (United States EPA TG OPPTS 850.1500) • Medaka extended one-generation reproduction test (MEOGRT) (OECD TG 240) • Avian two-generation toxicity test in the Japanese quail (ATGT) (United States EPA TG OCSPP 890.2100/740-C-15-003) • Sediment water chironomid life cycle toxicity test (OECD TG 233) • Zebrafish extended one-generation reproduction test (ZEOGRT) (draft OECD TG)

GD: guidance document; TG: test guideline.

characterize chemicals that are hazardous within estrogen, androgen, thyroid and steroidogenic modalities.

In assays included in CF levels 4 and 5, overt measures (for example, changes to the weight of a hormone-sensitive organ) are interpreted to provide information on whether a test chemical induces adverse effects. For example, in the extended one-generation reproductive toxicity study assay (CF5 in table 3.1), rodents that have been exposed to test chemicals since conception are euthanized at 13 weeks of age, and the weight of the testis and epididymis (along with many other organs) are recorded for males. Changes in the weight of hormone-regulated tissues are interpreted as evidence that a chemical may be acting through hormonal pathways, and alterations in organ size may be considered relevant in hazard assessment. Other hormone-sensitive outcomes are also evaluated in the assays in CF levels 4 and 5; for example, in the extended one-generation reproductive toxicity study assay, such endpoints include anogenital distance measured within the first four days after birth, nipple/areola retention measured around postnatal day 13, and puberty onset (ECHA and EFSA 2018). Anogenital distance is influenced by fetal androgen exposures and is associated with other male reproductive outcomes (Schwartz *et al*. 2019). Another example from a non-mammalian model is the avian reproduction assay (CF4 in table 3.1). In this assay, adult birds (duck or quail) are administered the test chemical in feed and then induced to lay eggs over a 10-week period; the eggs are incubated and hatched. Outcomes that are considered relevant to endocrine-mediated adverse effects include the number of eggs laid per hen, percentage of laid eggs that are cracked, viability and hatchability of laid eggs, and eggshell thickness.

3.3.4 Strengths and weaknesses of estrogen, androgen, thyroid and steroidogenic endpoints currently available in standard test guidelines

Estrogen, androgen, thyroid and steroidogenic endpoints – measurements that reflect an endocrine mode of action and/or an adverse effect that is relevant to an endocrine mode of action within the domain of estrogen, androgen, thyroid and steroidogenesis – are well described in many OECD testing guidance documents (ECHA *et al*. 2018; OECD 2005, 2017, 2018b). The feature of these guideline endpoints is that they do not depend on a predetermined hypothesis about either the mode of action or the adverse effects induced by a chemical. As a result, chemicals for which there is little or no a priori information about toxicity can be evaluated using these approaches to obtain signals illuminating a path of investigation for specific forms of toxicity, including endocrine disruption within the estrogen, androgen, thyroid and steroidogenic modalities.

The OECD testing guidance has been expanded in the past decade through the incorporation of additional endocrine-relevant endpoints. For example, in 2017, the European Union Reference Laboratory for Alternatives to Animal Testing and the European Network of Validation Laboratories took initial steps to validate 17 in vitro assays focused on thyroid hormone signalling

pathways. By 2022, the OECD had assembled a working group to evaluate the validation status of these assays. By late 2024, eight assays had been evaluated in depth, expanding the capacity to evaluate chemicals for their ability to activate the thyrotropin-stimulating hormone receptor, inhibit thyroid peroxidase, inhibit tyrosine iodination, bind to serum hormones that bind to thyroxine, inhibit deiodinase activity, activate thyroid hormone receptors, alter interfollicular thyroxine content, or alter thyroid hormone-dependent cell proliferation.

Another important example is that of the intense international efforts to develop a developmental neurotoxicity testing battery that relies on in vitro assays anchored to model developmental processes. Identification of chemicals that affect brain development leading to clinical issues such as autism or attention deficit disorders has global relevance. Nevertheless, testing chemicals for developmental neurotoxicity is resource intensive in terms of animal numbers, time and cost (Bal-Price *et al*. 2018). Because of this, the OECD test guideline programme initiated an international collaboration of stakeholders to develop an in vitro battery for developmental neurotoxicity testing (Sachana *et al*. 2021). These efforts are currently under way.

Despite major efforts to develop standard test guidelines for estrogen, androgen, thyroid and steroidogenic pathways, there remain significant weaknesses, as follows.

1. A large review of the literature by Kortenkamp *et al*. (2011) concluded that some currently used in vivo endpoints are less sensitive than other available measures for detecting certain endocrine-mediated effects, particularly developmental effects. Reliance on less sensitive outcomes for the identification of adverse effects could lead to "false negative" outcomes (that is, chemicals that are incorrectly deemed to not be EDCs). Furthermore, reliance on insensitive outcomes could contribute to inadequate health protection when identifying the doses at which risk is estimated to be significant; this is discussed in greater detail later in this chapter.

   Current test guidelines cover a subset of health outcomes associated with endocrine disruption and do not encompass all outcomes reported in observational or experimental studies (see chapter 2). Even within the estrogen, androgen, thyroid and steroidogenic modalities, some organs and health endpoints remain poorly evaluated. For example, expert reviews have identified limitations in the ability of validated test guidelines to capture effects of chemicals on mammary gland development and function, as well as diseases affecting this organ (Kay *et al*. 2022). Moreover, studies have reported that mammary gland endpoints may respond at exposure levels lower than those currently used as standardized endpoints (for example, uterine weight (Montévil *et al*. 2025)).

   Beyond the estrogen, androgen, thyroid and steroidogenic modalities, many health outcomes reported in the literature are not currently represented in standardized test guidelines. For example, no test guideline currently exists for endometriosis, despite accumulating evidence associating EDC exposure with this condition (Cano-Sancho *et al*. 2019; Caporossi *et al*. 2021; Conforti *et al*. 2021; Shirafkan *et al*. 2023; Sirohi *et al*. 2021). Likewise, neurobehavioural outcomes, including attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, and diminished IQ, as well as certain cancers and metabolic conditions, are absent from existing test guidelines.

   Beyond these outcome-level gaps, current test guidelines provide limited coverage of chemicals acting through many non-estrogen, androgen, thyroid and steroidogenic endocrine pathways. Pathways involving adrenal steroids, pancreatic and intestinal hormones, adipose and muscle-derived hormones, and the hypothalamic–pituitary feedback systems that regulate estrogen, androgen, and thyroid hormones themselves are represented to a limited extent in validated test guidelines or are absent entirely.

2. For wildlife, and especially invertebrate wildlife, the test guidelines that are available remain limited and do not encompass all



wildlife taxa that are exposed to EDCs and potentially affected by these chemicals. For example, there are currently no guidelines developed for thyroid in fish, and there are no tests at all for reptiles. Invertebrates are represented in only a few tests at higher CF levels, and these largely focus on screening for juvenile hormone activity and some reproductive outcomes (OECD 2024b), leaving other endpoints unexplored. The limited availability of mechanistic assays prevents the identification of many EDCs for invertebrates.

3. As stated above, there are also no tests developed to evaluate the effect of EDC exposure on the ability of organisms (vertebrates or invertebrates) to respond to additional stressors. The relevance of interactions between chemical exposures and other environmental stressors has been discussed in the context of global environmental change.

3.3.5 New approach methodologies

New approach methods are defined as "any technology, methodology, approach or combination thereof that can be used to replace, reduce or refine (i.e., 3Rs) animal toxicity testing and allow for more rapid or effective prioritization and/or assessment of chemicals" (Basu *et al*. 2025; Health Canada 2025). New approach methods encompass a range of techniques, including in silico (computer-based modelling), in chemico (chemical reactivity tests), and in vitro (cell-based assays), as well as refined alternative approaches such as omics technologies, in vivo studies using non-protected species (for example, many invertebrates), or in vivo studies using specific life stages of vertebrates (often focusing on fish or amphibian embryos) (ECHA 2016; US EPA 2018). While new approach methods mostly provide information on endocrine activity and in vivo assays are often needed to directly measure adversity, the use of fish and amphibian embryos can provide information relevant to both endocrine activity and adversity (Burden *et al*. 2022; Knapen *et al*. 2025; Knapen *et al*. 2026).

New approach methods can provide the necessary mechanistic data to group chemicals with a common mode of action. Initiatives such as Toxicology Testing in the 21st Century (Tox21) in the United States (Krewski *et al*. 2020) and ToxCast (Judson *et al*. 2010) have demonstrated the feasibility of testing thousands of substances in hundreds of high-throughput assays, and the Endocrine Disruptor Screening Program of the United States EPA was established to screen approximately 10,000 chemicals for endocrine-disrupting properties (US EPA 2012), though in practice only 52 chemicals completed tier 1 screening, and the programme did not proceed beyond tier 1 screening (Browne *et al*. 2017). Thus, new approach methods are not new to the task of identifying EDCs, but their novelty may lie in their application to refine, reduce or replace the use of animals in testing (Basu *et al*. 2025).

While new approach methods have been proposed to increase the speed and scope of chemical screening while reducing the cost (Basu *et al*. 2025; Health Canada 2025), consideration of new approach methods in regulatory contexts must include evaluation of their current limitations before deploying them as replacements for in vivo tests (Jaeschke and Ramachandran 2025; Sewell *et al*. 2024). Currently, validated regulatory new approach methods cover only a small subset of endocrine-mediated mechanisms, mostly focusing on limited aspects of estrogen, androgen, thyroid and steroidogenic modalities. Publications have identified limitations regarding the ability of current new approach methods to evaluate outcomes that involve interactions among multiple cell types, tissues or organs, as is characteristic of endocrine disruption, and have shown that even the most advanced in vitro new approach methods available cannot replicate whole-body physiology (Jaeschke and Ramachandran 2025; Knapen *et al*. 2026). Additional work is also needed to demonstrate whether existing new approach methods have been sufficiently validated for reproducibility and reliability, and whether their outputs are demonstrably relevant to human or wildlife health (OECD 2023a; Sewell *et al*. 2024).

Regulatory bodies have begun to formalize how new approach methods can and cannot be used. The Children's Health Protection Advisory Committee of the United States EPA has stated that new approach methods can be used for screening and hazard indication, but that conclusions about the absence of hazard cannot be drawn solely from new approach methods, a position consistent with the acknowledgement of the OECD that available new approach methods are insufficient to address adverse neurodevelopmental, endocrine and immune system perturbations (United States Environment Protection Agency 2021; OECD 2023b). A United States National Academy of Sciences report further noted that no authoritative compendium of available new approach methods exists with documented reliability and applicability (NAS 2023). Substantial efforts are under way to address these gaps, including the ongoing work of the OECD to validate new test methods (OECD 2023a), the development of integrated approaches to testing and assessment that combine new approach methods with existing in vivo data (OECD 2020), and other initiatives such as the European Partnership for the Assessment of Risks from Chemicals (Marx-Stoelting *et al*. 2023) and the developmental neurotoxicity testing programme of the National Institute of Environmental Health Sciences in the United States (European Food Safety *et al*. 2024). Current initiatives include the use of new approach methods for screening and prioritization purposes, while additional evidence is being developed to support broader regulatory applications.

3.4 Assessments and integration of evidence

In this section, we describe methods that are used to organize and evaluate the evidence that is produced from the use of validated assays and test guidelines, as well as evidence that is produced from other sources, including new approach methods, hypothesis-driven laboratory studies, epidemiology studies and observational studies of wildlife. The 2018 European Chemicals Agency and European Food Safety Authority guidance document (ECHA *et al*. 2018) provides information on how to assemble the evidence that a chemical influences estrogen, androgen, thyroid and steroidogenic as well as non-estrogen, androgen, thyroid and steroidogenic modalities, recognizing that most validated test systems used to identify EDCs do not have coverage of non-estrogen, androgen, thyroid and steroidogenic endocrine modalities.

Evidence produced from the validated approaches described in section 3.3 above can be critical in establishing the three features needed to determine if a chemical is an EDC, but evidence collected from other types of studies can also be used for these purposes. This evidence complements information derived from test guidelines, and can also raise new concerns that have not been observed with standard approaches.

Associations between exposure to EDCs and adverse health outcomes continue to be reported in epidemiological and wildlife studies (Muncke *et al*. 2023) (see also chapter 2). These observations have been cited by some

authors as indicating limitations in existing testing, assessment or risk management approaches for certain chemicals. Historical analyses have also documented numerous instances in which additional evidence emerging after initial assessments resulted in revised evaluations of chemical hazards (Gee 2006). For these reasons, epidemiological data constitute an important source of evidence that current testing strategies are not sufficient to identify and restrict exposures to chemicals of public health concern. When such data are available, they should contribute to weight-of-evidence evaluations.

3.4.1 Key characteristics approach

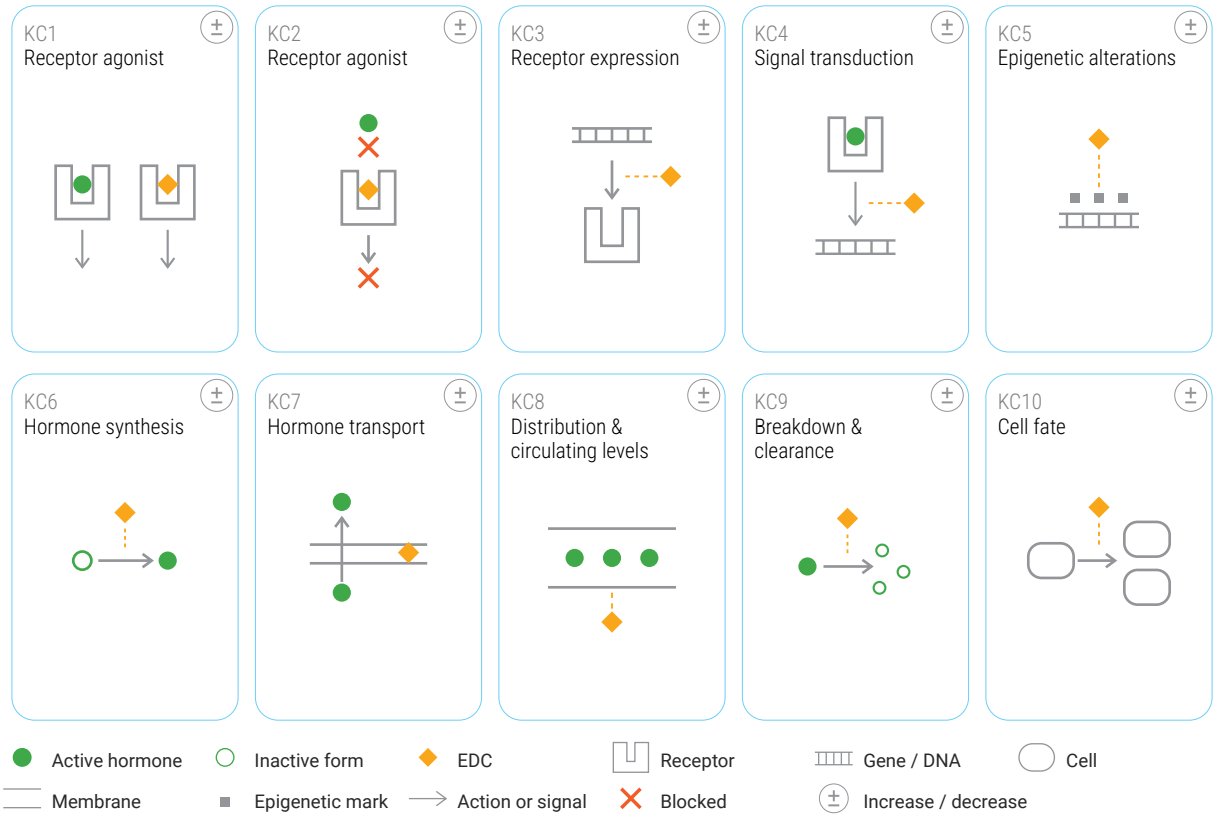
The key characteristics of EDCs were developed (La Merrill *et al*. 2020) based on the original work to establish the key characteristics of carcinogens (Smith *et al*. 2016) by examining common features of these chemicals. Thus, the key characteristics of EDCs do not represent a testing programme, but an approach by which evidence can be compiled to evaluate the effect of a test chemical on critical control points for hormone action.

There are 10 identified key characteristics for EDCs (figure 3.2), as follows.

- KC1: a chemical interacts with or activates hormone receptors (consistent with receptor agonist activities).
- KC2: a chemical can interfere with the ability of an endogenous hormone to interact with, bind to or activate a hormone receptor (consistent with receptor antagonist activities).

FIGURE 3.2

KEY CHARACTERISTICS OF EDCs



The ten key characteristics of endocrine-disrupting chemicals form an unordered set of mechanistic properties. They are not a pathway, sequence, or hierarchy: panel order and position carry no meaning, and a chemical may exhibit one characteristic or many. Each characteristic may be increased or decreased, with direction dependent on chemical, dose, tissue, and life stage.
Source: Adapted from La Merrill *et al.* (2020).

- KC3: a chemical alters hormone receptor expression.
- KC4: a chemical alters signal transduction (including changes in protein or RNA expression, post-translational modifications and/or ion flux) in hormone-responsive cells.
- KC5: a chemical induces epigenetic modifications in hormone-producing or hormone-responsive cells.
- KC6: a chemical alters hormone synthesis.
- KC7: a chemical alters the transport of a hormone across cell membranes.
- KC8: a chemical alters hormone distribution or circulating hormone levels.
- KC9: a chemical alters hormone metabolism or clearance.
- KC10: a chemical alters the fate of hormone-producing or hormone-responsive cells.

The key characteristics of EDCs point to the types of molecular initiating events that are critical for hormone action and, in turn, are relevant to determining if a test chemical has an endocrine mode of action. There are several important features of the key characteristics that are important to understand. First, the number of key characteristics associated with a chemical is not predictive of whether a chemical has an endocrine mode of action; some known EDCs display multiple key characteristics, while others display only one or a few. For example, the chemical perchlorate has strong evidence for only one key characteristic (KC6, thyroid hormone synthesis), but this offers vital and highly specific understanding of its mechanism of action (Brent 2014). Thus, the key characteristics should not be used as a checklist, but a process by which evidence can be assembled and evaluated. Second, the key characteristics approach can be used in the development of new or improved assays to inform regulators about the endocrine mode of action of chemicals or chemical mixtures. Several of the key characteristics are not currently represented or are only partially represented in the validated assays described in section 3.3 above for the identification of EDCs; nor are they represented in the newer high-throughput approaches that have been developed (such as ToxCast or Tox21).

3.4.2 Adverse outcome pathway approach

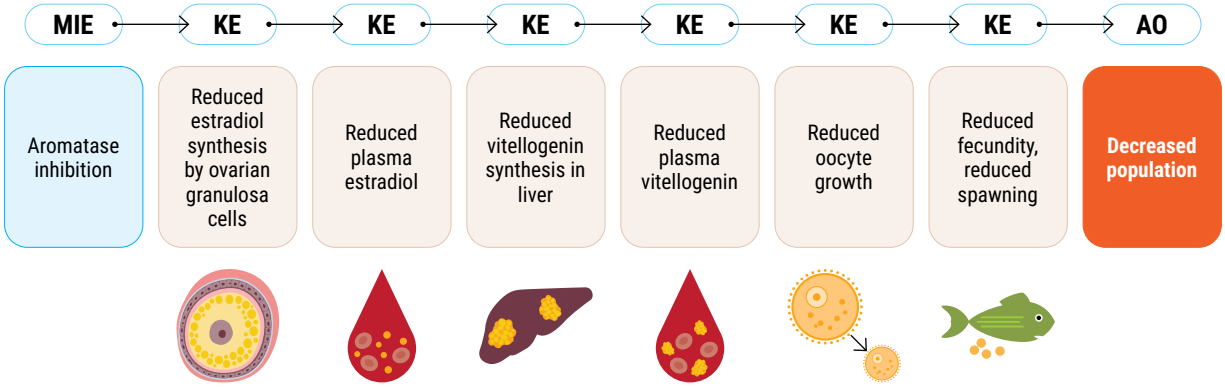
The adverse outcome pathway (AOP) framework, first introduced by Ankley *et al*. (2010), is a conceptual tool used in fundamental toxicology and regulatory hazard assessment to structure available information on toxicological processes. An AOP is a sequence of events that starts with a molecular initiating event (that is, the initial interaction between a chemical and a biological system) and leads to an adverse outcome on the organism or population level through a series of intermediate steps known as key events (which are measurable biological changes; see example in figure 3.3). Key event relationships describe the causal relationships between key events, detailing how one event leads to another within the pathway. Importantly, descriptions of key event relationships summarize the empirical evidence that supports these causal relationships, providing the scientific basis for the AOP.

Like the key characteristics approach, an AOP is considered a way of organizing evidence. Once the relationships between a molecular initiating event, downstream key events, and the adverse outcome are understood, this framework can be applied to the evidence that has been collected for specific chemicals. Also, as with the key characteristics, the AOP itself is chemical agnostic (Villeneuve *et al*., 2014); it describes disruptions of biological processes that are relevant to multiple chemicals, rather than being specific to a single chemical. This principle ensures that AOPs can be broadly applied to assess the hazards of various substances (Ankley *et al*. 2010; Villeneuve *et al*. 2014).

The AOP framework directly provides evidence and support for all three criteria for EDC identification, including demonstrating an adverse effect (downstream part of the AOP including the adverse outcome), identifying an endocrine mode of action (upstream part of the AOP including

FIGURE 3.3

EXAMPLE OF AN ADVERSE OUTCOME PATHWAY (AOP)



AO: adverse outcome; **KE:** key event; **MIE:** molecular initiating event.
The example AOP initiated by aromatase inhibition leading to reproductive dysfunction in fish (AOP 25 in the AOP-Wiki) is the first endocrine disruption AOP that has been endorsed by the OECD (Villeneuve, 2016) as an example of an AOP linking a molecular initiating event through a sequence of key events to an adverse outcome. Arrows represent key event relationships containing the empirical evidence and biological plausibility of the causal linkages between pairs of key events.

the molecular initiating event), and establishing a plausible link between the endocrine activity and the adverse effect (intermediate key events and key event relationships). AOPs enable a comprehensive, structured and formalized assembly of evidence; facilitate the identification of relevant assays; and inform the development of testing strategies that align with specific frameworks such as the "3R" principles for use of animals in testing (replacement, reduction and refinement). Thus, AOPs provide a structured way to understand and organize available evidence to inform hazard assessment but they do not themselves constitute experimental methods, testing strategies or risk assessments.

AOP-Wiki (access at aopwiki.org) is an open-access, community-driven resource where scientists collaboratively develop and document and review AOPs. Development of AOPs for EDCs has been very active, with over 100 currently available AOPs in AOP-Wiki at different stages of development, including multiple OECD-endorsed AOPs. Examples include the following.

- **Estrogen receptor agonists and antagonists.** AOPs currently under review include (a) estrogen receptor antagonism leading to reproductive dysfunction (AOP 30) via reduced vitellogenin synthesis in fish; and (b) activation of uterine estrogen receptor-alpha leading to endometrial adenocarcinoma in mammals (AOP 503). Additional AOPs are under development in this area, mostly focused on impaired reproduction in mammals and oviparous species as well as hormone-sensitive carcinomas in mammals.

- **Androgen receptor agonists and antagonists.** There are two endorsed AOPs linking androgen receptor agonism to reproductive dysfunction (AOP 23) in repeat-spawning fish (Villeneuve 2018), and to male-biased sex ratio (AOP 376), also in fish (Ankley *et al*. 2023; Villeneuve 2023). More have been developed and are in the process towards OECD endorsement, addressing outcomes such as impaired fertility, altered anogenital distance (Svingen *et al*. 2025), nipple retention (Holmer *et al*. 2025) and hypospadias (Elmelund *et al*. 2026).

- **Thyroid hormone system disruption.** There are seven endorsed AOPs, of which two (AOP 42, AOP 54) link reduced thyroid hormone synthesis to impaired cognitive function (Crofton *et al*. 2019), memory and

learning (Rolaki *et al*. 2019) in mammals. Five (AOPs 155–159) link reduced thyroid hormone synthesis and activation to impaired swim bladder inflation in fish (Vergauwen *et al*. 2022a, b, c, d, e). Others are under development (Gölz *et al*. 2022), mostly focused on impaired neuro(sensory) development, thyroid carcinoma (in rodents) and altered metamorphosis (in amphibians).

- **Steroidogenesis.** There are two endorsed AOPs (AOP 25, AOP 346) focused on aromatase inhibition leading to reproductive dysfunction (Conolly *et al*. 2017; Villeneuve 2016) and male-biased sex ratio (Ankley *et al*. 2023; Santana Rodriguez *et al*. 2023) via reduced estrogen synthesis in fish. Other AOPs under review describe aromatase inhibition leading to impaired fertility in adult female rodents, and PPARα activation in utero leading to impaired fertility in male rodents via reduced testosterone synthesis.

Efforts to develop AOPs related to non-estrogen, androgen, thyroid and steroidogenic modalities, including the involvement of different nuclear receptors (for example, PPAR, liver X receptor, pregnane X receptor, estrogen related receptor) in liver steatosis, obesity and diabetes, have been gaining traction. AOPs describing adverse outcomes resulting from the disruption of other non-estrogen, androgen, thyroid and steroidogenic pathways, such as retinoic acid signalling and glucocorticoid receptor interaction, are also under development.

3.4.3 Hazard identification and hazard assessment

Several guidance documents describe how to perform hazard identification for the endocrine-disrupting properties of chemicals. Within the European Union, guidance has been developed for biocidal products and plant protection products following the scientific criteria outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605, respectively (ECHA and EFSA 2018). Comparable frameworks exist in other jurisdictions, including the United States EPA Endocrine Disruptor Screening Program and OECD guidance on EDC assessment. Guidance has also been developed for how chemical manufacturers should report relevant information to regulatory authorities (OECD 2017), as well as for how different lines of evidence, including mechanistic data, in vivo studies, wildlife data, and human epidemiological data, can be assembled for hazard assessment.

Once assembled, the available evidence is integrated to evaluate endocrine activity, adversity, and the plausible biological link between the two – the three criteria that support identification of an EDC. Additional information, such as data on systemic general toxicity or other target organ effects, may be used to help contextualize whether an observed adverse effect is plausibly linked to endocrine activity. The integrated assessment then allows an evaluation of whether the available dataset is sufficient to support a conclusion on each of these criteria.

In practice, the data available are rarely complete, and regulatory decisions must be made with the evidence at hand. This challenge is particularly relevant for EDC assessment given the large number of chemicals in commerce for which few or no endocrine-relevant data exist. For this reason, approaches such as grouping of substances and read-across are frequently used to fill data gaps – using relevant information from structurally or mechanistically related "source" substances to predict the properties of "target" substances for which data are lacking. When applied appropriately, these approaches can reduce the need for additional experimental testing. However, read-across assessment is technically demanding, and its application to human health and ecotoxicological endpoints requires justification and efforts to ensure that grouping and read-across assessments are consistent, transparent and scientifically backed (ECHA 2017).

Strategies for integrating evidence streams

The OECD testing and guidance documents explain how to interpret and integrate findings from across different streams of evidence, including mechanistic data, data from laboratory animals demonstrating adversity, observational wildlife studies, and epidemiology data, to draw

conclusions about the hazard and risk of EDCs (ECHA and EFSA 2018; OECD 2018b). There is also a need to integrate data collected using test guidelines with evidence from studies that do not follow standardized approaches, including state-of-the-art hypothesis-driven research typically conducted in academic laboratories.

One of the most influential frameworks for integrating evidence from multiple streams is that developed by the International Agency for Research on Cancer, where evidence from animals, evidence of cancer risk in humans and mechanistic data are each evaluated as independent streams and then integrated, allowing chemicals to be classified as carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), possibly carcinogenic to humans (Group 2B), or not classifiable (Group 3) (IARC 2019). A similar multistream integration approach, the Systematic Review and Integrated Assessment (SYRINA) framework (Vandenberg *et al.* 2016), has been recommended for EDC assessments combining evidence for (a) an endocrine mode of action; (b) adverse effects; and (c) a plausible biological link between the two (Kassotis *et al.* 2020b). While several structured frameworks for systematic review and evidence integration have been developed for environmental health assessment, including the approach of the Office of Health Assessment and Translation of the United States National Toxicology Program (NTP 2019) and the Navigation Guide developed by the Program on Reproductive Health and the Environment of the University of California (Woodruff and Sutton 2014), SYRINA was specifically designed around the WHO/IPCS definition of an EDC.

OECD Guidance Document 150 (section B5) (OECD 2018b) provides guidance on using SYRINA as well as other approaches to evidence integration (OECD 2018a). In general, such approaches involve three steps: assembling the relevant evidence (typically using systematic review methods), weighing the evidence, and integrating the evidence. These steps account for both the relevance and reliability of the available data. Relevance refers to the appropriateness of data for the intended purpose of the assessment, while reliability is defined as "the inherent quality of a test report or publication relating to the preferably standardized methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings" (ECHA and EFSA 2018).

It is common in regulatory practice for evidence from standardized methods to be prioritized over evidence from non-guideline studies when interpreting the available data. This prioritization in part motivated the design of a major study in the United States on the EDC BPA, a chemical with well-documented endocrine activity and one of the most extensively studied substances in the EDC literature. The Consortium Linking Academic and Regulatory Insights on Bisphenol-A Toxicity (CLARITY-BPA) incorporated a large core study using a modified version of the extended one-generation reproductive toxicity test guideline, alongside a series of hypothesis-driven studies of organ-specific outcomes based on findings from prior academic research (Schug *et al.* 2013). The overarching goal of CLARITY-BPA was to determine whether the endpoints evaluated according to the test guideline were as sensitive as those evaluated in qualified academic laboratories. Integrated analyses of the guideline and academic laboratory components concluded that non-guideline endpoints provided evidence for an endocrine mode of action and adverse effects at substantially lower doses than those at which effects were detected using the extended one-generation test guideline endpoints (Heindel *et al.* 2020; Howdeshell *et al.* 2023). These analyses also demonstrated consistency between CLARITY-BPA findings and those of prior independent academic studies of BPA. The findings contributed to EFSA's 2023 comprehensive re-evaluation of BPA, which drew on a systematic review of all available evidence, including both guideline and non-guideline studies, and resulted in a substantially lower tolerable daily intake. This outcome reflects an ongoing scientific and regulatory debate about the appropriate weight to assign guideline versus non-guideline studies in hazard and risk assessment, a debate that has not yet been resolved consistently across regulatory jurisdictions. The CLARITY-BPA study provides an example of how guideline and non-guideline

evidence can be evaluated together within an integrated assessment to identify EDCs and more comprehensively characterize their adverse effects.

Integrated approaches to testing and assessment

Integrated approaches to testing and assessment are a weight-of-evidence method used during hazard and risk characterization, and to guide the generation of new data (OECD 2017). The use of integrated approaches to testing and assessment is appropriate when various kinds of evidence relevant to chemical hazards (for example, results from test guidelines, new approach methods and computational modelling) as well as other kinds of evidence (for example, biomonitoring data, production volumes and physiologically based toxicokinetic models) need to be combined to arrive at a conclusion on the toxicity of chemicals.

In general, an integrated approach to testing and assessment requires a degree of expert judgement for selecting information sources and applying a weight-of-evidence assessment, and the approach may depend to some extent on the nature and level of existing information. Building integrated approaches to testing and assessment is also an iterative process, allowing a decision maker to determine where more evidence is needed and guiding future testing around those needs.

3.4.4 Improving trust via use of systematic reviews and risk of bias tools

Systematic reviews use transparent and consistent methods to gather and evaluate all available evidence and reduce the potential for bias and error in evidence synthesis (Woodruff and Sutton 2010; Woodruff and Sutton 2011). Systematic reviews emphasize the identification of and reliance on studies with better design, conduct and reporting of results, which increases confidence in the resulting conclusions. Systematic review methods relevant to environmental exposure, including EDCs, have been developed more recently than in the clinical sciences, where they have been widely used for several decades to inform health care decision-making (Fox and Bero 2014). Systematic reviews improve upon risk assessment approaches that rely on a single study or a limited number of studies to inform conclusions (Beronius *et al.* 2014a; Krauth *et al.* 2013; Myers *et al.* 2009; Zoeller and Vandenberg 2015). Those non-systematic approaches use expert elicitation to identify and evaluate studies in ways that have been shown to be less transparent and more difficult to reproduce consistently across assessments, which may contribute to differences in assessment outcomes and potentially greater susceptibility to bias (Chartres *et al.* 2019; Mallor *et al.* 2008; Slovic *et al.* 1997).

While systematic reviews represent a more structured evidence identification approach compared to non-systematic approaches, they are not without limitations. The conclusions of a systematic review are constrained by the quality and completeness of the underlying literature; further, search strategy decisions, reviewer subjectivity in bias assessments and the affiliations of review authors can all introduce bias into the review process itself (Hartling *et al.* 2013; Lundh *et al.* 2018). The key feature of systematic reviews is application of a framework for documenting and evaluating potential sources of bias in a transparent and reproducible manner.

Best practices for systematic review have been established and recommended by the United States of America National Academies of Sciences, Engineering, and Medicine (Institute of Medicine 2017). Methods and analytical tools available to conduct systematic reviews for EDCs and other environmental agents that adhere to this rigorous approach include those described by the following entities:

- University of California, San Francisco, Navigation Guide (Woodruff and Sutton 2010; Woodruff and Sutton 2011)
- International Agency for Research on Cancer (Samet *et al*. 2020)
- SYRINA (Vandenberg *et al*. 2016)
- Office of Health Assessment and Translation of the United States National Toxicology Program (Rooney *et al*. 2016).

Risk of bias

Systematic reviews involve the use of tools to assess the risk of bias, or internal validity, of each study's design, conduct and reporting of results. Bias can also be introduced through non-methodological factors, such as sponsorship by industry or other interested parties, or financial conflicts of interest among study authors (Bero 2013; Chartres *et al.* 2020; Lundh *et al.* 2018; Savovic *et al.* 2012). Bias (or the risk of such bias) can lead to systematic error that may underestimate or overestimate the true study effect and alter conclusions (Eick *et al.* 2020). When the studies included in an assessment carry many sources of potential bias, confidence in the body of evidence will be lower than when fewer sources are present.

For many years, regulatory agencies and organizations used the Klimisch method (Klimisch *et al.* 1997), assigning higher reliability scores to studies conducted according to standardized test guidelines and in accordance with good laboratory practices. This approach has been increasingly criticized as inappropriate because there is no empirical evidence that studies compliant with good laboratory practices have a lower risk of bias, and giving priority to studies conducted according to standardized test guidelines is similarly problematic (Agerstrand *et al.* 2011; Beronius *et al.* 2014a; Beronius *et al.* 2013; Beronius *et al.* 2014b; Kortenkamp *et al.* 2012; Krauth *et al.* 2013; Zoeller *et al.* 2012).

There are common categories of bias that should be considered systematically across any evidence stream (box 3.2). The elements assessed for risk of bias in human experimental studies have been empirically developed and applied for several decades in clinical science (Page *et al.* 2016). One element that is not consistently assessed is financial conflict of interest. Empirical studies show that studies conducted by authors with a financial conflict of interest are more likely to report results favourable to the product being tested, even when those studies are of equal or lower risk of bias according to other assessed elements (Chartres *et al.* 2020; Lundh *et al.* 2018; Mandrioli *et al.* 2016). To account for this bias, financial conflict of interest should be part of the risk of bias assessment of individual studies (Chartres *et al.* 2026).

Box 3.2 Categories of bias influencing internal validity of studies

Categories of bias influencing the internal validity of studies include the following.

- **Selection bias.** Systematic difference in baseline characteristics between two groups, for example, selection of study participants with different age characteristics or health status.
- **Performance bias.** Systematic difference in treatment (aside from intervention) of two groups, for example, participants or personnel who are aware they are not receiving the intervention may seek other treatments.
- **Detection bias.** Systematic difference in how outcomes are assessed between two groups, for example, if the researcher is aware of which group is the treatment group (lack of blinding), the outcome may be assessed with bias; this is sometimes also called surveillance bias, which occurs when one group of participants is evaluated or followed more closely for an outcome compared to another group.
- **Attrition bias.** Systematic difference in loss to follow-up (or study withdrawal) between the two groups.
- **Reporting bias.** Systematic difference between reported and unreported findings, for example, selectively only reporting positive results of an analysis.
- **Funding bias.** Systematic difference in the direction of results and effect sizes, for example, industry-sponsored studies report more favourable results on the product under evaluation compared to studies with other or no sponsorship.

Subject matter expertise is required to evaluate each risk of bias element appropriately. Experts should therefore be consulted based on the specific Population, Exposure, Comparator, Outcome (PECO) statement being evaluated. Some risk of bias approaches assign an overall study rating, typically by scoring or weighting individual study elements. This approach has been the subject of criticism because it can result in the removal of studies from an analysis based on a single high-risk element, even when those studies contain important information (Eick *et al*. 2020), which may influence the conclusions of an assessment. Instead, an approach to conduct analyses that stratifies studies by extent of bias to assess the influence on overall outcomes, for example through meta-analysis, has been reported as best practice by the National Academies of Sciences, Engineering, and Medicine (National Academies of Sciences, Engineering, and Medicine 2021).

Review of reviews

When evaluating data-rich cases, a systematic review of existing systematic reviews may be conducted. Such a "review of reviews" approach requires a systematic search strategy comparable to that used in a primary systematic review, along with a selection strategy that reinforces inclusion and exclusion criteria, an assessment of the quality of the reviews, and a clear reporting approach. Tools available to assess the quality of systematic reviews include AMSTAR (Shea *et al*. 2009).

3.5 Key considerations for interpreting testing and assessment results

3.5.1 Hazard versus risk

Hazard identification focuses on systematically identifying properties that are intrinsic to chemicals or to mixtures. Endocrine disruption is one such hazard. Test guidelines and other approaches, including new approach methods and hypothesis-driven approaches, can be used to build evidence of a hazard.

Hazard identification is typically the first step in risk assessment. In the second step, hazard characterization (or dose–response), the goal is to *quantitatively* characterize the relationship between chemical exposure and adverse effects, that is, to quantify the probability of an adverse effect at a specific level of exposure. The third step in a risk assessment – exposure assessment – works to characterize an exposure and determine whether individuals are likely to be exposed at a level where an adverse effect is likely to occur.

The WHO/IPCS definition of an EDC is focused on hazard; having endocrine-disrupting features is an intrinsic property of the chemical that may or may not represent a risk. The definition does not address the relevance of the perceived dose at which the adverse effects are observed. In other words, an EDC is an EDC, even if no one is exposed to it. Yet many legislative approaches to address EDCs use risk-based rather than hazard-based approaches (Kassotis *et al*. 2020a). In the European Union, for example, chemicals with endocrine-disrupting properties that are regulated under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation can be authorized for use if the risk to human health or the environment can be deemed to be adequately controlled (by limiting exposures).

3.5.2 Thresholds

In principle, risk assessment provides a structured framework for evaluating the conditions under which human populations and wildlife may be exposed to toxic chemicals in ways that avoid their harmful effects (Abt *et al*. 2010). A foundational assumption of this framework is that a threshold of exposure exists below which no adverse effects will occur, referred to here as a "threshold of adversity" (Brescia 2020). However, there are multiple types of thresholds – a biological threshold, an experimental threshold, or a mathematical threshold (Slob 1999). The question is whether experimental or mathematical thresholds can accurately predict the "true" (biological) threshold, if one exists (Joint Research Centre 2013).

At the population level, a universal threshold of adversity cannot be established even where individual-level thresholds may exist. This is

because susceptibility to chemical exposure varies considerably across individuals and population groups, depending on factors such as genetic variation, life stage, sex, nutritional status and the presence of underlying health conditions (Buck-Louis *et al*. 2006). Because these factors shift individual dose–response relationships, any given exposure level may be without effect in most individuals while remaining harmful to more susceptible groups (Zeise *et al*. 2013). Furthermore, populations are rarely exposed to single chemicals in isolation; simultaneous exposure to multiple chemicals may further complicate the concept of a single-chemical population threshold (Kortenkamp 2008).

In toxicological studies, an observed "no effect" finding may reflect limitations in study design rather than a true absence of effect (Scholze and Kortenkamp 2007). These constraints apply regardless of whether a study follows standardized test guidelines or not. In epidemiological studies, a study is only capable of detecting an effect when it is large enough to be distinguished from chance variation (typically using a conventional significance threshold of $P \leq 0.05$). Effects occurring at lower exposure levels or in smaller, more susceptible subgroups may go undetected because the study lacks sufficient statistical power to identify them (Scholze and Kortenkamp 2007).

To manage the uncertainties inherent in deriving safe exposure levels from toxicological data, risk assessors apply uncertainty factors to health-based guidance values such as the tolerable daily intake. The conventional approach applies a 10-fold factor to account for extrapolation from animals to humans (interspecies variability) and a further 10-fold factor to account for variation in sensitivity within the human population (intraspecies variability) (Johanson *et al*. 2023). Additional factors may also be applied. The intent is to ensure that the resulting guidance value falls comfortably below any plausible biological threshold of adversity, including for sensitive subpopulations. However, uncertainty factors are designed to address a defined and relatively narrow set of uncertainties under the assumption of a monotonic dose–response relationship. Uncertainty factors are generally intended to address specific sources of uncertainty and are not expected to fully account for all endpoints, modes of action or dose–response patterns. This is particularly relevant for chemicals with endocrine-disrupting properties, where non-monotonic dose–response relationships are observed (Vandenberg *et al*. 2012), and where the endpoints of greatest concern, such as immune, neurodevelopmental, and metabolic effects, may not be captured in conventional regulatory tests. Interpretation of risk assessment outputs also may not fully account for the range of susceptibility present across diverse human populations, the complexity of real-world mixture exposures or the full scope of toxicological effects relevant to human health.

3.5.3 Potency

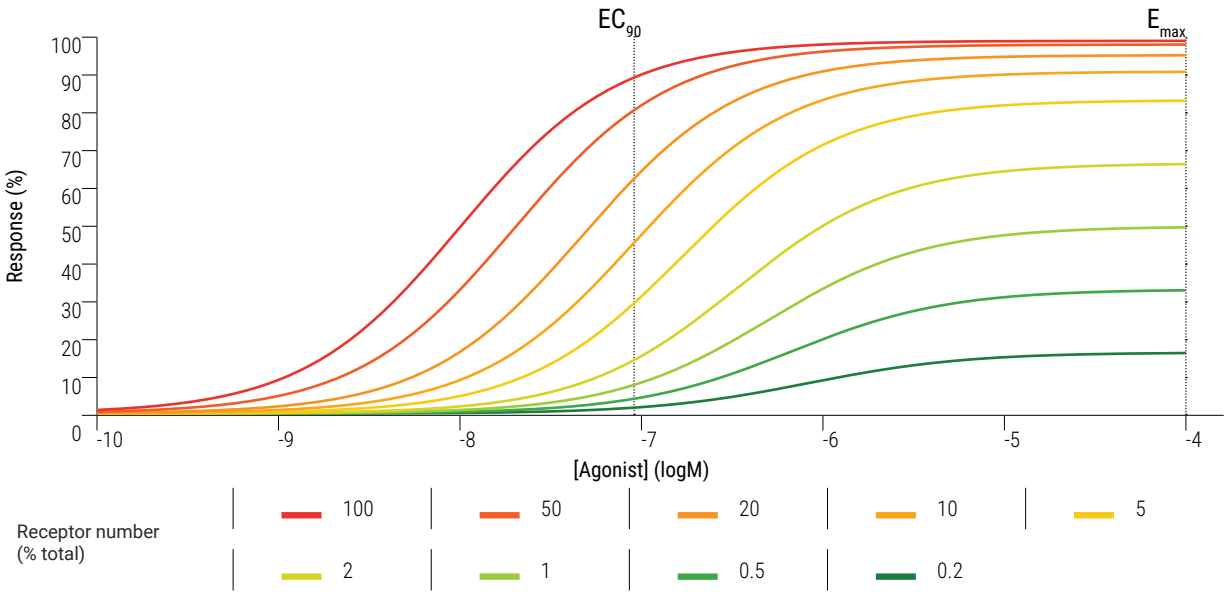
Interpreting the term "potency" can be challenging in the context of EDCs: if a chemical is "potent", it will produce harm at a lower exposure level than a chemical with lower potency. But the physiological control of tissue sensitivity to hormones makes this concept much more complicated in the context of EDCs. There are several important features of hormone action that make potency a complicated issue.

A. Hormones act on receptors

The ability of a hormone to have an effect depends not only on the hormone concentration, but also on receptor abundance (which reflects receptor concentration in cells or tissues) (figure 3.4). Therefore, the same hormone concentration can have a different magnitude of effect in two different tissues or at two different life stages, depending on receptor abundance. Up to the point at which downstream signalling capacity becomes limiting, increasing receptor concentration increases the maximal response to an agonist and, at a single level of response, can reduce the concentration of agonist required to achieve that response by many orders of magnitude (Charlton 2009). This can explain why one tissue, life stage or sex can be more sensitive to endocrine disruption than others.

FIGURE 3.4

THE RELATIONSHIP BETWEEN HORMONE CONCENTRATION, RECEPTOR CONCENTRATION, AND BIOLOGICAL RESPONSE



The dose-response relationship for a hormone depends on receptor concentration. As receptor number rises, the hormone behaves as though it were more potent: markedly less hormone is required to elicit an equivalent response. Note also that when receptor levels are low, the maximal attainable response falls short of the EC50 response seen at high receptor levels.
Source: Adapted from Charlton (2009)

B. Hormone receptor interactions allow amplification of the signal

Hormone signalling systems have built-in amplification mechanisms. For example, hormones that signal through cyclic adenosine monophosphate (cAMP) produce many cAMP molecules that go on to activate many regulatory molecules inside the cell, generating a response that is disproportionately large relative to the number of hormone receptor binding events (Sassone-Corsi 2012). Thus, even a relatively small perturbation of hormone activity by an EDC can, in principle, produce a disproportionately large downstream effect.

C. Additional mechanisms controlling tissue-specific hormone action

Beyond receptor abundance and signal amplification, additional layers of tissue-specific regulation further complicate the assessment of EDC potency. In the case of the thyroid hormone system, specialized transport proteins selectively transport T4 or T3 across cell membranes (Sharlin *et al*. 2018). The clinical significance of these transporters is demonstrated by the severe and irreversible neurological consequences of their genetic disruption in humans (Novara *et al*. 2017). Additionally, T4 must be converted to the biologically active T3 by deiodinase enzymes (types 1, 2 and 3). Regulation of these enzymes can profoundly affect thyroid hormone action in specific tissues or at specific developmental stages (Köhrle and Frädrich 2022). New assays are being developed to identify chemicals that interfere with these proteins (Reincke *et al*. 2024; Wagenaars *et al*. 2024).

Receptors can exert biological effects even in the absence of ligands. For example, the thyroid hormone receptor in amphibians has a dual

function: without ligand, it heterodimerizes with RXR to repress T3-inducible genes, preventing premature metamorphosis; when T3 levels rise, the heterodimer activates target genes to drive metamorphosis (Fu *et al*. 2018). This unliganded receptor function adds a dimension of complexity that is not captured by standard measures of receptor binding affinity or activation.

Taken together, these features of hormone action demonstrate that measures of binding affinity or receptor activation obtained in controlled in vitro systems cannot always be translated directly to in vivo responses because of biological complexity and associated uncertainties. When appropriately contextualized with toxicokinetic and toxicodynamic information, in vitro data can inform in vivo predictions. However, the relationship between in vitro potency estimates and in vivo adversity thresholds varies across tissues, developmental stages and biological systems, and might not be reliably accommodated by conventional uncertainty factor approaches.

3.5.4 Sex differences

Sex is an important biological characteristic that can impact the phenotype of individuals, as well as their susceptibility to environmental stressors. Hormones drive many of the physiological differences between males and females; this leads to obvious sex differences in the morphology of species, but also their risk of diseases. For example, thyroid cancer is almost three times more prevalent in women compared to men (Kazmi *et al*. 2025). In wildlife, feminization of males has been observed even when adverse effects on female reproductive development are not detected at equivalent exposure levels, illustrating that sex-specific sensitivity to EDCs can vary markedly between the sexes (Vandenberg 2023). For many other conditions (for example, cardiovascular diseases, autoimmune diseases, other cancers, and neurological and psychiatric disorders), the incidence, rate of progression and severity differs between the sexes (Dorak and Karpuzoglu 2012; Ober *et al*. 2008). Consistent with these biological differences, studies have reported sex-specific effects of EDCs (Dias *et al*. 2025). Not only do EDCs affect male and female reproductive outcomes, they also have sex-specific effects on neurobehaviour (Palanza *et al*. 2021), immune responses (Edwards *et al*. 2018) and metabolic disorders (D'Archivio *et al*. 2024; Heindel *et al*. 2017), among others.

In humans, exposure to EDCs is often influenced by sex or gender. For example, data from the United States National Health and Nutrition Examination Survey biomonitoring programme has shown that women are typically exposed to higher levels of parabens and phthalates compared to males (Hassan *et al*. 2024), and evidence from the national biomonitoring programme of the Republic of Korea has shown similar trends, even when controlling for occupation (Kim *et al*. 2023). Sex-biased exposures have also been documented for many EDCs that are persistent organic pollutants, where most exposures are anticipated to occur via food consumption (Dutta *et al*. 2023).

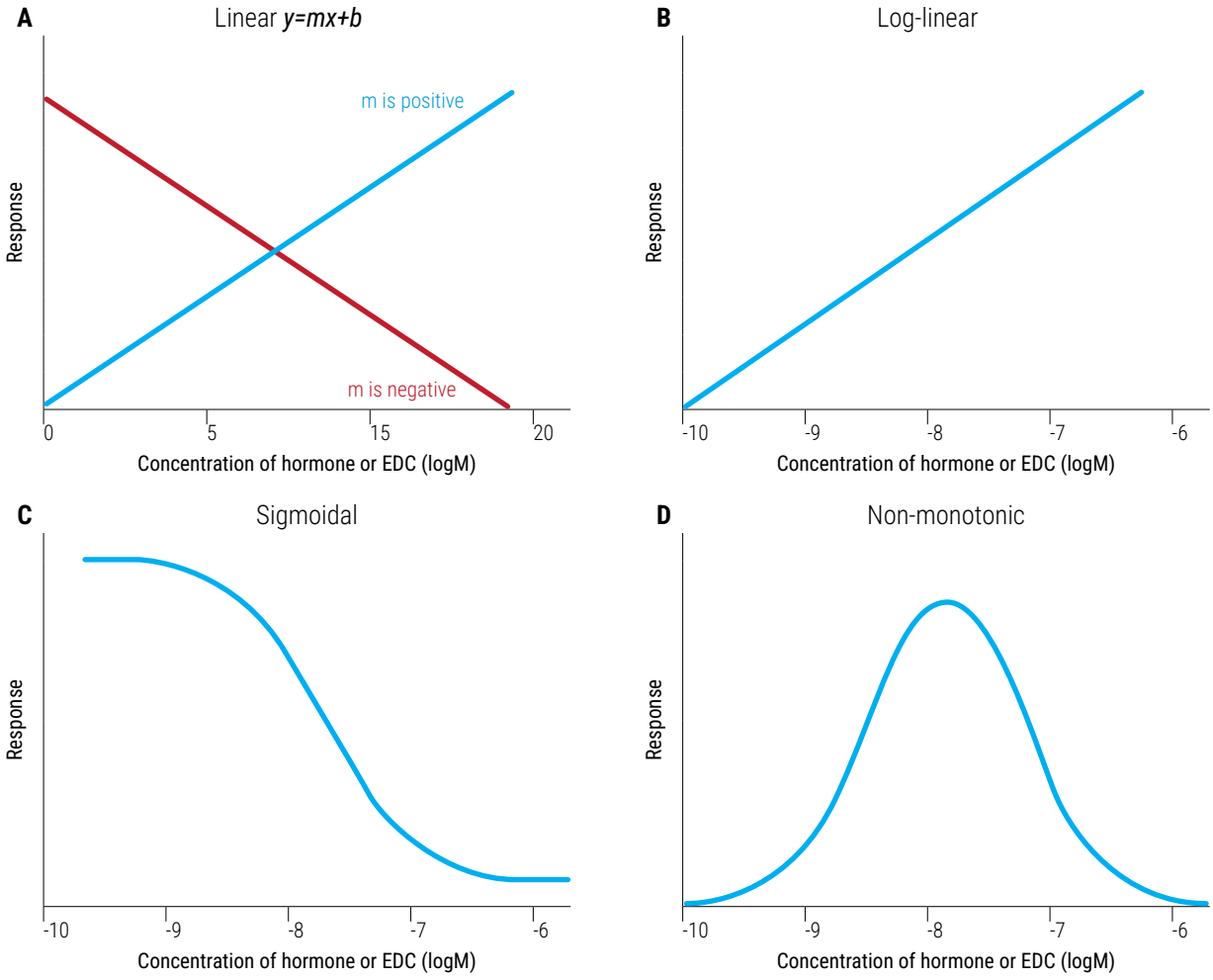
Sex is a biological variable that should be considered when designing new approaches to test chemicals for endocrine-disrupting properties to evaluate the results of toxicity testing, and when conducting hazard or risk assessments. Regulatory approaches that consider an outcome as an adverse effect only if it is observed in both sexes fails to acknowledge the many sex-specific effects of hormones on physiological responses (Vandenberg *et al*. 2023).

3.5.5 Dose–response

Hazard characterization (that is, dose–response assessment) is the second step of a risk assessment. A dose–response curve can be generated when multiple doses (or concentrations) are examined for the same endpoint (Vandenberg and Bowler 2014). The quality of the dose–response curve (that is, its ability to accurately predict the effects at doses that are not directly evaluated) is directly related to the number of doses examined; the fewer the number of doses evaluated, the lower the confidence in the characterization of the shape of the dose–response curve. The quality of the curve is also related to the range of doses examined.

FIGURE 3.5

EXAMPLES OF DOSE–RESPONSE CURVES



Curves are typically described based on mathematical terms or features, as follows.

- Linear dose–responses (figure 3.5A) are those where a biological response or effect increases or decreases at a constant rate over the range of doses tested. Although often observed over a short range of doses, they are infrequently observed when a sufficiently large number of doses are examined.

- Log-linear dose–responses (figure 3.5B) are those where a biological response or effect increases or decreases at a constant rate over log increases in the doses administered. These are unexpected over a wide range of doses.

- Sigmoidal dose–response curves (figure 3.5C) contain a linear component in the middle of the dose range that is examined, but feature a more modest increase or decrease in response at the lower and higher ends of the dose range.

Each of the three curves described above are examples of monotonic dose–responses, that is, curves that are defined mathematically by having a slope (or multiple slopes) where the sign of the slope (positive or negative) does not change over the range of the doses examined.

Non-monotonic dose–responses (figure 3.5D) are therefore defined as curves where the sign of the slope changes over the range of doses tested (from positive to negative, or vice versa).

Identification of non-monotonic dose–response patterns is generally facilitated by the inclusion of multiple dose groups; Lagarde *et al*. (2015) and Vandenberg (2014) explain why at least five dose groups are needed for robust characterization. Inclusion of more than five dose groups will provide better resolution on the shape of the curve. In the absence of five dose groups, responses that are consistent with non-monotonicity can be identified with other criteria (Vandenberg 2014), but these analyses are not definitive. Many in vivo approaches that utilize standard test guidelines do not include sufficient dose groups to characterize the shape of the dose–response curve, and independent academic studies frequently face the same limitation due to cost and animal welfare constraints. The consequence is that non-monotonic dose–response relationships are systematically underdetected across the evidence base as a whole.

The practical significance of this underdetection is most acute when risk assessors extrapolate from short-term, high-dose animal studies to predict long-term, low-dose effects in humans – which is precisely the extrapolation on which regulatory safety levels depend. Non-monotonic dose–response relationships may complicate extrapolation from tested dose ranges to lower exposure levels. A compound may produce no observable effect at high doses tested in a guideline study, while producing an effect at lower doses that were not tested.

3.5.6 Timing and critical windows

In the field of toxicology, hormones are often described based on their role in the adult. For example, adult maintenance of sexual function is dependent on testosterone (Cappola *et al*. 2015; Mullur *et al*. 2014) and follicle-stimulating hormone (Bagatell *et al*. 1994; Grisendi *et al*. 2014) among others. Similarly, hormones produced by the thyroid gland, including T4 and T3, play an important role in the regulation of metabolism, the maintenance of body heat and heart rate, and the balance of the sympathetic and parasympathetic nervous systems in adults (Cappola *et al*. 2015; Mullur *et al*. 2014).

In contrast, a physiologically relevant understanding of hormones acknowledges the role of these same hormones during development (Heindel *et al*. 2015; Heindel and Vandenberg 2015). Thyroid hormone insufficiency during early development, for example, can have consequential adverse effects on brain development (and other outcomes), with different effects depending on when the insufficiency occurs (Rovet 2014; Zoeller and Rovet 2004).

Diethylstilbestrol provides a well-documented example of the impact of developmental exposure to synthetic estrogens during early development. Female fetuses exposed to diethylstilbestrol during gestation through the mother are more likely to have uterine deformities and abnormal fimbriae of the oviduct, which are associated with increased risk of ectopic pregnancy, increased rates of other pregnancy complications and an increased risk of vaginal and breast cancers in adulthood (Newbold 2004; Reed and Fenton 2013). Additional studies have shown that the effects of diethylstilbestrol are transmitted to future generations, consistent with epigenetic alterations (Newbold *et al*. 2006).

The importance of exposure timing is equally evident in wildlife models. In fish, exposure to estrogenic or androgenic chemicals can change phenotypic sex, but this occurs at much lower concentrations when exposures occur during early development than at later developmental stages (Ankley and Johnson 2004). Similarly, thyroid hormone system disruption during development affects eye structures, swim bladder inflation and brain development (Baumann *et al*. 2016; Godfrey *et al*. 2017). These outcomes do not occur if exposures are isolated to later life stages (figure 3.6).

This understanding of the developmental effects of hormones, and those of EDCs when exposures

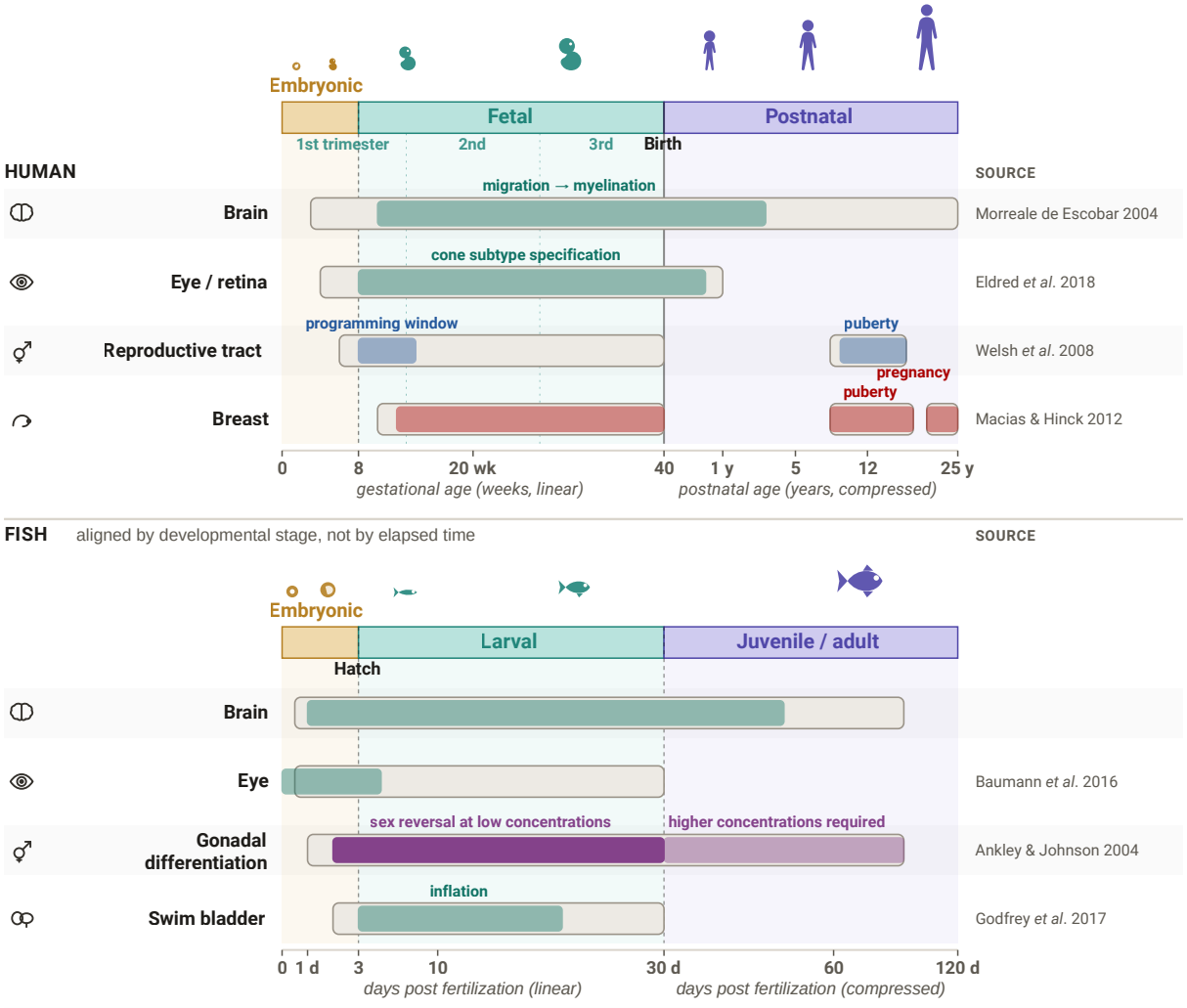
occur during critical windows of development, is important to consider when designing tests to evaluate EDCs. Tests that only evaluate the effects of chemicals in adults are likely to underestimate the number and severity of outcomes affected by EDCs compared to studies that administer exposures during critical windows of development.

Studies identifying these critical windows have largely focused on embryonic and fetal stages (Heindel 2019); however, evidence indicates that some organs, such as the brain and breast, continue to develop later into postnatal life (figure 3.6), and vulnerable windows can extend into adulthood. For example, mice exposed to

FIGURE 3.6

EXAMPLES OF HORMONE-DEPENDENT WINDOWS IN DEVELOPMENT

Pale bar: the organ is being built. Coloured bar: the part for which hormone dependence is documented.



These are examples, not a complete inventory. Rows were selected where three conditions hold: the hormone dependence of the process is documented, the window is defined with reasonable confidence, and the endpoint is recognizable. Systems absent from the figure are not systems without windows. The same exposure produces different outcomes at different times. Human and fish cannot share a time axis and are aligned by developmental stage. Boundaries are indicative rather than precise, varying by endpoint, species and the criteria used to define dependence. Sources are given per row; where a window is bounded by inference rather than direct measurement this is stated in the cited source.

BPA during pregnancy developed a phenotype consistent with type 2 diabetes four months after exposures had ceased (Alonso-Magdalena *et al*. 2010), providing evidence for a vulnerable window that extends into adulthood.

3.5.7 Mixtures

All living systems, including humans, are exposed to complex mixtures of chemicals present in the environment, in food and in consumer products. Yet, with few exceptions, chemical risk assessments consider the effects of single substances in isolation. Evaluation of chemicals individually may not fully account for effects arising from co-exposure to multiple substances.

Single-chemical assessments are appropriate if only one chemical in the mixture is toxic, or if empirical evidence demonstrated that the joint action of chemicals does not exceed the effect of the most toxic compound. However, experimental studies have demonstrated that chemicals that act on a common toxicological pathway produce combination effects that are larger than the effects of each component evaluated singly (Kortenkamp 2007; Silva *et al*. 2002). An increasing number of epidemiological studies have similarly indicated that mixtures pose such risks in human populations (Bornehag *et al*. 2018; Caporale *et al*. 2022).

To characterize the risks of chemical mixtures, approaches can either test the whole mixture or predict the effects of the mixture from information on the concentration, toxicity and mode of action of its individual components (Bopp *et al*. 2019). The small number of whole mixtures that may be practically tested, particularly in vivo, limits the applicability of whole mixture approaches. For this reason, component-based predictive approaches have been developed based on expectations of additivity. Comparison of predictions with the experimentally observed effects of the mixture allows assessment of whether the assumption of additivity is fulfilled and, if so, whether additivity is best described by the dose addition or response addition model (Kortenkamp 2007; Silva *et al*. 2002; Webster 2013).

Deviations from expected additivity are recognized as "toxic interactions"; synergism occurs if the observed toxicity is larger than expected, and antagonism in the case of responses falling short of expectations. In the last 30 years, several reviews have attempted to examine the frequency or magnitude of deviations from additivity (Martin 2023). The most comprehensive systematic effort to date compiled an inventory of 1,220 mixture experiments, of which 557 claimed deviations from additivity were quantitatively reappraised (Martin *et al*. 2021). Synergistic interactions were confirmed in approximately 5% of mixtures investigated in the literature (Martin *et al.* 2021; Martin 2023). Synergistic interactions can be substantial in magnitude, with increases in toxicity of up to 100-fold (Martin *et al.* 2021), and may potentially be more frequently observed with mixtures of EDCs (Elcombe *et al.* 2022; Martin *et al.* 2021).

Several methods to assess risk from chemical mixtures have also been developed. Methods based on response addition models require knowledge of effects that each component would provoke individually at the concentration found in the mixture, and this information is rarely available. As a result, existing mixture risk assessment approaches are invariably derived from the dose addition concept. These include approaches based on hazard index, toxic unit summation, point of departure index, relative potency factor and toxicity equivalency factors (Kortenkamp *et al.* 2011). These methods still require extensive knowledge of the hazard profiles of individual mixture components as well as their co-occurrence.

Scientific limitations for the assessment of mixtures are compounded by the structural design of regulatory systems, which were built to address single substances rather than co-exposure to multiple chemicals regulated under different legislative actions (Evans *et al.* 2016). This raises the question of how mixtures are assessed during risk assessment. In 2020, the European Union recognized the need for approaches that can be implemented to address potential mixture risks in its Chemical



Strategy for Sustainability, and announced the introduction of a mixture assessment factor to be applied during risk assessments under the REACH regulation (Commission 2020). A mixture assessment factor is a factor by which the regulatory safety threshold for an individual compound is divided to ensure the same level of protection against unintended mixture effects as the level of protection for single substances. A recent analysis by the Swedish Chemicals Agency found that a mixture assessment factor value of 20 was sufficient for over 95% of mixtures analysed (Kemikalieinspektionen 2015). The mixture assessment factor differs from other uncertainty factors applied in chemical hazard assessment – for example, those used to account for interspecies and intraspecies variability (Joint Research Centre 2016. Some critics of the mixture assessment factor argue that its use leads to double accounting of other uncertainties (Environment Agency 2022), based on an assumption that the default uncertainty factors represent worst-case scenarios. However, an analysis of the evolution of uncertainty factors revealed that default factors were intended to represent adequate rather than worst-case scenarios (Martin *et al.* 2013).

3.5.8 Beyond chemicals: interactions between EDCs and other stressors

Chemical exposures rarely occur in isolation from other environmental pressures. Living organisms during most of their lifetime cope with environmental conditions deviating from those used in experimental settings. In humans, exposure to stressors beyond chemicals are the norm, particularly in communities facing disproportionate environmental burdens. This point is particularly salient when considering the function of the endocrine system – that is, to regulate growth and development and most physiological responses, including responses to environmental signals (Little and Seebacher 2024). Human populations are already affected by climate change (for example, heat and extreme weather events), light and noise pollution, changes to food and water supplies, poverty, and migration (Stewart *et al.* 2021). Exposure to these stressors occurs in addition to chemical pollution, although there is some intersectionality (for example, populations with higher exposure to some chemical emissions are more likely to also experience poverty). Many non-chemical stressors are also known to affect endocrine

systems; for example, both EDCs and ambient temperatures are associated with thyroid hormone system disruptions (Stewart *et al.* 2021). Similarly, estrogenic pollutants, access to nutrition and stress have all been observed to influence pubertal timing (Parent *et al.* 2015). Studies have reported that the interactions between chemical pollutants and other stressors may be synergistic (Holmstrup *et al.* 2010). Taken together, these observations suggest that consideration of non-chemical stressors, in addition to chemical mixtures, may be needed for a more comprehensive understanding of the cumulative impacts of EDCs on health and ecological systems.

3.6 Summary and key messages

The testing and assessment of chemical substances for endocrine-disrupting properties has been an area of scientific and regulatory development for nearly three decades. During this period, test guidelines and guidance documents have been updated to reflect advances in understanding of the mechanisms through which chemicals can interact with endocrine systems, as well as the physiological roles of hormones in humans and wildlife. These developments have been accompanied by research aimed at identifying endocrine-relevant endpoints suitable for regulatory testing, characterizing mechanisms of hormone action and endocrine disruption, and improving the identification of biological events linking endocrine activity to adverse outcomes. This chapter concludes with the following key messages.

1. **A plausible link between adverse effects and an endocrine mode of action can be established without testing a specific chemical.** The adoption of the WHO/IPCS definition of an EDC means that identification of chemicals for EDC hazard requires three elements: (a) association with adverse effects; (b) an endocrine mode of action; and (c) a plausible link between the first two. Importantly, the evidence for this third feature can be assembled without testing on any specific chemical.

2. **EDCs are regulated across multiple jurisdictions using a range of testing and assessment frameworks.** International efforts have sought to increase harmonization of testing approaches and regulatory assessments. Discussions are ongoing regarding the inclusion of endocrine disruption as a hazard class within the Globally Harmonized System of Classification and Labelling of Chemicals. A 2025 OECD working group report concluded that a gap exists in the current Globally Harmonized System framework, which does not provide a mechanism to identify a chemical as an EDC in accordance with the WHO/IPCS definition. This discussion has significant implications for regulatory systems, including European Union Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation), which has incorporated endocrine-disrupting hazard classes that could be affected by decisions taken at the Globally Harmonized System level.

3. **Integrating human, animal and environmental evidence through a One Health approach can strengthen the identification and assessment of EDCs.** Currently, there are a number of test guidelines (OECD 2018b); see table 3.1.) that can be used to identify EDCs that act within the context of estrogen, androgen, thyroid and steroidogenic modalities: counting across the five levels of the OECD conceptual framework for the testing and assessment of EDCs, more than 30 test guidelines can evaluate whether a test chemical acts through an estrogen, androgen, thyroid or steroidogenic endocrine mode of action, but relatively few include endpoints relevant to endocrine-mediated adverse effects (Grignard *et al*. 2021; Kortenkamp *et al*. 2011). Furthermore, although testing has historically been divided between human health and environmental endpoints, the conservation of endocrine system function across vertebrate classes means that data generated across species could be more effectively integrated. Approaches such as the One Health framework and



cross-species extrapolation tools – for example, Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) – offer opportunities to bridge this divide.

4. **Despite advances in the knowledge of hormone systems and EDCs modes of action, current testing approaches do not capture all health outcomes associated with EDC exposure**. For example, developmental events (especially in the brain) continue to be poorly covered by assays (either in vivo or in vitro). Several reviews have identified limitations in currently available in vivo tests for detecting endocrine-mediated outcomes. Efforts are ongoing to address these gaps; for example, an in vitro battery for developmental neurotoxicity testing is currently being developed and validated, representing a significant step towards improving coverage of neurological endpoints in EDC assessment.

5. **Testing for ecosystem-level outcomes remains very limited, and the consequences of EDC exposure at the ecosystem level are poorly understood.** Most of the validated tests that are available to identify EDCs focus on human health (even when using laboratory animals). While a number of vertebrate wildlife tests exist within the OECD conceptual framework (including the amphibian metamorphosis assay, the fish sexual development test, and higher-tier tests such as the larval amphibian growth and development assay and the medaka extended one generation test used in the United States Endocrine Disruptor Screening Program), these are implemented in regulation in only a small number of jurisdictions. For invertebrates, only the arthropod metamorphosis assay is specific to endocrine disruption.

6. **Evidence can be collected from approaches that do not follow standardized or validated test guidelines.** Epidemiology studies, for example, never utilize test guidelines and yet are an important source of evidence for decision-making and the protection of public health, if and when such data are available. New approach methodologies have received considerable attention, particularly as regulatory and scientific agencies seek to reduce reliance on laboratory animal data. New approach methods are not designed as direct one-to-one replacements for animal tests; rather, they are intended to be used in combination with each other and with existing methods within integrated testing strategies. At present, available new approach methods are limited in number, and are used in combination with other sources of evidence. These have limitations for evaluating endocrine-mediated adverse effects. However, as more complex new approach methods continue to be developed and validated, their capacity to identify EDCs continues to be evaluated.

7. **Integrating evidence collected from across evidence streams (for example, in silico, in vitro, in vivo) is a central component for decision makers.** It is also critical that all evidence is included in these assessments. Systematic review methodologies that account for risk of bias are widely used frameworks for evidence identification, evaluation and integration.

8. **To date, the number of OECD-endorsed endocrine-related AOPs remains limited, which may influence the extent of their application in regulatory contexts.** There are numerous approaches that can

be used to organize and assess evidence, including the key characteristics approach, the AOP approach, and the use of integrated approaches to testing and assessment. These approaches are especially useful in determining whether a chemical acts via an endocrine mode of action, and the AOP and integrated approaches to testing and assessment can be used to evaluate whether a chemical induces adverse effects. Contributing factors include the significant time and resource investment required to develop AOPs, as well as historically limited recognition of AOP work as a publishable scientific contribution, though this has improved as AOP-focused publications are now accepted in peer-reviewed journals.

9. **There are numerous other issues that are relevant to EDCs that also impact the development and interpretation of EDC tests and testing approaches.** These issues challenge risk assessment of EDCs and call for extra caution, such as additional uncertainty factors. These include the following.

    - The existence and characterization of thresholds of adversity continue to be debated in toxicological and risk assessment literature as they cannot be experimentally demonstrated.

    - Binding affinity for an EDC is not a prediction of its potency.

    - EDCs do not have a single measure of potency, because a chemical's potency depends on the whole organism context.

    - The difference between hazard and risk is also critical for the design of EDC tests; hazard identification is key to identifying intrinsic properties of chemicals (such as whether a chemical is an EDC), but many jurisdictions use risk-based approaches, which consider the dose at which effects are observed and ask whether exposures can be adequately controlled. Application of risk-based approaches to EDCs has been the subject of scientific discussion, including with respect to non-monotonic dose–response relationships, which make testing and the extrapolation from tests to health protection strategies very challenging.

    - Testing must also account for the critical role that hormones play during development and must acknowledge that tests focusing on adult functions of hormones will not capture many effects associated with exposure during developmental periods.

    - Newer approaches are shedding light on how chemicals act within mixtures, and the need to account for the presence of mixtures in the real-world setting when considering the hazard and risk of EDC exposure has led some jurisdictions to propose to utilize mixture assessment factors in the risk assessment process.

10. **Human and wildlife exposures to EDCs have occurred in part because of testing and assessment strategies that failed to account for the specificities of EDCs.** However, significant improvements have occurred since the 2012 assessment.

3.7 Key implications

3.7.1 Scientific limitations of current testing methods

Current standardized testing methods do not address all endocrine-related mechanisms or health outcomes described in the scientific literature. While new approach methodologies may contribute to reducing reliance on animal testing, primarily in combination with other sources of evidence, at this time they cannot be implemented as replacements for in vivo testing in regulatory frameworks. The endpoints included in standardized test systems are concentrated largely on estrogen, androgen, thyroid and steroidogenic-mediated pathways; coverage of other endocrine-related outcomes is incomplete. In addition, some validated tests

require substantial time and resources, limiting the number of chemicals that can be assessed. For many chemicals currently in commerce, relevant testing data are limited or unavailable. As a result, the absence of data should not be interpreted as evidence of the absence of endocrine-disrupting properties.

3.7.2 Gaps in regulatory testing programmes

Testing programmes administered by organizations and government agencies, including the European Union, OECD, and United States EPA, provide frameworks for the evaluation of chemicals for endocrine-disrupting properties. Regulatory requirements and assessment approaches vary across jurisdictions, as do the endocrine-mediated endpoints included in testing and assessment frameworks. Scientific literature has identified additional endocrine-related mechanisms and health outcomes that are not fully represented in all current regulatory testing programmes. Ongoing activities in a number of jurisdictions aim to update testing approaches and incorporate advances in endocrine science into regulatory assessment frameworks.

3.7.3 Role of human and wildlife population data

Associations between EDC exposures and adverse health outcomes have been identified in human and wildlife population studies (see chapter 2). The availability of these data indicates that approaches to identify or control exposure to EDCs have been insufficient. Where human or wildlife data are available, they should be integrated into hazard and risk evaluations; several European Union regulatory frameworks require consideration of such evidence in assessments.

3.7.4 Strengthening the use of academic and independent research

Formal hazard and risk evaluations draw on evidence generated through standardized test guidelines. Academic and independent research studies can provide additional information relevant to hazard and risk assessment. Guidance and tools have been developed to facilitate the evaluation and use of such data in regulatory contexts, including the Science in Risk Assessment and Policy (SciRAP) platform (Beronius *et al*. 2018) and the American Thyroid Association's guidance on thyroid endpoint investigation (Bianco *et al*. 2014). The OECD has also published guidance on the generation, reporting and use of research data for regulatory assessments (OECD 2025b), providing a framework for integrating non-standard data in decision-making.

3.7.5 Mixture exposures, epidemiological evidence and priority actions

Humans and wildlife are not exposed to chemicals in isolation. Exposure to chemical mixtures, together with other environmental stressors, complicates the attribution of adverse outcomes to individual substances and creates gaps in standard risk assessment frameworks. Traditional epidemiological approaches face additional limitations in the absence of unexposed reference populations, a situation that has been reported for many environmental contaminants.

Research and regulatory initiatives have been undertaken to address these challenges. The European Commission has demonstrated through targeted funding – including Horizon 2020 programme projects such as EDC-MixRisk and Human Biomonitoring for Europe (HBM4EU) – that structured collaboration between researchers and regulatory bodies can produce methods of direct regulatory utility. These initiatives illustrate approaches for integrating scientific research with regulatory needs.

Areas of ongoing activity include research on mixture risk assessment, development and validation of new test methods, and collaboration between regulatory agencies and the research community. Since 2012, a range of initiatives have contributed to advancements in EDC testing and assessment methodologies, and their application in regulatory contexts. While it is critical to continue improving and harmonizing testing and assessment methodologies, doing so should not delay action, particularly for EDCs where the evidence base is already sufficient to support regulatory action and the promotion of safer alternatives.

4 Exposure to endocrine-disrupting chemicals

Lead author

Martin Scheringer (RECETOX, Masaryk University, Brno, Czech Republic, and ETH Zürich, Zürich, Switzerland)

Chapter authors

Daniel Heidland (ETH Zürich, Zürich, Switzerland) and Fiona Quin Zabel (University of Connecticut, Groton, CT, United States of America)

Contributing authors

Linda Schenk (Karolinska Institute, Stockholm, Sweden), Marlene Ågerstrand (Stockholm University, Stockholm, Sweden), Xanat Flores (Universidad de las Américas Puebla, Mexico), Ipek Imamoglu (Middle East Technical University, Ankara, Türkiye), Asif Qureshi (Indian Institute of Technology Hyderabad, Hyderabad, India) and Hiroshi Yamamoto (National Institute for Environmental Studies, Tsukuba, Japan)

This chapter summarizes, for a selection of confirmed EDCs, the evidence of human, wildlife and environmental exposure to these chemicals, along with a description of methods that are used to determine exposure to chemicals. It complements the information in Chapter 3, which reviewed the testing and assessment methodologies used to assemble evidence of endocrine disruption properties. The chapter starts with a brief overview of actors who have contributed to the identification of EDCs and their approaches, and highlights progress made since the publication of the *State of the Science of Endocrine Disrupting Chemicals - 2012*.

4.1 Identification of EDCs

Implementing legislation to control, monitor and regulate EDCs depends on their prior identification. The identification of EDCs continues to pose a challenge, as their mode of action is complex, and traditional toxicological methods cannot link observed adverse effects to them through endocrine pathways. There is no single test to assess the endocrine-disrupting nature of a chemical to satisfy scientific or regulatory requirements (Fouyet *et al*. 2024; Browne *et al*. 2020) (see chapter 3).

The general challenge for a harmonized identification process is the lack of agreement on how to define an adverse health outcome and an endocrine-mediated endpoint (Fouyet *et al*. 2024; Duh-Leong *et al*. 2023). To support informed decision-making, it is necessary to establish and agree on a comprehensive testing and validation framework in order to generate sufficiently robust evidence and enable confident conclusions (Fouyet *et al*. 2024). Consequently, defining threshold values for adverse effects is a complex task due to differences in targets, effects, developmental stages and species (Choi *et al*. 2024) (see section 3.5.2).

Overview report I: Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs, by the International Panel on Chemical Pollution, was published in 2017 and provides a compilation of global EDC-identifying initiatives (International Panel on Chemical Pollution [IPCP] 2017). The initiatives discussed in the report have since been expanded but differing legislations, their data requirements, and a general lack of consensus introduce complexity to the identification processes (Barton-Maclaren *et al*. 2022). Examples presented in this section focus on the OECD, European Union, United States


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of America and Japan due to the availability of well-developed EDC identification frameworks. However, important EDC-related activities are also underway in other jurisdictions, and experiences from other countries, including developing countries, are mentioned in Section 4.2.

4.1.1 Initiatives to identify EDCs: summary of the 2017 overview report

Overview Report I of the three 2017 overview reports highlights global initiatives by governments, non-governmental organizations and industry working to identify EDCs and potential EDCs. Major initiatives had made significant progress by establishing EDC priority lists, evaluating the existing literature and publishing data regarding industry self-regulation. Twenty-eight publicly accessible initiatives were compared for chemical selection criteria, evaluation process details and the overall initiative goal. Four categories of initiatives were established, namely initiatives that identified EDCs; initiatives where evaluation was ongoing; knowledge bases and available toolkits; and initiatives not specific to EDCs but that included EDCs. The most robust initiatives highlighted in the report were the REACH Candidate List of substances of very high concern of the European Union, the Substitute It Now! list of the International Chemical Secretariat, and the criteria established by the Government of Denmark. Initiatives with ongoing development were highlighted, including the two-tiered screening approach by the United States EPA and criteria established by the Government of Japan. Notably, the report focused on many of the limitations of these initiatives, including (a) the lack of universal criteria for establishing a chemical as an EDC; (b) failure to consistently identify or standardize Chemical Abstracts Service (CAS) numbers as chemical identifiers; and (c) the lack of data from developing countries. The report pointed out the importance of a common portal to share EDC information and improve data harmonization. Finally, the report established the basis for Overview report II by identifying a list of confirmed or potential EDCs, including alkylphenols, phthalates, UV filters, bisphenols and parabens (notably excluding chemicals used explicitly as pesticides or pharmaceuticals) (IPCP 2017).

4.1.2 OECD approaches to EDC identification

The OECD works towards providing guidelines to support coordinated efforts to improve global policies (OECD 2025b) (see section 3.3). The first chemical testing recommendations were presented in 1981, and they are updated on a rolling basis (Browne *et al*. 2020). EDCs were first included in the OECD test guidelines in 1997 (OECD 2018a; Browne *et al*. 2020). The OECD currently provides a five-level conceptual framework for the testing of chemicals for EDC properties (Browne *et al*. 2020; OECD 2018a; OECD 2018b). This framework offers more than 20 tests using OEDC test guidelines that generate various types of evidence from level 2 (in vitro) to level 5 (in vivo, life cycle) to be considered in the identification of EDCs (Browne *et al*. 2020; OECD 2018; Robitaille *et al*. 2022). OECD test guidelines for EDCs had been referred to in the 2012 report on the state of science of EDCs (UNEP and WHO 2013), but have since been modified according to new knowledge (OECD 2018a). OECD guidelines are widely used internationally and are developed through a transparent, consensus-based process supported by scientific expert review (Fouyet *et al*. 2024). It is essential that the EDC framework continues to be adaptive and accessible to all Member States (Browne *et al*. 2020). OECD members agree to the principle of mutual acceptance of data to encourage coordinated research efforts and reduce the mismanagement of resources, thereby improving the harmonization of testing processes and the sharing of outcomes (OECD 2018a; Browne *et al*. 2020).

The OECD also provides recommendations for the interpretation of results and analyses of relevant data (OECD 2025a) to promote a harmonized weight-of-evidence approach to decision-making.

The OECD further provides guidelines on integrated approaches to testing and assessment, which provide advice on how to combine existing data with new purposefully generated data, thus promoting the use of new approach methodologies (Barton-Maclaren *et al*. 2022) (for further information about new approach methods, see section 3.3.5).

4.1.3 Identifying EDCs in the European Union

The European Union has made important steps on EDC legislation and management (EU 2019). In its legislation, the European Union adopted the 2002 IPSC/WHO definition of EDCs (Choi *et al*. 2024; European Commission 2022). OECD guidelines have informed the European Union chemical risk assessment protocols and positively contributed to the European Union's management of EDCs. Additionally, the European Union is an active participant in the sponsoring and development of OECD guidelines (OECD 2026).

In 2007, the European Union fundamentally changed its chemical regulation approach with the introduction of the REACH regulation, which is widely regarded as one of the most comprehensive regulatory frameworks for chemicals management internationally (ECHA 2025; Rudén and Hansson 2010; EU 2007).

Under REACH, the Candidate List of substances of very high concern currently includes around 250 chemicals or groups of chemicals (ECHA 2026a) and, with the amendment of Article 57(f) (EU 2007) of REACH, endocrine disruption is considered a sufficient concern, in its own right, for inclusion of a chemical in the Candidate List of substances of very high concern. Currently, there are 31 chemicals or groups of chemicals listed as EDCs (ECHA 2026a).

The European Union assessment, based on a notification and verification system, depends on data produced following OECD guidelines, and can therefore investigate a report of endocrine-disrupting effects without an extensive amount of prior outside research. One limitation identified is the single-chemical approach, which slows down the identification and legislation of entire chemical classes that have been identified in research as potential EDCs. To overcome the limitations of a chemical-by-chemical approach, the European Union is moving towards a group-based approach (ECHA 2021).

The European Union introduced specific provisions addressing endocrine disruption in legislation for the regulation of pesticides, both for plant protection products (in 2009) and for biocidal products (in 2012) (EU 2012; European Commission 2009). Approval of a novel substance in a plant protection product is based on evidence of absence of endocrine-disrupting effects, otherwise the substance is defined as "high risk". Regarding detected adverse effect outcomes, these must be traced to an endocrine mode of action to signify an EDC. Therefore, European Union regulation bases the assessment of endocrine disruption effects on their detection as hazardous rather than a certain level of risk (which includes exposure in addition to hazard), focusing on the potential danger of endocrine disruption (Kassotis and Trasande 2021; Bourguignon *et al*. 2016).

Under European Union law, the responsibility for providing data on the safety of a new plant protection product that falls under this legislation lies with the producer and distributor. Pesticides are developed with toxicity intended for a specific type of target organism; therefore the evidence of adverse effect outcomes must be relevant to non-target organisms, specifically humans, and exposure must be "non-negligible" for the legislation to apply (European Commission 2009).

For biocidal products, prior to approval, assessment of potential endocrine disruption occurs via a tiered testing framework in eight possible steps, following OECD guidelines (EU 2012). These policies are designed to prevent the unintentional release of EDCs from biocidal product use. Further guidance on specifically

testing for endocrine-disrupting activity of these substances was released in 2018 (ECHA and EFSA 2018).

In 2023, two hazard categories on endocrine disruption were included in the European Union's Classification, Labelling and Packaging Regulation, one for human health and one for the environment (European Commission 2022). The corresponding European Chemicals Agency CLP guidance details the evaluation of the criteria for endocrine disruption, mentioning the three elements of endocrine activity, adverse effects, or a biologically plausible link (ECHA 2024).

4.1.4 Identifying EDCs in the United States of America

In the United States of America, the Endocrine Disruptor Screening Program was launched by the United States EPA after the Food Quality Protection Act was passed (and the Safe Drinking Water Act was amended) in 1996 (Juberg *et al*. 2014). The Endocrine Disruptor Screening Program operates on a two-tiered framework: tier 1 to assess actions to endocrine systems by reliability assessment of the literature, in vitro assays and in vivo short-term screening assays; and tier 2 to characterize adverse effects by long-term assays. The EPA assesses risks (not hazards) based on outside data and the reporting of substances as hazardous, especially for pesticides (US EPA 2015b).

Implementation of the programme has been associated with significant resource and time requirements. The tier 1 battery of the Endocrine Disruptor Screening Program costs around US$ 1 million per evaluated chemical (Judson *et al*. 2018). The resulting data are collected under the programme to assess whether endocrine-disrupting effects occur. Tier 2 then focuses on risk assessment based on dose–response, likelihood and duration of exposure, and makes use of mammalian and other vertebrate in vivo testing (US EPA 2015b).

The United States EPA has heavily focused on the estrogen, androgen and steroidogenesis pathways (Judson *et al*. 2018), with less attention given to other endocrine pathways, including the retinoid and glucocorticoid pathways (Fouyet *et al*. 2024). The first tests of pesticide active substances suspected of endocrine-disrupting effects were ordered in 2009, and the second set in 2013 (Juberg *et al*. 2014). The limited progress of the evaluations of the Endocrine Disruptor Screening Program was attributed to the difficulties of in vivo testing. The use of new approach methods has now been prioritized to more quickly evaluate EDCs on their compiled lists (Maffini and Vandenberg 2022), including the implementation of high-throughput screening assays (Duh-Leong *et al*. 2023). Complications related to the validity of the results from these tests have been noted (Duh-Leong *et al*. 2023). Progress has therefore been slower than originally anticipated, reflecting scientific, technical and resource limitations associated with endocrine disruptor assessment.

A key difference often noted in the literature is that the United States of America regulatory approach is risk based (factoring in exposure), while the European Union regulatory framework has largely adopted a hazard-based approach (considering primarily the toxicity of a chemical) (Kassotis and Trasande 2021). Additionally, the United States of America regulation relies on industry (particularly at the federal level) to determine whether exposure is considered "relevant". Risk-based approaches require a vast and comprehensive body of data to assess exposure, which is additional to data used to assess hazard, to an extent that hampers these regulatory approaches (Kassotis and Trasande 2021). On the state level within the United States, more stringent or EDC-specific legislation for the identification of EDCs may exist and may potentially be applied (Office of Environmental Health Hazard Assessment 2015).

4.1.5 Identifying EDCs in Japan

In Japan, the Environmental Agency (currently Ministry of the Environment) published Strategic Programs on Environmental Endocrine Disruptors (SPEED '98) in 1998 (Ministry of the Environment of Japan 2026). Under this programme, initially 67, then 65, chemicals were listed as having the highest priority for survey and research in order to clarify their occurrence, potency and endocrine-disrupting mechanisms and effects.

The programme promoted field investigations, research and method development, environmental risk assessment and international networking.

Following SPEED '98, the Ministry of the Environment published its Perspectives on endocrine disrupting effects of substances – ExTEND2005 in 2005 (Ministry of the Environment of Japan 2026). In this programme, instead of listing the high-priority chemical substances, chemicals were selected and assessed based on their detection in the environment in Japan and existing knowledge.

Since 2005, internationally harmonized test methods have been developed for fish, amphibians and invertebrates within the OECD, with continuous contributions by Japan (see sections 4.1.2 and 5.2).

In 2010, the Ministry of the Environment published Extended Tasks on Endocrine Disruption (EXTEND) 2010, adding necessary improvements to the EXTEND2005 programme 1998 (Ministry of the Environment of Japan 2026). Updates were published in 2016 (EXTEND2016) and 2022 (EXTEND2022), now with pesticides, pharmaceuticals and personal care products also subjected to EDC testing 1998 (Ministry of the Environment of Japan 2016; Ministry of the Environment of Japan 2022).

4.2 Exposure to EDCs and monitoring

Exposure to chemicals can be monitored either in the exposed, living organism (humans, animals or plants) or in the environment (water, soil, air, food and drink, the household environment or consumer products). Each matrix and method carries its own set of benefits and difficulties, and the choice of medium and method must be evaluated to offer the best-quality data. No single method to monitor exposure is exhaustive, nor can it offer a full, complete exposome picture. EDCs are grouped together by their effects on endocrine systems but are, as a group of chemicals, extremely diverse in their uses and physicochemical properties, and also with respect to non-endocrine-disrupting toxicity. Efforts to characterize exposure therefore have to reflect this diversity (Ismanto *et al*. 2022).

4.2.1 EDCs exposure and biomonitoring

The analytical methods used in biomonitoring and their accuracy and detection limits have improved substantially over recent decades. The scientific literature published on biomonitoring tripled from the 1980s to the 1990s alone. Biomonitoring has become an essential tool for tracking and managing exposure to chemical contaminants, including EDCs (Needham *et al*. 2007). Biomonitoring is particularly useful to assess and evaluate how changes in behaviour, physiology, socioeconomic conditions and protective measures affect concentrations of contaminants within the body of organisms (Jakubowski 2012), establishing a link between uses, emissions and the presence of EDCs in organisms. Consideration must be given to which biological matrix to analyse, when to collect the sample, which is the most relevant analyte, how the samples can best be stored and preserved, and which analytical method is best, considering these factors (Nauman *et al*. 1993). It is key here to assess the relevant matrix and the relevant chemicals, be it a parent compound, a biomarker or a metabolite (Juberg 2008). Biomonitoring elucidates the relationship between environmental exposure and bodily uptake, informing how regulation can assess threshold values (Juberg 2008).

As EDC research develops further, it is important to go beyond the identification of single chemicals and place greater focus on mixtures, and to facilitate the process of integrating chemical identification and quantification with potential adverse health outcomes (Scognamiglio *et al*. 2016).

Human exposure and biomonitoring

The three main exposure routes for humans are ingestion, dermal absorption and inhalation. The use and application of an EDC determine its likely exposure routes (Van Engelen *et al*. 2007).

Consumption of contaminated food and drink is the major exposure route for humans to ingest EDCs. Dermal absorption of chemicals in personal care products exposes humans to EDCs in a range of products, including cosmetics, laundry detergents, and cleaning and textile treatment products. Extensive use of personal care products

and pharmaceuticals is also a main contributor to presence of EDCs in water systems. Inhalation of EDCs occurs mostly within the built environment of humans (in the house, in cars and other vehicles, or in shared workplaces). Household dust often contains chemicals, and inhalation of it and of contaminated air exposes humans. This warrants inspection of which household objects contribute to dust formation (for example, couches, with resultant exposure to flame retardants) and how chemicals can partition into dust. Pets and young children are particularly vulnerable to this exposure route.

The focus in human biomonitoring was initially on occupationally exposed individuals. Occupational exposure refers to exposure in a workplace environment that is specific to a profession. Occupational exposure usually correlates to particularly high burdens of a particular type of contaminant, including some EDCs such as phthalates or 4-tert-octylphenol, therefore disproportionally affecting a particular segment of the population. For many chemicals, occupational exposure limits are defined (see following section).

The choice of analyte or matrix is advised by the EDC's properties: persistence, hydrophobicity or potential metabolic pathway. Urine is commonly used to identify non-persistent compounds with low hydrophobicity, particularly after metabolism (such as phthalates or BPA), while blood lends itself better to the detection of more persistent chemicals, as the formation of adducts (to albumin or haemoglobin) results in prolonged presence in the body (Needham *et al*. 2007).

Blood, including cord blood, and urine are two frequently used matrices (Needham *et al*. 2007), as well as saliva and milk (Juberg 2008). Other options include fatty tissue (Needham *et al*. 2007), bone, hair, nails, semen (Juberg 2008), sweat (Genuis *et al*. 2013) and tears (Amini and Okeme 2024). Each matrix has its own advantages, for example, being less invasively collected or more accurate for long-term exposure, and disadvantages, such as requiring surgical extraction. Human milk is monitored for its high fat content, leading to the higher content of hydrophobic contaminants, and it is also important for assessing potential exposure of newborns (Needham *et al*. 2007).

Collected samples may also be pooled, offering the advantage of a populationwide assessment of exposure and increased anonymity, as well as a simplified "control versus exposed population" comparison, and facilitating longitudinal studies of those populations (Heffernan *et al*. 2014).

The absence of a chemical in a selected matrix does not exclude prior exposure, nor can the detection of a contaminant be interpreted as a direct causal link to recorded health effects (Juberg 2008). Accurate assessment of the latter requires knowledge of metabolism and toxicity and is not wholly within the scope of biomonitoring. Time of testing and time of exposure are not easily linked, either for persistent chemicals or for easily metabolized and excreted substances (Juberg 2008).

An international programme for human biomonitoring of chemical contaminants is the Global Monitoring Plan under the Stockholm Convention on Persistent Organic Pollutants (Secretariat of the Stockholm Convention 2026a), which uses predominantly human milk as a matrix to sample for human exposure to persistent organic pollutants. Projects funded under UNEP and the Global Environment Facility have provided the majority of the data on chemicals in human milk to the Global Monitoring Plan (Malisch *et al*. 2023). There are currently no large-scale biomonitoring efforts focused exclusively on EDCs. The Endocrine Society, in its second statement, reaffirms that such efforts are essential for improving the understanding of how EDC exposure affects human health (Gore *et al*. 2015). EDCs and their impact on human health will best be understood through large, longitudinal, cross-generational studies that interrogate exposure and related health outcomes alike.

A range of human biomonitoring projects – Health and Environment-wide Associations based on Large Population Surveys (HEALS) (HEALS 2019), Environmental Health Risks in European Birth Cohorts (ENRIECO) (ISGLOBAL

2011), HBM4EU (HBM4EU 2025) and MERLON (Merlon n.d.) – have been carried out. The MERLON project is most relevant to EDCs; however, it is not undertaking any novel human biomonitoring data collection but focuses on reviewing, interpreting and collating data based on new approach methods. ENRIECO focused on prenatal exposure of a range of environmental contaminants, including known EDCs, establishing a framework that could be applied to EDC-specific research by comparing 37 birth cohort studies conducted within Europe (Gehring *et al*. 2013). HBM4EU was a broad project designed to answer many questions around chemical exposure, not just EDCs. Studies carried out under HBM4EU revealed widespread exposure of the general population to many chemicals, including EDCs such as phthalates and bisphenols, across the European Union (Govarts *et al*. 2023). Long-term ongoing projects, such as the National Health and Nutrition Examination Survey in the United States, which includes human biomonitoring and self-assessment of health, have informed policy decisions. In India, a national biomonitoring programme for chemicals is being initiated by the Ministry of Health and Family Welfare (Ministry of Health and Family Welfare 2026). Some limitations of past human biomonitoring programmes are their relatively short duration, their limited access to diverse populations, their limited number of examined chemicals and their limited focus on EDCs.

Occupational exposure to EDCs

An important tool for providing an overview of occupational exposure to EDCs is the job exposure matrix, widely used in occupational health research to estimate workers' exposure to hazards based on job titles and tasks. A job exposure matrix for EDCs has been published by van Tongeren *et al*. (2002) and further developed by Brouwers *et al*. (2009). This job exposure matrix identified 10 chemical groups of potential endocrine disruptors and scored the probability of exposure for 353 job titles in the United Kingdom of Great Britain and Northern Ireland, classifying 29% of job titles as probably or possibly exposed to EDCs. Another job exposure matrix was developed for alkylphenolic compounds in Spain between 1931 and 2014 (Martín-Bustamante *et al*. 2017), classifying 13.8% of 390 included job titles as potentially exposed to alkylphenolic compounds, including 3.7% specifically to octylphenol or nonylphenol.

These job exposure matrices have been used in other studies classifying primarily the exposure of pregnant women. A pooled analysis of 13 European cohorts (1994–2011) found 11.4% of pregnant women exposed to at least one EDC (Birks *et al*. 2016). Later reported cohort studies found similar patterns for working mothers, generally of live singleton births: 6.3% in Denmark (1997–2009) (Morales-Suárez-Varela *et al*. 2011), 14% in Switzerland (1990s) (Istvan *et al*. 2021), 20.1% in the Kingdom of the Netherlands (1997–2013) (Spinder *et al*. 2022), 7.3% in the United Kingdom of Great Britain and Northern Ireland (2001–2011) (Shirangi *et al*. 2020), and 26.9% in Spain (2003–2008) (Ish *et al*. 2022). In a cohort in China, 21.6% of mothers and 16.2% of fathers were classified as exposed (2011–2014) (Zhang *et al*. 2022). The cohorts in these studies are not necessarily representative of the full working population in their country but indicate that a non-negligible share of pregnant workers are exposed to EDCs at work.

Occupational exposure limits indicate that an exposure is considered significant enough to warrant regulatory limits. Several EDCs have occupational exposure limits set as eight-hour time-weighted averages, as listed by GESTIS ILV (international limit values for chemical agents database under the Institute for Occupational Safety and Health of the German Social Accident Insurance) (GESTIS 2026).

An important group of EDCs with occupational exposure limits is phthalates, which are widely used as plasticizers and additives, and thus used in the manufacture of a wide range of plastic materials and consequently articles containing plastic. Some also function as solvents in inks, coatings and adhesives. Occupational exposure occurs in manufacture of (for example) polyvinyl chloride (PVC) products, construction, flooring installation and recycling. Several phthalates are restricted within the European Union, and BBP, DEHP, DBP, DCHP and diisobutyl phthalate are regulated through occupational exposure limits in the range 1 to 10 milligrams per cubic metre



(mg/m^3) in various countries globally (GESTIS 2026). Studies on occupational exposure have mainly focused on DEHP and most often in the context of PVC product manufacturing, but overall, a range of diverse workplaces were studied, including hairdressing salons and dental offices (Fréry *et al*. 2020). Highest exposures have been measured during manufacturing and recycling; for the DEHP metabolite MEHHP, levels have been reported to reach 700 micrograms per gram (µg/g) creatinine, though most studies reported around 50 µg/g creatinine (Fréry *et al*. 2020). Air measurements of raw material workers in PVC manufacturing found air concentrations of 32.7 µg DEHP per m^3 (geometric mean) (Fong *et al*. 2014).

Another plastic-related chemical, BPA, is widely used in epoxy resins and specialty waxes and has been used in thermal paper. Within the European Union, the use of BPA in thermal paper has been restricted since 2020, allowing no more than 0.02% by weight (European Commission 2016). BPA has an occupational exposure limit in several European countries, with time-weighted averages ranging from 2 to 5 mg/m^3 (see GESTIS ILV) (GESTIS 2026). Urinary BPA levels vary widely; in the manufacture of liquid paint hardener, levels reached 100–170 micrograms per litre (µg/L) (Heinälä *et al*. 2017). Among epoxy resin workers, levels ranged from not detectable to 98.50 nanograms per millilitre (ng/mL) (Zhuang *et al*. 2015) or even up to 1.935 ng/mL in urine (Wang *et al*. 2012). Zhuang *et al*. (2015) reported a BPA concentration in sampled dust exceeding 20 mg/m^3. A Malaysian study of workers in a plastic injection moulding factory detected air concentrations in the range of 8–28 ng/m^3, and the median urinary level was 3.81 ng/mL urine (Kouidhi *et al*. 2017). For workers in manufacturing of thermal paper, median concentrations in the post-shift urine were in the range of 130–250 µg/L, while highly exposed workers reached 1.500 µg/L One United States of America study showed cashiers, handling thermal papers, to have average urinary levels of 8.92 µg/L (Ndaw *et al*. 2016).

The alkylphenol 4-tert-octylphenol is mostly used as an intermediate in manufacturing of ethoxylates, phenolic resins, polymers, antioxidants, and rubber and plastic products. It is regulated with an occupational exposure limit in Switzerland and Germany, in both cases with a time-weighted average of 4 mg/m^3 (see GESTIS ILV) (GESTIS 2026). No scientifically published studies regarding occupational exposure were retrieved.

In summary, there are limited quantitative occupational exposure data available for many substances, including recognized EDCs, and the heterogeneity in measurement matrices and reporting formats across studies complicates direct comparison of results. However, in particular for phthalates and BPA, it is clear that exposures can vary significantly between and within sectors, indicating that underlying workplace conditions vary widely.

Furthermore, from a gender perspective, occupational exposure to EDCs is also frequently shaped by gender-segregated labour markets. As a result, exposure patterns and associated risks may differ across worker populations, underscoring the need for exposure prevention strategies that address these distinct risk profiles and ensure equitable access to workplace protection.

Wildlife biomonitoring

Wildlife exposure routes include water (and food), air, and soil. Exposure to EDCs occurs through uptake from food and water consumption, inhalation of contaminated air, and life in a contaminated medium (for example, fish, molluscs, and amphibians in contaminated water, and worms or nematodes in soil).

The biomonitoring of animals is linked to the monitoring of natural environments. Sentinel or bioindicator species are used to monitor the general contamination level: these are often predators, particularly in marine environments, at the top of the food chain (for example, whales or seals). Alternatively, species can be chosen to understand pollution of a particular biome or environment, such as frogs or fish for rivers and lakes, chickens for agricultural areas, or, historically, birds of prey.

4.2.2 Environmental monitoring of EDCs

Soil is an important source of exposure, as it is a component of agricultural areas, where often plant protection products are used, and also of industrialized areas and landfills. Soil contamination often leads to exposure through food. Consistency in soil measurements can pose a challenge because of the high heterogeneity of soils. Exposure is often measured in affected animals. Soil contamination is often linked to contamination of water (through run-off or percolation).

Water contamination by EDCs leads to exposure of all forms of aquatic life; chemicals can be detected in fish, marine mammals (both are common biomonitoring targets), and algae and other life forms. Water contamination is easier to detect and characterize than soil contamination because of the faster mixing of water bodies, leading to greater homogeneity. For some chemicals and areas, water contamination can be linked back to wastewater treatment plants and, thereby, human exposure to chemicals in wastewater.

Water resources act as contaminant reservoirs, and often chemicals in water bodies act as a source of transformation products, accumulate in organic matter or sludge, are transported, and enter the drinking water cycle (Ismanto *et al*. 2022; Leusch *et al*. 2018). The modern water cycle results in the presence of contaminants such as EDCs in all bodies of water. EDCs can be extremely harmful to the aquatic ecosystem and pose a difficulty for the future of water resource management for human and environmental health (Xiao *et al*. 2023).

The detection of some EDCs in treated wastewater and drinking water sources indicates that conventional wastewater treatment processes are not equipped to effectively remove these contaminants. Consequently, additional treatment approaches and technological improvements are needed (Ismanto *et al*. 2022). An ideal remediation scenario for water contamination would combine multiple remediation technologies into hybrid treatments, with the use of enzymes at the forefront of water-based EDC remediation (Ismanto *et al*. 2022). A wide range of treatment techniques for the removal of EDCs exists, but cost and availability still pose a hindrance to their large-scale implementation (Ismanto *et al*. 2022).

Air analysis, particularly in the case of highly persistent EDCs, shows that even remote areas and life forms are not safeguarded by distance from contamination with EDCs (Hung *et al*. 2016). Atmospheric long-range transport of organic contaminants, including various EDCs, has been documented extensively since the 1980s (Simonich and Hites 1995; Muir *et al*. 1988; Dewailly *et al*. 1989). Many organic chemicals survive for longer times than expected during atmospheric transport, which leads to their long-range transport. Recently, this was again documented for a large set of current-use pesticides reaching the Arctic by atmospheric transport from Europe (Mayer *et al*. 2024). Oceanic long-range transport also contributes to the global distribution of organic chemicals, including EDCs. Plastic additives, such as UV filters and flame retardants, travel over long distances with plastic debris carried by ocean currents (Andrade *et al*. 2021).

4.3 Exposure and monitoring: developments since 2012

4.3.1 Key findings from the 2012 report

The UNEP 2012 report on the state of science of EDCs (UNEP and WHO 2013) included typical persistent organic pollutants, such as PCBs, DDT and PBDEs, as endocrine-disrupting compounds, but also expanded the scope to phytoestrogens, PFAS, plasticizers, modern pesticides, pharmaceuticals and metals. Many of these compounds were noted to

be bioaccumulative. The report emphasized the impact of day-to-day human exposure to household products and maternal transfer as routes of exposure to EDCs, in addition to occupational exposure.

Wildlife exposure was assessed both by environmental samples and internal tissue sampling, with some used as bioindicators of pollution (for example, PAHs detected in seabird blood following oil spills). Concentrations were primarily reported from the Baltic Sea, the Great Lakes and the Arctic, following long-term monitoring efforts in those regions. Legacy pollutants (such as PCBs) showed slow but consistent declines in wildlife. The 2012 report also noted a decline in DEHP concentrations in the environment following regulation and subsequent increase in the substitute, diisononyl phthalate.

Human exposure was reported through ingestion (for example, pesticides in drinking water, persistent organic pollutants in fatty foods or BPA in food containers), inhalation (for example, PAHs from indoor wood burning), and dermal exposure (for example, from cosmetic products). Children were reported to have disproportionately high levels of exposure associated with hand-to-mouth activity and a greater ratio of eating and breathing to body mass. Most common sample types reported include milk, blood and urine, while several alternatives were proposed (for example, hair). Metabolite compounds were measured in human tissue samples for phthalates, BPA and PAHs.

Government-driven biomonitoring programmes (for example, the National Health and Nutrition Examination Survey in the United States) were found to provide valuable population wide data (for example, by identifying ubiquitous persistent organic pollutants in the United States population); identify communities of concern (for example, women with elevated pesticide levels in the Salinas Valley of California); and shed light on population trends (for example, United States children with PBDE levels approximately three times higher than those of their mothers).

Finally, the 2012 report highlighted two major issues: (a) a lack of comprehensive lists of chemicals on the market; and (b) analytical deficiencies in identifying and quantifying EDC exposure to a sufficient level of sensitivity.

4.3.2 Progress since 2012 and remaining challenges

The 2002 report Global assessment of the state-of-the-science of endocrine disruptors listed a few concise but open-ended research needs, some addressing how to better monitor and understand exposure in the future (IPCS 2002). These have largely been pursued: there has been an increase in research outside the United States and Europe, including efforts to set up long-term human biomonitoring programmes, and there has been successful monitoring of sentinel animal species to better understand and remedy wildlife exposure. Subsequently, the 2012 report, particularly chapter 3, describes a broader range of research needs for the future (UNEP and WHO 2013). The points illustrated below highlight the changes that have occurred since then.

Generally, there has been a steady and evident increase in research output on the topic of EDCs since 2012 (Suramya *et al*. 2024; de Oliveira Santos *et al*. 2023). A search using Web of Science and the term "endocrine disrupting chemicals" showed a threefold increase in the number of scientific articles published after 2012, compared to the time period before (1994–2012). The same trend is calculated with Scopus and the terms "endocrine AND disrupting AND chemicals". Overall, Web of Science and Scopus present 16,306 and 13,038 results for EDCs, respectively. These large and growing bodies of literature provide an expanding evidence base for reviews and assessments. The increasing number of publications reflects that the topic of EDCs has become more relevant and the body of information on EDCs has substantially expanded. There has been a general rise in publishing of scientific literature (Hanson *et al*. 2024), but this alone does not account for the increasing trend of EDC literature observed here.

Between 2013 and 2016 a dedicated journal, Endocrine Disruptors, was published (Taylor & Francis 2026). Since 2017, the Endocrine Society, an association established over 100 years ago,

began publishing their own journal, partially focusing on the same issues, while taking a human health-focused stance on issues of endocrine disruption. Both of these journals contributed to the increase in EDC research after 2012. The Endocrine Society published two statements on the danger potentially posed by EDCs – one in 2009 (Diamanti-Kandarakis *et al*. 2009), the other in 2015 (Gore *et al*. 2015). Both are highly cited publications, as they briefly and efficiently summarize some key concerns about EDCs and their impacts, particularly within the United States, where the Endocrine Society resides, and make some recommendations for filling knowledge gaps and improving research robustness. The statement of 2009 is considered an influential contribution to scientific and policy discussions on endocrine disruption and a generally increased awareness of the topic. During this period, a number of jurisdictions, including Canada, the European Union and the United States of America, further developed regulatory approaches relevant to endocrine-disrupting chemicals.

Since 2012, a number of chemicals have been added for consideration as EDCs or suspected EDCs. Examples include BPS, BPF, benzophenones, cinnamate derivatives, 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) and novel pesticides. While these may already have been studied prior to 2012, they were only mentioned by name or not included in the 2012 report. This represents a considerable update.

Since 2012, there has been a considerable increase in biomonitoring studies, primarily for human populations, but also in wildlife. These provide better knowledge of concentrations for a range of contaminants in a variety of matrices, over time. Data collected in biomonitoring programmes, whether they are designated studies or part of larger programmes, help connect contamination trends with potential adverse health effects in surveyed populations. One such programme is HBM4EU, the European human biomonitoring programme, running from 2016 to 2022 (HBM4EU 2025). The United States has conducted a similar survey, the National Health and Nutrition Examination Survey, since the 1960s, and more consistently since 1999 (National Health and Nutrition Examination Survey n.d.). China, between 2017 and 2018, launched a pilot investigation of human biomonitoring designed as a baseline measurement for the country's population, across different provinces (Cao *et al*. 2021). The Republic of Korea has established human biomonitoring programmes under the Korean National Environmental Health Survey and the Korea National Health and Nutrition Examination Survey (Lee *et al*. 2025; Hong *et al*. 2024). There have been calls for better regional biomonitoring, especially in less industrialized countries (Tamayo-Ortiz *et al*. 2022), and efforts for harmonized biomonitoring in more recently industrialized countries, for example Brazil (Campos *et al*. 2021). Accordingly, considerable progress has been made to better monitor human exposure to EDCs globally, but important geographical gaps remain.

In terms of EDC research, China was the main contributor to published research between 2013 and 2022 (de Oliveira Santos *et al*. 2023). Additionally, Brazil, France, India, Japan, Republic of Korea, Spain and the United States increasingly published in this time frame. For more recently industrialized countries, such as Brazil, China and India, an increase in research pertaining to EDCs reflects broader growth in scientific activity and increased attention to environmental health issues. New biomonitoring methods, using hair, for example, have been developed for faster, less invasive testing for pollutants (Fäys *et al*. 2021; Robin *et al*. 2024) beyond persistent halogenated organics (Schramm 2008). Hair analysis-based methods have also been recently implemented in wildlife biomonitoring (Gonkowski *et al*. 2023; Gonkowski *et al*. 2024), as well as the analysis of faecal matter (Wang *et al*. 2020; Eccles *et al*. 2024). These approaches provide additional opportunities for more efficient, less invasive monitoring of environmental contamination and wildlife exposure.

Consistent biomonitoring of select populations may offer substantiated indications of potential adverse health effects of the surveyed chemicals. This meets one of the goals of the 2002 report, as monitoring of predator sentinel species, such as polar bears (Eccles *et al*. 2024), is a useful strategy for detecting contaminations in

the environment, how this contamination exposes wildlife and how concentrations culminate at the top of the food chain. The increased attention to terrestrial mammals, in contrast to the heavy historical focus of aquatic species, also indicates an expansion of biomonitoring efforts and knowledge.

Additionally, there has been a shift away from the single-chemical approach; studies are increasingly looking into health effects brought about by mixtures of EDCs and aiming to detect more than one contaminant at a time in collected samples. Hormones and their receptors are complex and multifaceted, and as more is discovered about the endocrine system, more can be said for potential EDC interference (Vandenberg *et al*. 2012). Increasing recognition that humans and wildlife are exposed to multiple chemicals simultaneously may also help lawmakers: current legislation usually regulates or bans a single chemical or isomers of it; regulatory action encompassing a whole compound class may prove more useful in reducing global contamination and potentially averting negative health effects in exposed populations (Fenner and Scheringer 2021). While single-chemical approaches have been an important component of chemicals regulation, a number of authors have argued that approaches addressing groups of related chemicals may be needed, given the large number of synthetic chemicals in commerce (Wang *et al*. 2020; Fenner and Scheringer 2021).

Regulatory restrictions on individual EDCs (see section 5.2) have, in some cases, been associated with the introduction of structurally similar substitute chemicals, raising concerns about regrettable substitution (Sweetman 2020). Bans and regulations set forth for single chemicals often imply that the industry adapts to this by switching to a related chemical that has not been regulated, in order to minimally disrupt production. This often means that, for synthetic organic compounds such as BPA, a structurally related, functionally similar chemical is employed, such as BPS. However, evidence suggests that structurally related compounds may have similar effects, and so the replacement of a known EDC with a related chemical that is untested may not solve the initial problem.

There are remaining challenges to the science of EDCs. The 2012 report reiterates that an EDC is a substance or a mixture that is (a) exogenous; (b) operates through and affects the endocrine system; (c) causes an adverse health effect; and (d) causes that effect as a consequence of action in the endocrine system (UNEP and WHO 2013).

The last point remains one of the most challenging aspects of EDC identification, particularly in human populations (Lamb *et al*. 2014). An additional difficulty of human monitoring of adverse effects is posed by the lack of a consistent control population since a wide range of EDCs or suspected EDCs are often measured in large parts of the population (Pedersen *et al*. 2024; HBM4EU 2025; Encarnação *et al*. 2019).

4.4 Select EDCs in focus

The following is a collection of EDC classes or individual chemicals that have been selected both to provide cases of important EDCs and to illustrate key exposure routes, concepts and changes since 2012. These chemicals have been identified among those listed by the European Union as confirmed EDCs (provided in annex III) (Danish Environmental Protection Agency 2026).

4.4.1 Bisphenols (BPA, BPS and BPF)

Bisphenol A (BPA) is a known EDC. It was first synthesised in 1891 and entered commercial use in the 1950s (Kordbacheh and Karahalil 2023; Moreno-Gómez-Toledano 2025), despite being known as a xenoestrogen (Zhu *et al*. 2023) since the 1930s. BPA is included as an EDC in the list of substances of very high concern under REACH (see annex III). The European Union has identified a need to group bisphenols, including BPA, BPS and BPF, for regulation (ECHA 2022).

Use and exposure

BPA is the monomeric building block of polycarbonate plastic (King 1999). Its main industrial application is in durable polycarbonate thermoplastics. It is also used in the production of epoxy resins (Kordbacheh and Karahalil 2023) and as a plasticizer in other polymers, such as PVC (López-Cervantes and Paseiro-Losada

FIGURE 4.1

BISPHENOLS (BPA, BPS, and BPF)



2003). Under heat, UV irradiation, and basic and acidic conditions, as well as through ageing of the material (Kordbacheh and Karahalil 2023), monomeric BPA has the potential to leach out of these products (Vasiljevic and Harner 2021). Use in food packaging leads to leaching into food and exposure of humans via ingestion (Woodruff 2024; Foley *et al*. 2025; Kordbacheh and Karahalil

2023; Moreno-Gómez-Toledano 2025; Vandenberg *et al*. 2009). BPA has been banned from food contact materials in the European Union since January 2025 (European Commission 2024). BPA also finds application in thermal (for example, receipt) paper (Kordbacheh and Karahalil 2023; Thayer *et al*. 2016) and packaging of personal care products (Foley *et al*. 2025), leading to exposure from skin contact and dermal absorption (vom Saal and Vandenberg 2021). Children, due to their higher hand-to-mouth activities, are at higher exposure risk from BPA used in toys (Gonkowski *et al*. 2023; López-Cervantes and Paseiro-Losada 2003; Moreno-Gómez-Toledano 2025; vom Saal and Vandenberg 2021). Restrictions and bans have been placed on BPA in receipt paper, as well as in children's products (for example, toys and baby bottles) (Gonkowski *et al*. 2023; Kordbacheh and Karahalil 2023). BPA is also detected in household dust (Zhu *et al*. 2023), leading to exposure through inhalation. While BPA in air can be detected, it has a short half-life, principally posing a risk when stabilized by being associated with particulate matter (Vasiljevic and Harner 2021). It is impossible to determine all sources of exposure, in part also because it is undisclosed which products contain BPA (Vandenberg *et al*. 2013).

BPS and BPF are two of the main BPA alternatives, with BPS replacing BPA in thermal paper, and BPF being increasingly used in paints, lacquers and plastics (Rochester and Bolden 2015) and epoxy resins (Li *et al*. 2019).

In the European Union, BPS has replaced over 60% of thermal paper BPA, which was restricted in 2016 (Kordbacheh and Karahalil 2023). An example of occupational exposure of bisphenol contamination is in people working at checkouts. A study from 2016 found that urine and plasma concentrations of BPA and BPS for cashiers were significantly higher after their shift than before, and then in the control population (which also presented as contaminated with these chemicals). The study also identified a new analogue (4-hydro xy-4'-isopropoxydiphenylsulfone or BPSIP) for the first time (Thayer *et al*. 2016a; Thayer *et al*. 2016b).

Analysis of thermal paper receipts from various commercial settings in Türkiye showed exposure levels exceeding total daily intake limits set by the European Food Safety Authority for BPA (Akcetin *et al*. 2025).

Endocrine-disrupting properties

BPA acts on estrogen receptors (even at low concentrations) (Erkekoglu *et al*. 2016), resulting in adverse effects on female reproduction (Woodruff 2024), and has been connected to premature births and miscarriages (Rodriguez Martin *et al*. 2023; Li *et al*. 2019; Golub *et al*. 2009) and to polycystic ovarian syndrome. BPA binds to thyroid hormone receptors (Vandenberg *et al*. 2009) and androgen receptors (Golub *et al*. 2009; Garrison *et al*. 2021). It is a suspected obesogen, being linked to higher body mass index, obesity and type 2 diabetes mellitus (Vandenberg *et al*. 2013a). Other adverse effects, such as neurological dysfunction in children (Vandenberg *et al*. 2013b) and cardiovascular disease (Vandenberg *et al*. 2013b; Rochester 2013), have been reported. BPA already displays responses at low doses (Vandenberg *et al*. 2013a), as evidenced by mammalian and human studies; this makes it difficult to determine safe thresholds (vom Saal and Vandenberg 2021).

BPS has only been studied as an EDC since 2002 (Rochester and Bolden 2015). Study of BPF as an EDC dates back to 1998, but less literature has been published over time compared to BPS (Rochester and Bolden 2015). For both, estrogenic effects have been established (den Braver-Sewradj *et al*. 2020; Shao *et al*. 2021); thyroidogenic and androgenic activity is also evident (Rochester and Bolden 2015; Encarnação *et al*. 2019). Adverse neuroendocrine effects, similar to or even greater than BPA, have been detected for both (Rosenfeld 2017). Almost all tests have been conducted in vitro or by means of animal models; there is a pressing need for longitudinal human studies to comprehensively assess the potential health risks associated with BPS and BPF exposure. The lack of such studies may be partially due to the ubiquitous contamination with bisphenols, resulting in the absence of a control population. Since animal and laboratory models indicate the risk and potential of endocrine-disrupting effects of these chemicals, their use might prove regrettable in the future. In almost all comparisons in a study from 2015, BPS and BPF

were chemically of the same or similar potency to BPA, with BPF showing increased potency in some tests (Rochester and Bolden 2015). The same risk could be posed by almost all BPA analogues and substitutes that maintain the same structure, such as bisphenol B (BPB) (Serra *et al*. 2019).

Biomonitoring

BPA has been detected ubiquitously, among all age groups, globally (Vandenberg *et al*. 2013b; Rochester 2013; vom Saal and Vandenberg 2021; Vasiljevic and Harner 2021). BPA has become one of the most studied EDCs currently in use, amassing a wealth of literature over the last 20 years (vom Saal and Vandenberg 2021). The difficulty in replacing it with unstudied analogues lies in the risk of repeating mistakes from the past. In the face of regulatory changes and increased public awareness exerting pressure, the industry has moved away from BPA in some applications such as baby bottles. The introduction of "BPA free" labels on plastic products is a sign of both these factors. This label is not legally binding, and products may still be contaminated by production or packaging even though they are BPA free (Foley *et al*. 2025). Overall, however, production of BPA has not slowed down significantly, and in parts is predicted to grow still (Statista 2019; Mordor Intelligence 2026). Additionally, BPA analogues such as BPS and BPF have entered the market.

BPA, BPF and BPS make up the majority of detected bisphenols. The studies on adverse effects in humans have considerably increased since 2012, with around 50 being published that same year (Rochester 2013). Prior to that, extensive epidemiological studies were less frequent and usually took a cross-sectional approach (detecting at a single point in time) (Golub *et al*. 2009). As of 2012, BPS and BPF could already be detected at concentrations similar to those of BPA in human matrices (Rochester and Bolden 2015). In a study of pregnant Chinese women (2014–2015), BPA was detected in 72% of participants, BPF in 97% and BPS in 64% (n = 941) (Li *et al*. 2019). Detection of BPF in particular has increased in biomonitoring over the last two decades (Li *et al*. 2019).

Either BPA or BPS (not BPF) was found in 100% of boars (n = 54, hair, Poland, 2020–2022), higher in females and with higher concentrations of BPA (10–500 picograms per milligram (pg/mg) of dry weight) in more industrialized or inhabited regions (Gonkowski *et al*. 2023). The same is true for 64–100% of samples from fish and molluscs in the Pearl River, China. This was in agreement with previous samples from soil, sludge and water collected there (Peng *et al*. 2023).

Key developments since 2012

The 2012 report makes no substantial mention of bisphenols other than BPA (BPS and BPF are listed but not discussed). This has shifted as BPA is being replaced, and alternatives are steadily increasing in production volume. While previously it was only BPA that posed a concern, now there are three very common and a range of less common alternatives to BPA deserving attention. It would be advisable to extensively test novel bisphenols for their properties, including endocrine disruption, prior to their use in industry and release, rather than to begin using them and wait for toxicology and epidemiology to catch up.

4.4.2 Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) were first introduced in the 1920s and were globally banned between the 1970s and 1990s. Despite this, they continue to be a concern (Hutzinger 2018; Bräuner *et al*. 2016; Zani *et al*. 2019).
Their identification as ubiquitous and persistent pollutants is what first drew attention to them in 1966, while DDT was being investigated (Hutzinger 2018; Reddy *et al*. 2019), and finally resulted in their regulation through the Stockholm Convention on Persistent Organic Pollutants in 2004.
Interest in them as EDCs has been more recent. PCBs are a large group with 209 congeners, depending on the degree of chlorination (Klocke *et al*. 2020). They are persistent and ubiquitous (Reddy *et al*. 2019; Encarnação *et al*. 2019). Higher chlorination congeners are less volatile, more hydrophobic (Avila *et al*. 2025), and more persistent in the environment (Reddy *et al*. 2019), and are increasingly likely to accumulate in organic sediments or fatty tissue; this impacts accumulation, exposure routes and potential adverse effects (Zani *et al*. 2019).

FIGURE 4.2

POLYCHLORINATED BIPHENYLS (PCBs)



Twelve PCBs have coplanar phenyl rings due to their chlorination patterns, and are therefore classified as "dioxin-like" (Reddy *et al*. 2019; Wen *et al*. 2025). Their degradation is slower than that of their non-coplanar counterparts (Reddy *et al*. 2019). Dioxin-like, coplanar PCBs have received particular attention as EDCs (Bräuner *et al*. 2016).

Use and exposure

PCBs were used in a range of industrial applications, such as construction (Bräuner *et al*. 2016), hydraulic fluids, fire retardants, plasticizers, electric transformers and capacitors (Breivik *et al*. 2002a, 2002b; Hutzinger 2018; Encarnação *et al*. 2019), and paints and pigments (Klocke *et al*. 2020). They were also used as additives to plant protection product formulations to increase their insecticidal properties (added to DDT, lindane, carbaryl and organophosphorus compounds) (Hutzinger 2018).

The unintentional production of PCBs is a large and continued source of contamination (Stockholm Convention 2026b). Their synthesis and release occurs during chemical manufacturing, particularly pesticides (Wen *et al*. 2025), but also from incorrect disposal and incineration of PCB-containing waste (Reddy *et al*. 2019).

Overall an estimate of 1 million to 1.5 million tonnes of PCBs were produced intentionally worldwide since the late 1920s (Stockholm Convention 2026b). Despite an overall decrease in PCB contamination in food since the 1970s, ingestion

of meat, fish and animal products was and is believed to be the principal exposure route for human contamination (Bräuner *et al*. 2016); Reddy *et al*. 2019), particularly for high chlorination PCBs (Wen *et al*. 2025). There is evidence suggesting that exposure to lower-chlorination, more volatile PCBs through inhalation is a more significant factor than previously believed, but this is not unanimous (Saktrakulkla *et al*. 2020; Zani *et al*. 2019). While dermal absorption is possible, it is an unlikely route for the general population and is limited to occupational exposures (Reddy *et al*. 2019; Zani *et al*. 2019). In humans, urine, faeces and milk are the main monitoring matrices (Reddy *et al*. 2019). For wildlife, fatty tissue is used most frequently.

The presence of PCB-containing waste in landfills, particularly e-waste, results in releases of PCBs to air, particularly where containment measures are absent or inadequate (Reddy *et al*. 2019; Zani *et al*. 2019). The high stability of PCBs means that they are easily transported through air to even remote ecosystems, such as the Arctic (Reddy *et al*. 2019). Soil exposure similarly occurs from landfill waste disposal and from atmospheric transportation and deposition (Reddy *et al*. 2019).

Endocrine-disrupting properties

PCBs are likely to act via a range of endocrine mechanisms to produce different adverse outcomes (Hutzinger 2018). Many PCBs are xenoestrogens (Soto *et al*. 1995), impacting fertility and reproduction, as evidenced by wildlife monitoring and laboratory studies (Kadhim *et al*. 2024). Even at low estrogenicity, the presence of multiple persistent PCBs in one biological system can give rise to cumulative effects (Soto *et al*. 1995).

PCBs can interact with the thyroid system (Babić Leko *et al*. 2021). Non-dioxin-like PCBs are known to produce adverse neurodevelopmental and neurotoxic effects (Saktrakulkla *et al*. 2020; Klocke *et al*. 2020).

Dioxin-like PCBs bind to and affect the aryl hydrocarbon receptor (Saktrakulkla *et al*. 2020; Wen *et al*. 2025; Encarnação et al. 2019), which is linked to changes in gene expression and hormone production (Wen *et al*. 2025), resulting in, for example, liver hypertrophy, fertility issues and cancer (Reddy *et al*. 2019; Buha Djordjevic *et al*. 2020). Prenatal exposure to dioxin-like PCBs results in reduced production of key hormones, such as cortisol and cortisone, while increasing production of androstenedione and dehydroepiandrosterone (Wen *et al*. 2025), thereby damaging development.

Biomonitoring

Human biomonitoring efforts have historically focused on site-specific contamination. For example, a study from Italy found high quantities of PCBs in almost all participants (between 400 and 900 ng/g serum), associated with proximity to a former production plant (Zani *et al*. 2019). The higher contamination levels in older subjects highlights the accumulation potential of PCBs (Ritter *et al*. 2011; Zani *et al*. 2019).

A study testing fatty foods in remote regions of Iowa, United States of America, in 2020, found a wide range of PCB congeners in collected samples, confirming that even without site-specific contamination, ingestion exposes the population (Saktrakulkla *et al*. 2020). The association with other chlorinated agricultural products in the food samples tested may support the hypothesis that PCBs are not being kept out of production lines and are still being made and released as by-products (Saktrakulkla *et al*. 2020).

A Danish study – Health Effects of PCBs in Residences and Schools (HESPERUS) – determined high levels of airborne contamination from PCBs released from paint and lacquer in schools and apartment buildings. The study focused on low chlorination, semi-volatile PCBs (Bräuner *et al*. 2016). Two cohorts (schoolchildren and residents), for a total of almost 100,000 individuals, were identified. Of the schoolchildren cohort (n = 66,769), 78% were exposed to some amount of PCBs, with 26% being exposed to high quantities (above 1,000 ng/m^3 air, requiring an action plan). The cohorts of this study are now continuously monitored to determine, with greater certainty, what adverse health outcomes are expected upon prolonged PCB exposure through inhalation (Bräuner *et al*. 2016).

A Polish study examining livestock feed (2013–2022) found that 5% of examined samples

contained PCBs above indicated European Union threshold values (Pajurek *et al*. 2024), and non-dioxin-like PCBs were most abundant in fish-based feed (oil and meal).

The persistence and affinity for lipid tissue of PCBs lead to their long-term accumulation in animals that consume contaminated feed, consequently exposing humans through meat consumption. An overview of PCB levels measured in human milk is provided via the dashboard of the Global Chemicals Monitoring Programme led by UNEP and funded by the Global Environment Facility (UNEP 2017).

Monitoring of wildlife often focuses on aquatic predatory species high in the trophic chain. PCBs have been found in the blubber of a range of Alaskan seal species, with older specimens and male ones presenting higher averages. Of the organochlorine pollutants that were being investigated, PCBs made up the largest fraction. Monitoring levels over the last two decades has shown an average decrease in PCBs found, indicating that regulation of these chemicals has positively contributed to changes in environmental concentrations (Olnes *et al*. 2025).

PCBs were also found in eggs of wild birds in a 2020 study. It determined that higher lipid content of the eggs correlated to higher PCB burden, which in turn was related to a higher rate of feeding on fish, particularly in sites for which a higher PCB contamination was known (Hammond *et al*. 2025). Fish are again identified as a key factor in food-related contamination with PCBs.

Overall, evidence points towards the slow decline of PCBs in the environment over the last two decades (Hung et al. 2016; Saktrakulkla *et al*. 2020). In the future, the removal and remediation of PCBs should be prioritized, as well as the enforcement of current global regulations. PCB clean-up is a cost- and labour-intensive process that generates high waste volumes for low extraction and removal percentages (Reddy *et al*. 2019).

Key developments since 2012

PCBs are among the most researched environmental contaminants and are consequentially extensively covered in the 2012 report, but were mostly discussed for their persistent, bioaccumulative and toxic properties rather than their endocrine-disrupting effects (UNEP and WHO 2013). Ongoing work on PCBs should focus on better understanding adverse health effects, and on the removal and remediation of their ubiquitous contamination.

4.4.3 Nonylphenols

The term nonylphenols (NPs) refers to a class of structural isomers of a phenol ring with a nine-carbon alkyl chain (linear or branched) (De la Parra-Guerra and Acevedo-Barrios 2023). One of the most commonly generated and detected NP isomers is 4-NP, with the linear alkyl chain in the 4 position of the ring (Lee *et al*. 2023; Mao *et al*. 2012; De la Parra-Guerra and Acevedo-Barrios 2023). NPs are included as EDCs in the list of substances of very high concern under REACH (see annex III).

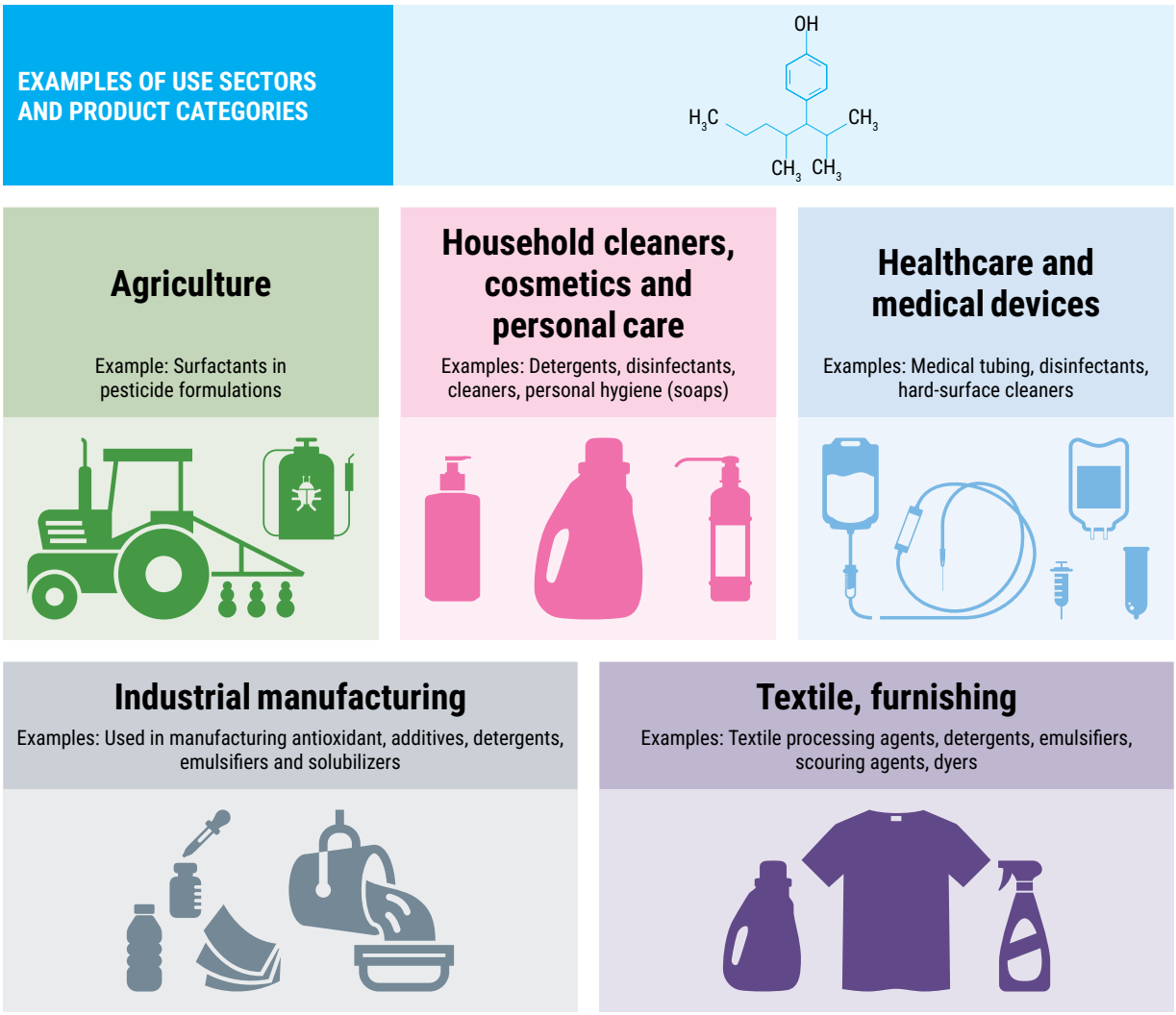
Use and exposure

NPs are known EDCs and are high production volume chemicals (De la Parra-Guerra and Acevedo-Barrios 2023; Lalonde and Garron 2021). NPs have no natural sources (Mao *et al*. 2012) and are mainly used in the production of nonylphenol ethoxylates (NPnEOs), and were otherwise used as solvents (Fairchild *et al*. 1999). NPnEOs are non-ionic surfactants and emulsifiers used in various industries (for example, detergents, textiles, paints, paper, pesticides and steel manufacture) since the 1960s (Lalonde and Garron 2021). They have also found application as spermicides (De la Parra-Guerra and Acevedo-Barrios 2023; Hwang *et al*. 2024). A comprehensive 2023 review described NPs and NPnEOs as "emerging pollutants" (De la Parra-Guerra and Acevedo-Barrios 2023), but this is a mischaracterization.

NPs are the degradation product of NPnEOs (Loos *et al*. 2008), facilitated by UV irradiation, anaerobic degradation in water (De la Parra-Guerra and Acevedo-Barrios 2023; Funari Junior *et al*. 2025; Araujo *et al*. 2017), heat in water (Isidori *et al*. 2007), anaerobic treatment of wastewater (Mao *et al*. 2012; Nimrod and Benson 1996; Lalonde and Garron 2021), and microbial biodegradation

FIGURE 4.3

NONYLPHENOLS (NPs)



(Lee *et al*. 2023; Mao *et al*. 2012). Treatment of NPnEOs in wastewater treatment plants results in an increase of NPs in the effluent, and therefore contamination of surface water (Isidori *et al*. 2007).

The main exposure route for humans is probably ingestion of polluted water and food (Funari Junior *et al*. 2025). In 2002, NPs were detected in German supermarket food at levels of 0.1–19.4 micrograms per kilogram (µg/kg) (Guenther *et al*. 2002). In 2013, NP in Italian public and bottled drinking waters was evaluated: in all samples, concentrations varied from below the quantification limit (7.7 µg/m^3) up to a maximum of 84 µg/m^3 (Careghini *et al*. 2015).

Fetuses can already be exposed in utero, as 4-NP can cross the placental barrier, and neonates are additionally exposed from accumulated NPs in milk (Funari Junior *et al*. 2025).

Endocrine-disrupting properties

The EDC properties of NPs have been suspected since the 1930s (Gautam and Chaube 2021), known since 1978 (De la Parra-Guerra and Acevedo-Barrios 2023), and solidified throughout the early 1990s (Nimrod and Benson 1996). NPs are xenoestrogens and their activation of the estrogen receptor alpha (ERα) receptors can cause a cascade of adverse effects (De la Parra-Guerra and Acevedo-Barrios 2023; Araujo *et al*. 2017; Isidori *et al*. 2007). 4-NP has additional

adverse effects on neurological development (Lee *et al*. 2023; Acir and Guenther 2018) and has been connected to decreased sperm count and testicular cancer (Funari Junior *et al*. 2025), as well as being a suspected obesogen and allergy trigger (De la Parra-Guerra and Acevedo-Barrios 2023). Additionally, alkylphenols can have a synergistic effect with other contaminants and increase their endocrine-disrupting effect even at very low (nanomolar) concentrations (Acir and Guenther 2018).

NPs are amphiphilic and bioaccumulative (Careghini *et al*. 2015; De la Parra-Guerra and Acevedo-Barrios 2023; Funari Junior *et al*. 2025; Acir and Guenther 2018), preferentially adsorbing to organic matter, soil and sediment, but can be transported and dispersed in water (Mao *et al*. 2012; Araujo *et al*. 2017). These pollution reservoirs make monitoring and removal of NPs difficult. There is extensive literature on the adverse effects of alkylphenols and their parent compounds on animals. Aquatic organisms are most sensitive to NP exposure (Lalonde and Garron 2021). At higher concentrations, NPs are acutely toxic to aquatic biota (De la Parra-Guerra and Acevedo-Barrios 2023), but lower doses can cause equal harm via other routes.

Biomonitoring

There are few significant longitudinal studies on human exposure to NPs or octylphenols, with most information on endocrine-disrupting effects deriving from animal or laboratory models. Adverse effects have been recorded; for example, prenatal exposure to alkylphenols has been linked to lower childhood IQ and memory skills (Long *et al*. 2024), but studies including human data remain sparse.

Another 2013 study on prenatal NP exposure concluded that higher than median urinary concentrations of NPs were linked to decreased maternal weight gain and shorter and smaller neonatal body size (Tsai *et al*. 2013).

In 1999, research established that salmon birth rates (or return rates) declined due to 4-NP used as a solvent of pesticide spray in Canadian forests with Metacil 1.8D for spruce budworm control (Fairchild *et al*. 1999). NPs were found at about 40 ng/g in 12 dead orcas (2006–2018) and as the main contaminant in them (Funari Junior *et al*. 2025). While no direct link to mortality was drawn, the abundance detected was concerning.

Despite regulation of 4-NP and NPnEOs since 2003 in the European Union (Araujo *et al*. 2017; De la Parra-Guerra and Acevedo-Barrios 2023), including prohibition in cosmetic production since 2009 (EU 2009), and regulation by the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade since 2019 (Rotterdam Convention 2026), NPs persist in the environment and are recorded in environmental, human and animal matrices.

Key developments since 2012

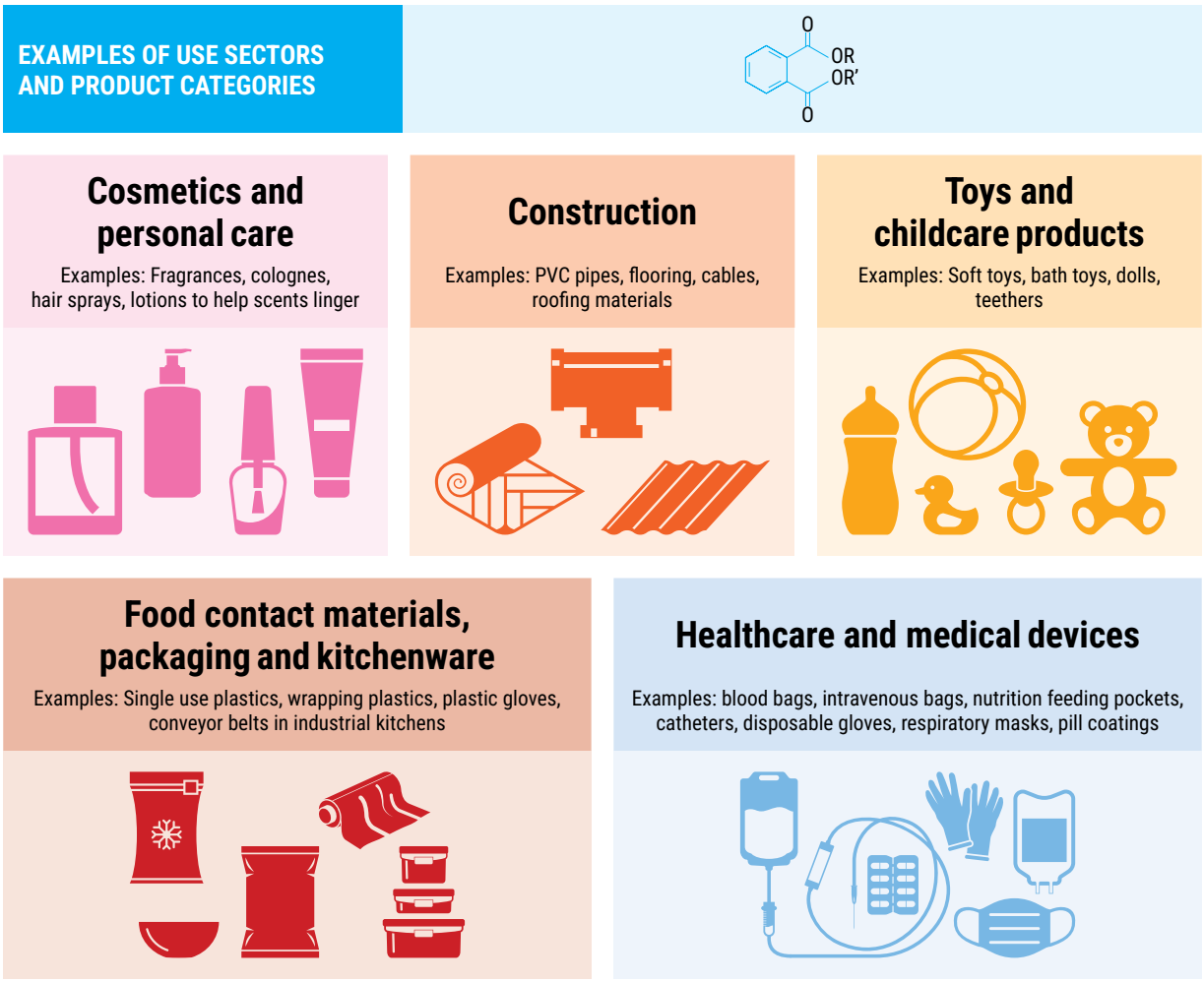
The 2012 report refers to nonylphenols regularly, particularly mentioning that their estrogenic effects may be weak, but that evidence also demonstrates the constructive interference with other EDCs (UNEP and WHO 2013). Regulations had been placed on 4-NP far prior to 2012, but the continued detection of it means it is an ongoing problem.

4.4.4 Phthalates

Phthalates are structurally related esters of phthalic acid, but present a complex, structurally diverse and large class of substances.
Several phthalates are included as EDCs in the list of substances of very high concern under REACH (see annex III). Based on size and therefore molecular weight, they can be categorized as low- and high-molecular-weight phthalates (Hauser and Calafat 2005; Mérida *et al*. 2023; Martín-Pozo *et al*. 2021). Low-molecular-weight phthalates are mainly used as solvents, fixatives, diluents, lacquers and adhesives, and are therefore common in personal care products (Hauser and Calafat 2005; Mérida *et al*. 2023; Martín-Pozo *et al*. 2021). Examples include diethyl phthalate, dimethyl phthalate and diisobutyl phthalate. High-molecular-weight phthalates are used as plasticizers (in PVC or other vinyl plastics) (Hauser and Calafat 2005; Martín-Pozo *et al*. 2021; Mankidy *et al*. 2013; Mérida *et al*. 2023; Giuliani *et al*. 2020), and are therefore found in food contact materials (Giuliani *et al*. 2020), flooring (Mérida *et al*. 2023), textiles (Gonkowski *et al*. 2024), and medical devices and

FIGURE 4.4

PHTHALATES



pharmaceuticals (Wang and Qian 2021; Hauser and Calafat 2005; Sree *et al*. 2023). Phthalates account for around 80% of additives in single-use plastics (Sree *et al*. 2023). Phthalates are non-persistent (Hauser and Calafat 2005).

Four phthalates, in the context of EDCs, are at the centre of current research: dimethyl phthalate, diethyl phthalate, DEHP and butylbenzyl phthalate (Bu *et al*. 2020). Endocrine-disrupting effects have been reported for a number of phthalates, but their mechanism of action is still under question, and each member of the class poses its own unique challenges (Mankidy *et al*. 2013).

Use and exposure

Phthalates are, as plasticizers, not chemically bound to the polymers they are employed with, so can leach out (Heudorf *et al*. 2007; Mankidy *et al*. 2013). This, in combination with their common use, has caused widespread exposure: phthalates of some kind are ubiquitous in humans (Mérida *et al*. 2023) and in animals (Foley *et al*. 2025).

Ingestion alone can account for the intake of phthalates above quantities recommended (tolerable daily intakes) by regulatory bodies (Heudorf *et al*. 2007). Their common presence in food contact materials means that ingestion of contaminated food is one of the key exposure routes for humans (Chang *et al*. 2021; Hauser and Calafat 2005), particularly for DEHP and DBP (Heudorf *et al*. 2007). The use of phthalates, such as DBP, in pill coatings and drugs adds to the ingestion-based exposure of the general public

(Heudorf *et al*. 2007). Exposure is also possible through dermal absorption (degradation from diesters to monoesters on the skin, then dermally absorbed). Phthalates may be characterized as semivolatile organic chemicals (Wang and Qian 2021), with low-molecular-weight phthalates being more volatile than their high-molecular-weight counterparts. Nonetheless, inhalation is a potential exposure route for both (Bu *et al*. 2020), as phthalates associate with household dust (inhalation of high-molecular-weight phthalates) (Heudorf *et al*. 2007).

The use in medical devices is a source of exposure by injection (Sree *et al*. 2023). Intrauterine exposure also occurs (Assens *et al*. 2024; Heudorf *et al*. 2007). Lastly, the use in children's toys is of particular concern: increased mouthing activities mean that ingestion of plasticizers occurs, demonstrated by higher DEHP concentrations measured for children (Heudorf *et al*. 2007). Toddlers and children are particularly vulnerable to endocrine disruption, which has led to most regulations being placed on phthalate content in toys and products intended for children (Wang and Qian 2021).

Leachate from plastic waste is of particular concern for environmental exposure (Seibert *et al*. 2019), particularly since current wastewater treatment methods do not seem to be adapted to the high volume of contaminants, such as phthalates, in sludge and influent water, resulting in leftover contaminants in the effluent and, eventually, in drinking water (Seibert *et al*. 2019).

Metabolism of phthalates to their monoester derivatives means that assessment of exposure in the body is difficult. MEHP measured in the body can come from internal metabolisms of DEHP or from exposure to MEHP, formed in the environment by DEHP abiotic degradation (Heudorf *et al*. 2007). MEHP also seems to account for only around 10% of originally absorbed DEHP, and it has the shortest half-life of examined metabolites (Heudorf *et al*. 2007). Metabolism occurs quickly and excretion then follows through urine and faeces (Hauser and Calafat 2005). For human studies, urine is the primary matrix tested to assess exposure to phthalates (Assens *et al*. 2024; Hauser and Calafat 2005).

Endocrine-disrupting properties

Phthalates have estrogenic effects (Mankidy *et al*. 2013), but evidence suggests they do not act through the estrogen receptor (like other EDCs, such as BPA) but via the Peroxisome Proliferator-Activated Receptor Alpha (PPAR-α) (Heudorf *et al*. 2007; Sree *et al*. 2023). Additionally, the contribution to oxidative stress (particularly for DEHP and diethyl phthalate) affects the ordinary workings of the endocrine systems (Mankidy *et al*. 2013). They exert anti-androgenic activity and potential adverse effects on reproductive systems in vertebrates (Wang and Qian 2021; Sree *et al*. 2023; Assens *et al*. 2024). Phthalates are suspected obesogens (Ahn and Jeung 2023), interfering with thyroid hormones (Heudorf *et al*. 2007; Seyoum and Pradhan 2019; Giuliani *et al*. 2020) and other metabolic pathways, as well as being linked to increased incidences of diabetes mellitus (Ahn and Jeung 2023).

Biomonitoring

Generally, phthalates have a short half-life in most animals and also in humans (less than a day for the parent compound, up to three days for monoester metabolites) (Martin *et al*. 2022). The ester chain length appears directly related to retention time (Sree *et al*. 2023). Consequently, single exposures may pose no danger, but the chronic presence of phthalates and their metabolites in human matrices lends the opportunity for adverse effects.

Associations between phthalate exposure and adverse health outcomes have been studied since the 1970s (Wigle *et al*. 2008). Many phthalates have been identified as EDCs but this is not free of controversy (Hauser and Calafat 2005). A 2004 study (Rais-Bahrami *et al*. 2004) on a small cohort (19) of adolescents who, due to medical reasons, had been exposed to high quantities of DEHP in infancy (42–140 mg/kg of body weight) is at times cited as an example of DEHP's harmlessness to humans (Heudorf *et al*. 2007). In their adolescence, they did not demonstrate any adverse health outcomes that could be linked to this effect (Rais-Bahrami *et al*. 2004). The researchers however stressed that exposure was not chronic and, most importantly, that DEHP had not been metabolized to MEHP in the infants' bodies (Wigle *et al*. 2008). As DEHP is not acutely

toxic until quantities of at least 1 g/kg of body weight (Heudorf *et al*. 2007), and metabolites seem to be the key compounds of phthalate endocrine-disrupting activity (Hauser and Calafat 2005), this does not demonstrate the safety of DEHP.

A Danish pilot study on mothers and daughters (n = 176) made a connection between high maternal phthalate metabolite concentrations during pregnancy and adverse health effects in their adolescent daughters (smaller uterine volume, lower number of ovarian follicles, effect on insulin-like growth factor 1) (Assens *et al*. 2024).

In animals, particularly aquatic ones, phthalates are found just as regularly (Net *et al*. 2015; Marmara *et al*. 2024). Consumption of contaminated fish also contributes to human exposure. Novel biomonitoring studies have confirmed that even wild terrestrial mammals (boars) are exposed to phthalates, at relatively high concentrations for some individuals. Exposure is largely traced back to human activities, both of industry and of general environmental pollution (Gonkowski *et al*. 2024).

Key developments since 2012

A significant shift in phthalate research in the last decade has been the investigation of multiple members of the class in the same system, under the same conditions, or mixtures thereof, thus moving away from a single-chemical approach (Mankidy *et al*. 2013).

As in the case of other EDCs, the controversy surrounding phthalates has sparked interest in alternatives that are technically suitable, but whose safety has not yet been established. One such potential substitute is DINCH, which is already being studied as an EDC (Warner and O'Neil 2022).

Unlike phthalates, DINCH has a cycloaliphatic structure. It is one of the main substitutes considered for phthalates, but it may be a case of regrettable substitution. Phthalate toxicity is dependent on the length and structure of the alkyl or aryl side chains (Sree *et al*. 2023), so the replacement of the aromatic ring with an aliphatic ring might not remove the toxicity to the extent desired.

There is already evidence for nephrotoxicity and impairment of development of neurological pathways, as well as fertility interference. European human biomonitoring reports a steady increase in concentrations (Vogel *et al*. 2023; Rodriguez Martin *et al*. 2023), but there are yet to be extensive DINCH-focused studies. It warrants greater future attention and inclusion in phthalate-based studies.

4.4.5 Triphenyl phosphate

Triphenyl phosphate (TPP) is an aryl organophosphate ester, used in large part to replace brominated flame retardants. It is included as an EDC in the list of substances of very high concern under REACH (see annex III).

Use and exposure

TPP is an organophosphate flame retardant and plasticizer (Gyllenhammar *et al*. 2017; Hu *et al*. 2023; Morisseau *et al*. 2009). Following the regulation of PBDEs through classification as persistent organic pollutants under the Stockholm Convention (Secretariat of the Stockholm Convention 2026b; Wang *et al*. 2018; Hu *et al*. 2023), the production volumes of aryl organophosphate esters such as TPP have greatly increased (Wang *et al*. 2021; Hu *et al*. 2023). Organophosphate flame retardants are produced with the intention of increasing human safety, specifically by protecting humans from fire hazards. However, these chemicals also have inherent hazards to ecosystems, including causing developmental toxicity in a wide range of species (Germain and Winn 2024).

TPP is a ubiquitous environmental contaminant, and its stability, as is the case for most aryl organophosphate esters, facilitates long range water- or air-based transport to remote locations (Germain and Winn 2024).

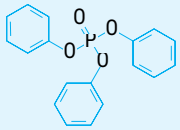
While TPP is a common aryl organophosphate ester, other regions of the world, such as China, rely on other organophosphate flame retardants, which are also visible in human biomonitoring results (Qin *et al*. 2021).

The addition of organophosphate flame retardants to furniture, textiles, electronics and

FIGURE 4.5

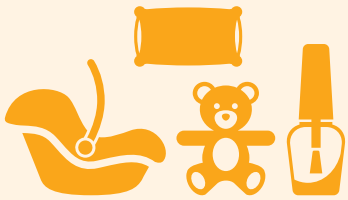
TRIPHENYL PHOSPHATE (TPP)

EXAMPLES OF USE SECTORS AND PRODUCT CATEGORIES



Toys and childcare products

Examples: Foam-containing children's and baby items including changing mattresses, bath mats, car seats, nursing pillows, highchair cushions, varnishes, nail polish and other plasticized consumer products



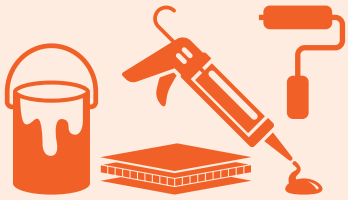
Textile, furnishing

Examples: Flame retardants in protective workwear, firefighter uniforms, upholstery, curtains, carpets



Building and construction

Examples: Insulation foam, roofing paper



Electronic and electrical equipment

Examples: Plastic casings, circuit boards, electrical connectors, insulation materials

building materials results in their dispersion and accumulation in indoor areas (Wang *et al*. 2021). Therefore, humans, particularly toddlers and children, as well as pets, are mainly exposed through household dust inhalation or ingestion (Qin *et al*. 2021; Hu *et al*. 2023; Wang *et al*. 2021). Dust ingestion, particularly from e-waste, is also a main occupational exposure of concern for aryl organophosphate ester (Qin *et al*. 2021). Aryl organophosphate esters have also been reported in food and drinking water (Wang *et al*. 2021), leading to ingestion as a source of exposure. Ambient air and soil monitoring in a populated city in Türkiye indicated aryl organophosphate ester levels higher than those of PBDEs, revealing a clear replacement of the latter, resulting in much higher exposure to aryl organophosphate esters (Kurt-Karakus *et al*. 2018).

Unlike PBDEs, aryl organophosphate esters undergo metabolism in humans (Qin *et al*. 2021; Hu *et al*. 2023; Germain and Winn 2024), but metabolites have shown similar biological effects (Wang *et al*. 2018); when assayed, TPP and diphenyl phosphate produced similar endocrine effects (Wang *et al*. 2018; Wang *et al*. 2021).

Endocrine-disrupting properties

Aryl organophosphate esters have been shown to disrupt all three major axes of the endocrine system (the hypothalamic–pituitary–gonadal, hypothalamic–pituitary–adrenal, and hypothalamic–pituitary–thyroid axes), resulting in adverse effects on fertility, fetal development, glucose regulation and thyroid hormone regulation (Hu *et al*. 2023). TPP alters gene expression, sex hormone balance (estrogen receptor agonist

and androgen receptor antagonist) (Wang *et al*. 2018), as well as altering thyroid function, metabolic pathways and fetal development (Germain and Winn 2024). The dangers for epigenetic endocrine effects make exposure during key developmental stages particularly hazardous (Germain and Winn 2024). Aside from TPP, other aryl organophosphate esters may act differently, such as TDCPP, being an estrogen receptor alpha (ERα) antagonist (Ji *et al*. 2022). Human exposure to TPP has been associated with reduced sperm counts and increased prolactin production (Hu *et al*. 2023). TPP is particularly toxic to aquatic life, causing a range of developmental issues (Ding *et al*. 2022). Doubt persists on whether TPP is a human EDC (Ding *et al*. 2022).

Biomonitoring

TPP is pervasive in water systems and, while not generally acutely toxic to aquatic organisms, endocrine-disrupting effects occur on a chronic exposure basis (Wang *et al*. 2018; Germain and Winn 2024). It is common in interior vehicle and household dust, at high quantities, between the µg/g and mg/g scales (Wang *et al*. 2018; Wang *et al*. 2021).

Organophosphate flame retardants are regularly detected in humans and the environment (Germain and Winn 2024; Hu *et al*. 2023). The use of organophosphate flame retardants as additives means they are not chemically bonded to the materials and may freely and over time leach out into the environment (Wang *et al*. 2018). The hydrophobicity of TPP (Ding *et al*. 2022) results in accumulation in fatty substrates, as well as in human milk, leading to high neonatal exposure (Wang *et al*. 2018).

TPP is the most commonly detected aryl organophosphate ester in humans, with some studies detecting it at 100% frequency, up to 910 ng/g dry weight of hair (Robin *et al*. 2024).

A decade ago, TPP was detected (through its metabolite diphenyl phosphate) in up to 35 ng/mL urine in first-time mothers in a Swedish study (Gyllenhammar *et al*. 2017). These concentrations were similar to those detected in a number of studies from the United States of America (Li *et al*. 2025; Gyllenhammar *et al*. 2017). Similar, if not higher, diphenyl phosphate concentrations are still detected globally, but it is important to note that diphenyl phosphate can form as the metabolite of a range of aryl organophosphate esters (Wang *et al*. 2021).

Key developments since 2012

The 2012 report mentions TPP only as an additive to plastics and in relation to brominated flame retardants (UNEP and WHO 2013). Following the increased introduction of organophosphate flame retardants, however, research on them has increased.

TPP is a common aryl organophosphate ester but has already been regulated in many parts of the world with new, substituting chemicals in the class being found in human or environmental matrices regularly (Hu *et al*. 2023), produced and released without prior investigation of their potential adverse health outcomes.

4.4.6 Pesticides

Modern agriculture has relied heavily on the use of agrochemicals to support food production for an ever-growing human population (Devi *et al*. 2022). In line with that, the extensive use of pesticides has become an increasingly common agricultural practice that has already laid a heavy burden on the environment ever since the Green Revolution of the 1960s (Devi *et al*. 2022; Leoci and Ruberti 2021). Up to the 2010s, EDC research focused primarily on pesticides (Pravednikov *et al*. 2024). Of all chemicals discussed here, pesticides are the only ones designed specifically with biological toxicity intended (Vandenberg *et al*. 2020; Combarnous 2017; Barr 2008).

Major pesticide chemical groups include organochlorines, organophosphates, carbamates, dithiocarbamates and triazines. Later additions, claimed to be safer alternatives, are pyrethrins (and pyrethroids) and neonicotinoids (Zhou *et al*. 2025; Devi *et al*. 2022). As examples to illustrate issues relevant to exposure to and regulation of pesticides, this section will discuss atrazine, chlorpyrifos and metiram in greater detail.

FIGURE 4.6

PESTICIDES

EXAMPLES OF USE SECTORS AND PRODUCT CATEGORIES

Agriculture

Examples: Herbicides, insecticides and fungicides used in agroindustry, farming, and households



Atrazine is a triazine herbicide, one of the most studied exponents of this group (Barr 2008), and one of the most common global herbicides since the 1970s (Vandenberg *et al*. 2020). Chlorpyrifos is an insecticide of the organophosphate class (Miranda *et al*. 2023; Hazarika *et al*. 2020). Metiram is a dithiocarbamate fungicide that has been in use for over 40 years (Shaalan *et al*. 2024).

Use and exposure

Pesticides comprise all those agrochemicals used for the elimination of competing species and harmful pests, for the protection of crops and domesticated animals (Kitamura *et al*. 2006). "Pesticides" is an umbrella term for biocidal products (which include rodenticides and disinfectants) and plant protection products. These include herbicides, insecticides (the two most abundant classes of plant protection products) (Barr 2008), bactericides and fungicides (Devi *et al*. 2022; Leoci and Ruberti 2021).

Use of all agrochemicals, including pesticides, has grown consistently over the years and is predicted to keep growing (Zhou *et al*. 2025; Devi *et al*. 2022). The top three users of pesticides are China, the United States and Brazil, with the European Union and India close behind (Leoci and Ruberti 2021; Devi *et al*. 2022). Asia as a continent accounts for 50% of global pesticide use (Leoci and Ruberti 2021; Devi *et al*. 2022). African countries report the lowest, but growing, average use of pesticides (Zhou *et al*. 2025; Leoci and Ruberti 2021). South Africa and Nigeria are however among the greatest commercial exporters of pesticides, after the United States and Thailand (Leoci and Ruberti 2021). The United States of America is the largest consumer of herbicides (Zhou *et al*. 2025; Devi *et al*. 2022).

Aside from crop protection, insecticides such as N,N-diethyl-m-toluamide (DEET) have been used to control vectorborne diseases (such as malaria) and protect the population from them (Khatib *et al*. 2022).

Ingestion of contaminated food and water is the primary human exposure route (Mnif *et al*. 2011). The scientific literature lacks research on other potential exposure routes, so there may be a research bias towards this conclusion (Pravednikov *et al*. 2024). Household use and agricultural drift of pesticides lead to exposure through inhalation (Mnif *et al*. 2011). Proximity to production and administration sites of pesticides can also lead to chronic human exposure via air or direct contact with contaminated water (Saraswat *et al*. 2024). Exposure of professionals working in agriculture is disproportionately higher than that of the general population and occurs on a chronic basis (Moreira *et al*. 2025; Kalofiri *et al*. 2021; Willenbockel *et al*. 2022; Combarnous 2017). Depending on the application method, dermal absorption and inhalation are relevant exposure routes here.

Organophosphates are still in use today and are some of the most used pesticide active ingredients globally (Miranda *et al*. 2023; Sidhu *et al*. 2019). While not bioaccumulative, as in the case of organochlorines, they present higher acute toxicity and pose risks of their own (Khatib *et al*. 2022), leading to partial restrictions and bans in the early 2000s (Barr 2008). Under regular environmental conditions, organophosphates should break down rapidly (Sidhu *et al*. 2019).

Chlorpyrifos exposes humans through their diet and farmers are particularly vulnerable to exposure when mixing, loading and spraying it (Hazarika *et al*. 2020). Household use of the insecticide contributes to its accumulation in dust and deposition on surfaces, disproportionately exposing children (Kitamura *et al*. 2006). Early research on the absorption of organophosphates in humans suggested that orally ingested pesticides were readily excreted, but dermal dosing left large amounts in the skin's surface, even after some time had passed (Kitamura *et al*. 2006). This suggests that dermal exposure may lead to longer retention of the pesticides in question and more potential harm.

Triazines share strong structural similarity; they are more persistent and bioaccumulative than organophosphates (Carlier *et al*. 2024). For example, atrazine can be described as persistent in the environment, not degrading in groundwater, soil (Jablonowski *et al*. 2009) and sediment (Vandenberg *et al*. 2020). Atrazine is, after glyphosate, the most commonly used herbicide almost everywhere but the European Union, where it was banned in 2004 (Vandenberg *et al*. 2020). Notably, this ban was based on evidence of its damage to aquatic ecosystems and contamination of drinking water, and was not based on evidence of endocrine-disrupting action. It degrades slowly, especially in groundwater and soil, and ubiquitously contaminates surface water after use (Vandenberg *et al*. 2020). In the rest of the world, atrazine is still in regular use, particularly in the United States of America (US EPA 2015a).

Dithiocarbamates such as metiram are employed as fungicides and, at times, rodent repellents (Mehran Anjum, Ali and Iqbal 2017). They have been found to be acutely toxic to aquatic organisms (Mehran Anjum, Ali and Iqbal 2017).

Endocrine-disrupting properties

Many pesticides have been known to interfere with the endocrine system, among other toxic pathways (Kalofiri *et al*. 2021; Leoci and Ruberti 2021). Negative effects on fertility (particularly in female reproductive systems) is one of the main adverse outcomes connected to pesticide use, and one of the first that drew the interest of researchers (Leoci and Ruberti 2021). This was a particular focus in the 1990s, when all EDCs were synonymous with xenoestrogens (Vandenberg *et al*. 2020). But the chemical diversity and abundant use of pesticides imply a broader array of potential effects.

Public awareness of other EDCs is generally limited, but pesticides have carved a space for themselves in the layperson's consciousness as inherently associated with endocrine-disrupting effects (Kelly *et al*. 2020; Wee *et al*. 2024).

While active ingredients in pesticides are regulated, tested and registered (declared and scrutinized), almost 90–95% of commercial pesticide product formulation is made up of additional substances, whose composition is often confidential as part of manufacturers' confidential business information (Leoci and Ruberti 2021). While these are described as "inert ingredients", the combined effect of these additional substances or of individual non-pesticide ingredients is at times the "true culprit" (Kalofiri *et al*. 2021), as illustrated previously (see the salmon and 4-NP case mentioned in section 4.4.3) (Fairchild *et al*. 1999).

The endocrine effects of organophosphates, unlike organochlorines, are more disputed, but evidence has connected organophosphates with metabolic disorders, obesity, fertility issues and growth delays (Miranda *et al*. 2023). They do not display consistent estrogenic activity, but have significant anti-androgenic effects (Mnif *et al*. 2011; Kitamura *et al*. 2006), which is the case for chlorpyrifos (Mnif *et al*. 2011). Some organophosphates were shown to be particularly active on the thyroid function in multiple living organisms (Kitamura *et al*. 2006). Chlorpyrifos acts as an androgen receptor antagonist (Mnif *et al*. 2011). It adversely impacts reproductive pathways, probably through

progesterone receptors (Hazarika *et al*. 2020). Some of its metabolites are also more potent than the parent compound (Mnif *et al*. 2011).

Atrazine is an androgen inhibitor and exhibits weak estrogenic effects (Mnif *et al*. 2011). It achieves these effects by aromatase activity enhancement (Galbiati *et al*. 2021). Additionally, it disrupts the hypothalamic–pituitary–adrenal axis (Mnif *et al*. 2011), and appears to disrupt dopamine pathways (Galbiati *et al*. 2021). Other triazines, such as ametryn and desethylatrazine, also display endocrine-disrupting effects on estrogenic, androgenic and thyroid-based pathways, much like atrazine (Carlier *et al*. 2024).

Metiram causes thyroid-mediated adverse effects (Choi *et al*. 2024; Liszewska *et al*. 2024). Breakdown products of metiram may also have anti-thyroid potential (Choi *et al*. 2024; Shaalan *et al*. 2024), as well as inducing teratogenicity, neurotoxicity, immunotoxicity and carcinogenicity (Shaalan *et al*. 2024).

Beyond the active ingredients, additives (which make up the majority of the pesticide formulation) may facilitate or in fact cause endocrine-disrupting effects, leading to an additive or even synergistic cocktail effect (Combarnous 2017). Additionally, the use of pesticides results in the formation of metabolites, sometimes even formed in plants themselves (Saraswat *et al*. 2024; Mnif *et al*. 2011), that exhibit additional or diverging toxicity from their parent (Miranda *et al*. 2023).

Biomonitoring

A 1995 model predicted that only around 0.1% of applied pesticide reached the targeted pest (Collier *et al*. 2016), and pesticide use remains inefficient, often because of improper application practices (Devi *et al*. 2022). Despite 30 years of considerable improvements in application methods, efficacy, and pesticide specificity, the majority of an applied pesticide does not reach the target organism, but disperses further in the environment, where it can have hazardous consequences (Mehran Anjum, Ali and Iqbal 2017; Collier *et al*. 2016). The enormous increase in crop output facilitated by agrochemical use is, according to recent analysis, plateauing, as considerably more pesticides have to be employed to achieve similar or greater outputs than before (Devi *et al*. 2022), which will probably exacerbate these effects unless more sustainable alternatives are implemented. Modern design of pesticides aims towards low persistence, and most pesticides are designed to have short half-lives and relatively poor stability beyond their application area and time frame.

Depending on each pesticide class, and the chemicals within them, biomonitoring relies on different matrices (usually urine (Willenbockel *et al*. 2022), and at times blood or serum) and aims to detect different compounds (parent, metabolite or reaction products) (Barr 2008), but may sometimes only be able to conclude on exposure to a pesticide class (Willenbockel *et al*. 2022). This makes pesticide biomonitoring hugely complex.

Human biomonitoring indicates that pesticide contamination is ubiquitous, among all populations and regions, linking it to the consumption of pesticide residues in food (Mnif *et al*. 2011). Linking certain biomarkers in humans to pesticide exposure has focused mostly on organophosphates (Moreira *et al*. 2025). To monitor pesticide levels in the environment, a range of sentinel species may be used to monitor pesticide levels in the environment (León *et al*. 2021), but the determination of contamination by pesticides such as atrazine is layered. They often metabolize quickly, so detection of only one or some of all possible metabolites means reaching inaccurate conclusions about exposure (Vandenberg *et al*. 2020).

Beyond simply detecting pesticides in humans and animals, there is a particular need to establish correlations between biological effects and biomonitoring data for this class of EDCs (Willenbockel *et al*. 2022).

Key developments since 2012

The 2012 report lists a variety of diseases, including cancers, male and female reproductive issues, delayed puberty, birth defects, and inhibited expression of sexual markers, as consequences of pesticide use and exposure, but links between these are not always clear (UNEP and WHO 2013). Due to the extensive use of organochlorine and organophosphate pesticides, there was a strong focus on these two

classes, which has shifted as organochlorines become more obsolete and organophosphates are no longer common in some parts of the world.

4.4.7 4-methylbenzylidene camphor

4-methylbenzylidene camphor (4-MBC, or enzacamene) is a chemical UV-B filter (Carou *et al*. 2009) and is included as an EDC in the list of substances of very high concern under REACH (see annex III).

Use and exposure

4-MBC has been used in commercial products since the 1970s (Provencher *et al*. 2022). Chemical-based sunscreens are the most popular choice globally (Lorigo, Quintaneiro, *et al*. 2024), and 4-MBC is one of many ingredients used in them. Use of 4-MBC in personal care products exposes humans to it via dermal absorption (Matta *et al*. 2020; Wang *et al*. 2016). After absorption, 4-MBC can accumulate in various tissues, including the placenta (Somade 2023). A positive correlation was established between concentrations of UV filters and average UV irradiation in the region from which samples were collected, highlighting that the use of sunscreen was a major factor in exposure (Liu *et al*. 2022).

Since 2024, 4-MBC is no longer included in the European Chemicals Agency list for permitted UV filters (ECHA 2026b), shifting from 4% as the maximum concentration allowed in ready-to-use products under European Union regulation (EU 2009; Nitulescu *et al*. 2023) to being classed as an EDC under both cosmetics regulations and assessment of substances of very high concern under REACH. 4-MBC was never permitted in some countries, including Japan (Lax *et al*. 2023), and was in use in the United States only till 1978 (Provencher *et al*. 2022).

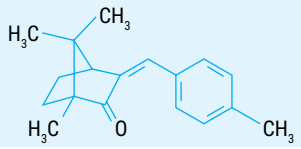
Endocrine-disrupting properties

4-MBC displays estrogenic activity (Somade 2023; Kunz *et al*. 2006; Wang *et al*. 2016), and can lead to the disruption of the mammalian gonadal axis in a sexual dimorphic mode (Wang *et al*. 2016; Carou *et al*. 2009). There is evidence for its toxicity to the thyroidal axis, making it a potential obesogen (Nitulescu *et al*. 2023; Somade 2023). It is also a progesterone receptor agonist (Wang *et al*. 2016; Chantelouve and Ripoll 2022). It has been shown that the combination of benzophenone-3, 4-MBC, and octyl methoxycinnamate is constructive in its toxic effects on mortality and genotoxicity (Lorigo *et al*. 2024), making products using a combination of these increasingly toxic.

FIGURE 4.7

METHYLBENZYLIDENE CAMPHOR (4-MBC)

EXAMPLES OF USE SECTORS AND PRODUCT CATEGORIES



Cosmetics and personal care

Examples: Sunscreens (lotions, sprays, gels) and products with added UV protection such as day creams, face moisturizers, lip balm, makeup foundation



Biomonitoring

A study from Germany on children showed that 4-MBC is still present in single cases, but not on a population-wide basis (Murawski *et al*. 2021), from 70% of samples showing presence in 1995 to 0–5% in 2019 (Schmidtkunz *et al*. 2023). However, a Canadian study on the concentration of UV filters in Arctic bird eggs found 4-MBC still at high concentrations in samples from 2019 (Provencher *et al*. 2022). Differences in body burdens across species also indicate that exposure via the food web is a factor, and the study of a range of species is important.

Key developments since 2012

4-MBC is listed in the 2012 report, but it is not discussed in detail, occurring only under the "UV filter" umbrella term (UNEP and WHO 2013). In the meantime, it has been strictly regulated in many parts of the world.

4.4.8 Triclosan

Triclosan is a polychlorinated hydroxydiphenyl ether (Witorsch 2014) that has been employed as an antibacterial agent since the 1970s (Yueh and Tukey 2016; Thompson *et al*. 2005), after being deemed generally safe during the initial patenting process (Maksymowicz *et al*. 2021).

Use and exposure

Triclosan was designed as a wide-range antimicrobial (G+ and G– bacteria efficient) (Yueh and Tukey 2016; Maksymowicz *et al*. 2021) and antifungal ((Vosátka *et al*. 2018), operating by inhibiting a bacterial enzyme responsible for fatty acid synthesis ((Andreae and Nowak-Węgrzyn 2017). Triclosan has had a marked negative impact on the environment (Saquib *et al*. 2021; Halden 2014), particularly aquatic ecosystems.

Triclosan was first introduced for medical uses but then made its way into a wide range of personal care products (for example, creams, toothpaste, detergents and soaps) and other consumer products (plastic or textile based) (Saquib *et al*. 2021; Witorsch 2014; Wang and Tian 2015; Thompson *et al*. 2005; Yueh and Tukey 2016; Maksymowicz *et al*. 2021), resulting in widespread human and environmental exposure. It was in large part introduced to personal care products as a replacement to parabens (Wang and Tian 2015), following stricter regulations on their use due to their endocrine-disrupting properties. Continuous extensive use of household products with triclosan can also increase antibiotic resistance in bacteria (Vosátka *et al*. 2018; Saquib *et al*. 2021).

The dispersion of triclosan in water leads to a series of adverse outcomes. Photolytic transformation of triclosan to chlorinated dibenzodioxin products contributes to the danger of triclosan (Kliegman *et al*. 2013; Saquib *et al*. 2021). In addition, transformation (chlorination) to chloroform (carcinogen) is also possible (Rule *et al*. 2005). These findings highlight that transformation products can be of high importance for chemical risk assessment (Escher and Fenner 2011).

Currently, triclosan exposure in the European Union continues although the chemical is not produced there, due to restrictions (ECHA 2026c), but may still be present in imported products because several regions globally still favour triclosan as an antimicrobial agent (Matthews 2026). The United States began a phase-out in 2016 by regulating its use in certain personal care products; the continued detection of the chemical leads to the conclusion that these products were not the only or key source of exposure (Levasseur *et al*. 2024). Prior to regulations, triclosan was very common, used globally in products at average concentrations between 0.1% and 0.3% (Vosátka *et al*. 2018).

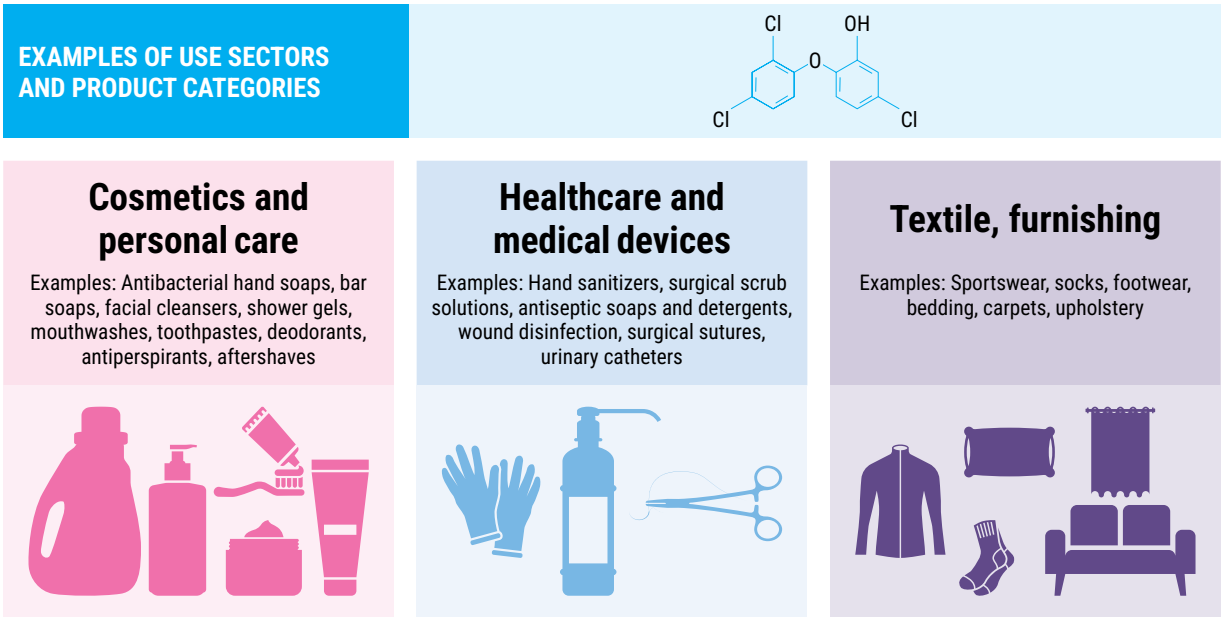
The primary exposure route is dermal absorption, followed by ingestion, as both relate to the use of personal care products such as creams and toothpastes. Use of triclosan-containing products leads to concentrations in blood in the range of nanomols to micromols per litre of blood (Witorsch 2014).

Endocrine-disrupting properties

Triclosan is of particular concern to thyroid homeostasis (Dann and Hontela 2010; Halden 2014). Developmental risk to children is increased by the high concentrations of triclosan in human milk and generally breast tissue (Dann and Hontela 2010). Early childhood exposure has been associated with obesity (Heindel *et al*. 2022) and sensitization to seasonal, inhalant and food allergens (Andreae and Nowak-Węgrzyn 2017).

FIGURE 4.8

TRICLOSAN



There is, as for other EDCs, debate on the extent of adverse effect outcomes from triclosan contamination. A 2014 review, funded by the Colgate Palmolive company, concluded that the examined in vitro and in vivo data showed the endocrine-disrupting effects of triclosan but there was not enough evidence to conclude that triclosan was a human EDC or that levels in humans would be high enough to initiate adverse effects (Witorsch 2014).

Biomonitoring

The high hydrophobicity of triclosan allows it to bioaccumulate in environmental matrices (organic matter in soil or sediment), but also in the lipid tissue of organisms (Thompson *et al*. 2005; Saquib *et al*. 2021; Levasseur *et al*. 2024).

After use, an estimated 96% of triclosan from personal care products is washed into water systems (Dann and Hontela 2010); in wastewater treatment plants triclosan is adsorbed to sludge in high concentrations (Thompson *et al*. 2005), but around 10% pass wastewater treatment and enter river systems. In 2002, triclosan was determined as one of the top 10 contaminants in United States of America rivers, sparking some action to reduce levels, but it remains one of the principal contaminants (Halden 2014). The main triclosan metabolite, methyl triclosan, is probably also an EDC (Witorsch 2014). It has become a key wildlife biomonitoring chemical (Lin *et al*. 2023). O-methylation of triclosan undoes its antibacterial effect (Vosthka *et al*. 2018), but retains potential endocrine-disrupting potency.

Triclosan is commonly detected in humans. There is a correlation between higher age and socioeconomic status, both relating to a higher triclosan burden in monitored subjects (Yueh and Tukey 2016). A 2017 study also detected higher blood contents of triclosan in children whose parents expressed concern over microbial contaminants (Okman and Yalçın 2024), highlighting exposure from personal care products such as hand sanitizers. Exposure, as mentioned, primarily occurs from these personal care products, but also from water and ingestion of food. Malaysian tap water (in 2020) was determined to contain 2.6 ng/L of triclosan, ranking it as the second-highest endocrine-disrupting contaminant (Wee *et al*. 2020, 2024).

A pilot study from 2024 on triclosan human biomonitoring made use of silicon wristbands

as a passive sampling device and compared it to spot urine sampling. Wristbands performed similarly if not better, detecting triclosan at a 100% frequency. While there was only a small sample size, the study's participants all showed consistent concentrations of triclosan (estimated daily uptake of 3.6 ng/g per day) (Levasseur *et al*. 2024).

The high triclosan burden of water results in the contamination of aquatic organisms. Evidence shows that aquatic organisms (including algae, molluscs and fish) are particularly sensitive to the effects of triclosan (Dann and Hontela 2011).

Key developments since 2012

Triclosan was discussed in the 2012 report. It was mentioned particularly in connection with wastewater treatment plants, with release of triclosan leading to continued exposure of aquatic organisms (UNEP and WHO 2013). By 2012, only a small number of studies had been published that directly investigated the endocrine-disrupting effects of triclosan in humans (Andreae and Nowak-Węgrzyn 2017), which has now changed.

Substitution of triclosan may pose a challenge; it was in large part integrated in personal care products to replace long-chain parabens. Under pressure of increasing regulation, the chemical chlorhexidine has been introduced as a potential replacement. It is already being investigated for endocrine-disrupting effects and could be another case of regrettable substitution (Raps *et al*. 2024). There is a need to have broad spectrum action and high efficacy towards pathogens but low toxicity to non-target, multicellular organisms, including aquatic and terrestrial biota and humans (Halden 2014).

4.5 Lessons learned from select EDCs: regrettable substitution

The term "regrettable substitution" first appeared in the literature in 2011 (Maertens *et al*. 2021), and broadly describes the substitution of an industrial chemical, determined as no longer desirable, with a functional analogue that, in time, demonstrates similarly problematic or even worse characteristics than the predecessor (Maertens *et al*. 2021). Substitution centres on the goal of hazard reduction while aiming to maintain the functionality of a certain product. Beyond the actual chemical in question, also the upstream and downstream processes must be carefully scrutinized (Maertens *et al*. 2021); as discussed, at times a chemical's metabolites pose greater hazards than the parent industrial compound, just as some chemicals that are known EDCs are by-products to non-harmful or less harmful chemicals.

In industry, the successful production and integration of novel, "safe" chemicals present (where consumer awareness exists) a market advantage. While there are a range of examples of elimination of hazardous EDCs from use following scientific establishment of their risk, substitution has historically proven far more complex. In large part, there is a financial barrier: currently employed chemicals present, if not always a low one, at least a known, established cost. Replacing this with an unknown constitutes a business risk (Tickner *et al*. 2015). Additionally, because of financial and temporal constraints, direct functional analogues, such as BPS replacing BPA, may be attractive substitutes because they can often be integrated into existing production processes with limited modification or disruption to current production lines, which is deemed preferable to a search for a more complex (in the example: non-bisphenol) alternative.

BPA is frequently cited in discussions of regrettable substitution (Maertens *et al*. 2021; Warner and O'Neil 2022), especially in the EDC area. BPA is one of the most researched EDCs (Ben-Jonathan and Hugo 2016), yet is still not under any general, international ban. BPA analogues and replacements, such as BPS, BPF, BPAF and BPB, have been slowly replacing BPA in some products due to increasing public pressure and legal regulation (Morales-Grahl *et al*. 2024). Despite this, the production volumes of BPA are not decreasing, indicating an expansion of its use rather than a substitution (Moreno-Gómez-Toledano 2025). It may be argued that, initially, these substitutions were performed simply to label products "BPA free", and to fulfil certain regulatory requirements, particularly for products designed for children, which were the first to be scrutinized (Morales-Grahl *et al*. 2024; Moreno-Gomez-Toledano 2025). Overall, the

introduction of BPA alternatives did not receive the warranted scrutiny given the extensive information on BPA's adverse effects (Morales-Grahl *et al*. 2024).

Other examples of regrettable substitution are the replacement of PFOA with GenX (Morales-Grahl *et al*. 2024), of brominated flame retardants with phosphorus-based alternatives (Dodson *et al*. 2012), and of phthalates with DINCH (Gyllenhammar *et al*. 2017), or the cycle of triclosan replacing parabens and in turn now being replaced by chlorhexidine (Raps *et al*. 2024), all confirmed or suspected EDCs.

Case study: regulatory action on TBT

As a case of effective substitution in the area of EDCs, TBT may be considered. TBT is a biocide, introduced in the 1960s (Matthiessen 2013; Lagadic *et al*. 2018), for use in anti-fouling paints, as well as a preservative applied to wood, paper, textiles, pesticides and plastics (Barbosa *et al*. 2022). The use in paints applied to ships and boats, in particular, revealed the endocrine-disrupting effects of TBT.

Research into TBT quickly revealed that TBT caused sexual abnormalities in marine wildlife (Matthiessen and Gibbs 1998). TBT has been found to alter sex ratios and reproductive systems dramatically in a range of marine species, primarily gastropods and fish (Lagadic *et al*. 2018), most notably causing irreversible imposex in gastropod molluscs (Barbosa *et al*. 2022), contributing to severe declines in affected populations (Matthiessen 2013). Humans were also exposed to TBT via ingestion of contaminated food and drink, where it may also act as a human EDC (da Costa *et al*. 2025; Barbosa *et al*. 2022). Historically, TBT is widely regarded as one of the earliest well-documented examples of endocrine disruption in wildlife; its effects were well known by the mid-1980s (Matthiessen 2013).

Although some countries restricted the use of TBT in anti-fouling paints as early as 1982, it was not until 2003 that a more comprehensive ban was enacted (forbidding new TBT uses and a total ban of TBT paints in 2008 under the International Convention on the Control of Harmful Anti-fouling Systems on Ships) (Matthiessen 2013; Lagadic *et al*. 2018). Nevertheless, the first steps taken to regulate TBT may be described as rather swift; some delays in bans were caused by limited alternative options and slow ratification of legislation by the international community (Matthiessen 2013).

The persistence of TBT means that environmental contamination and exposure still continues (Matthiessen 2013; Lagadic *et al*. 2018), with TBT persisting in sediments and slowly entering the surrounding water (Barbosa *et al*. 2022; Matthiessen 2013). TBT also continues to be released from improper disposal of TBT-containing waste, as well as from illegal production and use of TBT-containing paints (da Costa *et al*. 2025). There have been significant recoveries of affected mollusc populations following the 2003 ban (Matthiessen 2013), but the effects of TBT are still visible today (da Costa *et al*. 2025).

The TBT case illustrates that even quick regulatory action may not guarantee full recovery of affected ecosystems from pollution by persistent contaminants (Matthiessen 2013), making precautionary and proactive regulatory approaches important.

Precautionary action

Generally, precautionary action has been called for repeatedly in the context of chemicals assessment (European Environment Agency 2013). Precautionary action often faces the criticism that the impacts of concern are still uncertain. However, in many cases, subsequent evidence has supported earlier concerns regarding chemical risks (Scheringer *et al*. 2026; European Environment Agency 2013). Furthermore, for an increasing number of chemicals, including many EDCs and potential EDCs (see chapter 2), concerns about hazardous properties have been substantiated over the last 20 years with new evidence. This means that action to reduce exposure to these chemicals would no longer be just precautionary, but preventative or even protective.

Regarding prospective testing for endocrine-disrupting properties, testing protocols have been developed to explore the endocrine-disrupting potential of novel chemicals

and, at least partially and proactively, mitigate risk prior to release. One such protocol, the Tiered Protocol for Endocrine Disruption, was designed in 2013 (Schug *et al*. 2013). However, online resources for this protocol have not been updated in over a decade and, aside from anecdotal academic use, the protocol does not seem to have been adopted (Warner and O'Neil 2022). Beyond their academic interest and relevance, there is little effect from these protocols unless their implementation is mandated by law or financially encouraged.

4.6 Key implications and recommendations

Since the publication of the first and second reports on the state of the science of EDCs, much has changed in all areas of EDC research. The understanding of exposure to EDCs has also expanded, but there are important goals to keep in mind in order to better understand and to reduce human and wildlife exposure to EDCs.

- **Since 2012, the greatest change in the area of exposure to EDCs has been the development of large-scale human biomonitoring projects. It is essential to maintain and even expand these efforts and encourage their use in linking population wide changes to detected levels of EDCs.** For this, the data generated by these projects need to be made accessible in a harmonized way, making them available for use. There is a need for longitudinal and multigenerational studies to best understand which effects may be caused by exposure to EDCs at key developmental stages.

- **EDCs are a global problem, so the sharing of data on their use, properties, other toxic effects, exposure routes and potential substituents is essential, on a global scale.** This requires greater adherence to harmonize processes, both for testing and for the evaluation of results.

- **The monitoring of wildlife should also be expanded, particularly that of terrestrial mammals,** because this contributes to the protection of wildlife populations and also improves the general understanding of EDC effects, including in humans (adopting a One Health approach).

- **Further harmonization and research efforts are needed in the identification of EDCs.** The European Union has developed the most established regulatory frameworks for the identification and management of EDCs. Other jurisdictions continue to develop or expand assessment systems for EDCs. It is essential for research in this field to have an agreed-upon foundation to work from, providing data to help identify new EDCs and to firmly establish the identification and characteristics of known ones, and to develop a methodology to consistently and coherently record which EDCs are identified through these processes.

- **It is important that industries are encouraged by the public, civil society organizations and governments to more effectively reduce emissions of, and exposure to, the chemicals they manufacture and use, and make increased efforts to substitute EDCs with safer alternatives.**

- **Anthropogenic EDCs are inevitably part of the global environment now.** It is therefore a priority to reduce exposure from environmental reservoirs of EDCs through a range of measures, including clean-up, remediation, containment and food monitoring, in order to avoid continued and future exposure and associated health effects.

5 Socioeconomic and policy analysis for EDCs

Lead authors

Leonardo Trasande (New York University, United States of America) (section 5.1) and Martin Scheringer (RECETOX, Masaryk University, Brno, Czech Republic, and ETH Zürich, Zürich, Switzerland) (section 5.2)

Chapter authors

Brij Mohan Sharma (RECETOX, Masaryk University, Brno, Czech Republic, and ETH Zürich, Zürich, Switzerland) (section 5.1), and Matthis Schäfer (ETH Zürich, Zürich, Switzerland) (section 5.2.)

Contributing authors

Marlene Ågerstrand (Stockholm University, Sweden), Alexandra Harrington (Lancaster University, United Kingdom of Great Britain and Northern Ireland), Xanat Flores (Universidad de las Américas Puebla, Mexico), Ipek Imamoglu (Middle East Technical University, Ankara, Türkiye), Asif Qureshi (Indian Institute of Technology Hyderabad, Hyderabad, India), and Hiroshi Yamamoto (National Institute for Environmental Studies, Tsukuba, Japan) (section 5.2)

Socioeconomic analyses help quantify the health, environmental, and economic costs associated with EDC exposures, many of which are not reflected in market prices. These externalities provide a key rationale for policy intervention, as regulation can help internalize social costs, correct market failures, and promote outcomes that better align private gains with societal welfare.

5.1 Socioeconomic costs and impacts of EDCs

5.1.1 Introduction to socioeconomic analysis

In *The Wealth of Nations*, published in 1776, Adam Smith described the criteria for the proper functioning of the free market economy, arguing that markets function most effectively when producers and consumers have access to relevant information, enabling prices to better reflect the characteristics and value of products. In economic terms, toxic effects of industrial production are externalities in that they are not accounted for in market transactions by the sellers or buyers. To give an example, electricity production from coal-fired power plants can produce particulate matter that affects the lungs of people who do not produce the electricity or directly use it. Because these externalities arise, the electricity is overproduced and sold at a cost below the societally optimal price that a free market would establish. Though he did not coin the "polluter pays principle", Smith recognized that economic activity could impose costs on others beyond those directly involved in a market transaction.

In 1920, Arthur Pigou described the notion that a tax on production equivalent to the size of the externality would return the market to proper function. By making the private cost equal to the social cost there is a return to the market equilibrium. The Pigouvian tax is a prototype theoretical approach to executing the "polluter pays principle". Instead of banning these risky or harmful activities altogether (including the risk of EDC), Pigou advocated for correcting the market via taxes with the goal of directing the producer to pay for the full societal cost arising from these risks, i.e., taxes that fund social safety nets, such as unemployment benefits, medical insurance, and pension schemes. Taxes, in theory, would disincentivise excess risk and damage

without destroying the economic activity itself. In 1981, the United States of America Institute of Medicine (now the National Academy of Medicine) developed the following approach to assess environmental disease-related externalities, which remains widely used to this day and is depicted in equations 1 and 2 (Institute of Medicine 1981).

Equation 1

Disease burden = disease rate × AF × population size

Equation 2

Attributable costs = disease rate × AF × population size × cost per case

where "cost per case" refers to discounted lifetime cost attributable to a particular disease, including direct costs of health care, costs of rehabilitation and lost productivity; disease rate and population size refer, respectively, to either the incidence or prevalence of a disease and the size of the population at risk; and AF is the attributable fraction, which is defined by Smith *et al*. in the context of environmental health as "the percentage of a particular disease category that would be eliminated if environmental risk factors were reduced to their lowest feasible concentrations" (Smith *et al*. 1999). AF models have been used widely to estimate the role of social, behavioural and environmental factors in disease processes and to guide prevention. The AF is a composite value and is the product of the prevalence of a risk factor multiplied by the relative risk of disease associated with that risk factor, and can be estimated using the Levin equation or its derivations (Hanley 2001).

Equation 3

$$AF = \frac{prevalence_{exposure} * (RR - 1)}{[1 + (prevalence_{exposure} * (RR - 1))]}$$

where RR = relative risk of morbidity associated with the exposure.

Experience has shown that accurate information on costs of illness can help focus preventive efforts (Leigh *et al*. 1997; Fahs *et al*. 1989; Landrigan *et al*. 2002). A further rationale for developing data on the costs of disease is to permit direct comparison with the costs of other categories of illness, an exercise that may be useful in priority setting and allocation for prevention programmes (Arrow *et al*. 1996). These methods have been leveraged to document the economic benefits of policy actions such as the phase-out of lead in gasoline, which to this day produces annual lifetime economic productivity benefits of US$ 110 billion to US$ 319 billion in the United States of America (Grosse *et al*. 2002) and benefits of US$ 2.4 trillion globally (4% of GDP) (Tsai and Hatfield 2011).

The most substantial barrier to quantifying EDC-related externalities is the argument by some economists that they should rely on strict causal attribution to EDCs, which would be extremely limiting. Sixty years ago, during a period of intense debate about the health effects of tobacco, Sir Austin Bradford Hill gave a landmark lecture on criteria for causation. Exposure must precede effect for causality to even be considered. Hill identified additional elements that should be considered, such as consistency, exposure–response relations, biological plausibility, effect size and specificity. What has been easily forgotten from Hill's lecture is the need for context in considering the totality of evidence. The stakes involved clearly matter; Hill used the example of restricting the use of a drug for morning sickness for pregnant women, suggesting that we might act on "relatively slight evidence" of harm, as "[t]he good lady and the pharmaceutical industry will doubtless survive". Similarly, for an occupational carcinogen, "fair" evidence would be sufficient. He closes by emphasizing: "All scientific work is incomplete – whether it be observational or experimental … That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time." (Hill 1965)."

There is always some uncertainty in estimating EDC exposure from epidemiology studies, especially where there has been exposure to multiple categories of chemicals, for example. The consistent findings from multiple epidemiological studies on EDCs are further supported by laboratory studies that further identify mechanisms by which they contribute to disease and disability across the lifespan (Diamanti-Kandarakis *et al*. 2009; Gore *et al*. 2015).

The coalescence of scientific data in support of highly probable causation has supported a growing literature documenting economic costs associated with EDC exposure.

5.1.2 Approaches to quantifying EDC-related externalities

The following shows an example of an approach to estimate costs incorporating an evaluation of probability of causation through structured frameworks. Other examples of cost estimates are then presented. In 2015, a steering committee of scientists adapted the Intergovernmental Panel on Climate Change (IPCC) weight-of-evidence characterization for probability of causation based upon levels of available epidemiological and toxicological evidence for one or more chemicals contributing to disease by an endocrine disruptor mechanism (Trasande *et al*. 2015). To evaluate the epidemiological evidence, a steering committee of scientists overseeing the project adapted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group criteria (Atkins *et al*. 2004a; Atkins *et al*. 2004b). The steering committee also adapted definitions promulgated by the Danish Environmental Protection Agency for evaluating laboratory and animal evidence of endocrine disruption (Hass *et al*. 2012). A steering committee then leveraged the IPCC approach to assessing probability of causation based upon the available epidemiological and toxicological evidence for one chemical or a group of chemicals (brominated flame retardants, phthalates, organophosphate pesticides, DDT and BPA) contributing to disease by an endocrine disruptor mechanism (Mastrandrea *et al*. 2005).

The steering committee then applied a modified Delphi approach to evaluating the strength of the epidemiological and toxicological evidence and the nature of the association between exposures and outcomes (Clayton 1997). The Delphi method was developed on the premise that group judgements are more valid than those of individuals (Juri 1971), and has been applied successfully and with high consistency and rigour across many disciplines, including health and education. Disease-specific expert panels achieved consensus at least for probable (greater than 20%) EDC causation for IQ loss and associated intellectual disability, autism, attention-deficit/hyperactivity disorder, childhood obesity, adult obesity, adult diabetes, cryptorchidism, male infertility and mortality associated with reduced testosterone. Only for testicular cancer was 0–19% probability of causation identified. Specific results from each of the expert panels are described in accompanying manuscripts (Bellanger *et al*. 2015; Hauser *et al*. 2015; Hunt *et al*. 2016; Legler *et al*. 2015).

The panels also selected the best available exposure–outcome associations from the available epidemiologic literature. Exposure–outcome relationships were applied against population-based biomarker data to generate the EDC-attributable disease burden. Disease burden estimates were then multiplied by estimates of the cost of illness for each relevant disease and disability, using available published data. Recognizing that attributable cost estimates were accompanied by probabilities, the steering committee performed a series of Monte Carlo simulations to produce ranges of probable costs across all the exposure–outcome relationships, assuming independence of each probabilistic event. Even after reducing the costs by the degree of uncertainty in the observed exposure–outcome associations, the societal burden posed by the EDCs considered by the expert panel was identified to be substantial, with attributable disease costs of US$ 340 billion per year in the United States of America (2.3% of GDP), 163 billion euros per year in the European Union (1.2% of GDP) and Can$ 24.6 billion per year in Canada (1.3% of GDP), based on 2010 population figures (table 5.1.) (Bellanger *et al*. 2015; Hauser *et al*. 2015; Hunt *et al*. 2016; Legler *et al*. 2015; Malits, Naidu and Trasande 2022; Attina *et al*. 2016). Extrapolating from these estimates for the European Union, the United States of America and Canada the global costs of diseases associated with EDC exposure could amount to approximately 1% or more of global GDP under conservative assumptions, equivalent to an estimated US$1.1 trillion in 2025.

These reports regarding EDC costs did not include estimates of the health effects of PFAS. The health- related costs associated with

PFOA and PFOS exposure in United States of America were estimated in 2018 to range from US$ 5.5 billion annually, with possible projections of up to US$ 62.6 billion per year in the United States of America (Obsekov *et al*. 2023). A European estimate of PFAS-related disease costs measured an overlapping but different set of attributable end-points and obtained similar results (52–84 billion euros per year) (Goldenman *et al*. 2019). A 2022 publication documented around 50,000 deaths in the United States of America in individuals aged 55–64 years that were attributable to phthalate exposure, with lost productivity of US$ 23.8 billion per year (Trasande *et al*. 2024; Trasande *et al*. 2022).

Comparison of these externalities in different countries can also reveal the impact of different policy frameworks. For example, cognitive loss (US$ 44.7 billion per year) due to organophosphate pesticides was identified to be vastly lower in the United States of America compared to Europe (US$ 121 billion per year) (Bellanger *et al*. 2015; Attina *et al*. 2016). This difference has been attributed, in part, to the 1993 Food Quality Protection Act (FQPA) in the United States of America, which established more stringent restrictions on organophosphate pesticide residues in food, whereas comparable regulatory measures were adopted later in Europe (Trasande 2017). Similarly, PBDE-related disease costs were estimated at US$ 240 billion in the United States of America compared with US$ 12 billion in Europe, reflecting higher exposures linked to California's furniture flammability requirements, which mandated the use of flame retardants in furniture between 1975 and 2013 (Attina *et al*. 2016).

Focusing on the proportion of endocrine-disrupting chemicals' use in plastics (for example, bisphenols, phthalates, PBDE and PFAS) reveals their substantial contribution to disease and disability. In the United States of America alone, US$ 250 billion per year in disease- and disability-related costs can be directly attributed to plastics (Trasande *et al*. 2024). These analyses can also provide insights into disparities in disease burden and associated costs across racial and ethnic groups in the United States of America. While such disparities arise from multiple interacting social, environmental, and economic determinants, disproportionate exposure to chemicals used in plastics has been identified as one potential contributing factor (Attina *et al*. 2019; Bloom *et al*. 2019).

5.1.3 Gaps and future directions

Research from developed countries has highlighted the substantial economic burden associated with health outcomes linked to exposure to a limited subset of EDCs and a small subset of their related health effects. However, these studies probably underestimate the true cost of EDC pollution and exposure for several reasons: (a) they do not account for heightened exposures near industrial facilities; (b) cost assessments are not available for all EDCs and their associated health effects; (c) existing methods evaluate the impacts of individual EDCs rather than the combined effects of the mixture of EDCs, despite evidence suggesting that exposure to a cocktail of these chemicals may have more severe health consequences than any single EDC alone (Caporale *et al*. 2022); and (d) current estimates do not account for the interplay between lifestyle factors (for example, consumption of ultra-processed foods) and EDC exposure (for example, to plasticizers), which may further exacerbate health risks (Yates *et al*. 2024).

Assessments on the economic costs of EDC-related health outcomes are missing for many developing countries, even though EDC pollution levels in these regions are comparable to those in developed nations (Sharma *et al*. 2021). One exception is a study that analysed data on PFAS exposure from 70 countries and estimated approximately 461,635 (95% confidence interval (CI): 57,418–854,645) cases per year of low-birth-weight babies during the past two decades, predominantly from Asian regions (Fan *et al*. 2022). Recent systematic reviews have addressed the gap in biomonitoring data partially by estimating exposure percentiles at the regional level, at least for phthalates and bisphenols (Acevedo *et al*. 2025a; Acevedo *et al*. 2025b).

The most common social issues in developing countries directly linked to known EDC pollution include mass displacement and loss of income, for example, the decline in fishing activities and


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products in EDC-contaminated areas, which in turn lowers living standards among marginal coastal communities, as well as the loss of domesticated farm animals (such as cows). A notable example is the endosulfan disaster in India, where endosulfan was sprayed on cashew plantations in Kerala for over two decades. This led not only to a sharp rise in serious health conditions among local inhabitants – including cancers, neurobehavioural disorders, congenital malformations in girls and abnormalities in the male reproductive tract – but also to significant social issues. These included mass displacement, delayed or inadequate compensation and welfare support from state agencies, and neglected social rehabilitation and education for affected individuals, including children who developed disabilities due to exposure to endosulfan (Irshad and Solama 2022). Notably, the disaster also exacerbated gender-related challenges, with women caretakers of the victims bearing the greatest burden, experiencing severe psychological distress and a diminished quality of life even two decades after the episode (Pillai *et al*. 2023).

In developing countries, marginalized and socioeconomically disadvantaged communities often bear a disproportionate burden of chemical pollution, including EDCs. For instance, several African countries have become key destinations for illegal offloading of hazardous e-waste – a major source of EDCs – from the developed world. This not only exacerbates relocation of environmental hotspots of EDC pollution but also disproportionately harms vulnerable populations already facing multiple socioeconomic and environmental stressors, reinforcing systematic inequalities (Akese and Little 2018).

An example demonstrating the disproportionate risks of EDC exposure and its associated social consequences can be found in Agbogbloshie, Ghana – one of the world's largest e-waste processing sites – which receives once-cherished household possessions from Europe and the United States of America. Here, child labour is rampant, with children as young as 5 years engaged in hazardous e-waste activities without adequate protection, exposing them to various EDCs of e-waste origin and their associated severe health risks (Lebbie *et al*. 2021). For instance, consuming just one chicken egg from Agbogbloshie results in an intake of chlorinated dioxins 220 times higher than the daily limit set by the European Food Safety Authority. Additionally, the site is plagued by socioecological violence among scrap dealers and informal waste recyclers, with workers suffering from high rates of mental health issues due to a combination of extreme poverty, toxic exposure and chronic stress. Stigmatization, exploitation

and systemic neglect in society further worsen their psychological and socioemotional well-being (Lebbie *et al*. 2021). These conditions highlight the deep-seated social risks associated with EDC pollution and exposure, disproportionally affecting the most vulnerable segments of society in developing countries.

Examples such as these emphasize a flaw in the human capital (cost of illness) method used to generate EDC-attributable cost estimates in the previous section. Cost of illness omits psychosocial costs, such as pain and suffering. Economists have proposed a complementary method, the willingness to pay approach, which was used to estimate a larger United States of America disease cost due to chemicals used in plastics (US$ 920 billion per year in the United States of America) (Landrigan *et al*. 2023). The willingness to pay methodology applies a value of a statistical life in preventing mortality due to EDCs. Value of a statistical life estimates arise from surveys presented to people asking them to describe how much they would be willing to pay to reduce the probability of dying by a percentage (for example, 0.001%) (Viscusi 1992). There are substantive arguments about the ability of the public to wrestle with the meaning of small reductions in mortality (or for that matter chronic diseases in which willingness to pay is modelled).

Using willingness to pay methods, Hyman *et al*. (2025) recently estimated the global burden of cardiovascular mortality due to phthalates, and the attributable portion due to plastics. In 2018, an estimated 356,238 deaths globally were attributed to DEHP exposure, representing 13.5% of all cardiovascular deaths among individuals aged 55–64 years (Hyman *et al*. 2025). Of these, 349,113 were attributed to the use of plastics. South Asia and the Middle East suffered the greatest percentage of cardiovascular deaths attributable to DEHP exposure (16.8%). The Middle East, South Asia, East Asia and the Pacific accounted for the largest shares of DEHP-attributable cardiovascular disease deaths (73.2%). Globally, DEHP resulted in 10.473 million years of life lost.

As a proxy for the social cost of a year of life lost, many investigators use a US$ 50,000 per life-year or quality-adjusted life year (QALY), a benchmark commonly applied in cost-effectiveness analyses in the United States of America (Grosse 2008). Some researchers extrapolate to elsewhere on the globe from this value using a purchasing power parity correction (Attina and Trasande 2013), but this implies a difference in the value of human life based upon place. If all the years of life lost are valued equally at $50,000 each, then the social costs of plastic-induced mortality through DEHP exposure would total US$ 510 billion. A more conservative valuation of US$ 1,000 per year of life lost would place the social cost at US$ 10.2 billion. An alternative to social cost of a year of life lost is using the value of a statistical life to estimate the economic cost of lives lost due to DEHP exposure. Based on the United States of America Department of Transportation's definition, by which the value of a statistical life was valued at US$ 10.5 million in 2018 and of US$14.2 million in 2025 (United State of America Department of Transportation, Office of the Chief Economist 2026), the total cost for 356,238 deaths would amount to US$ 3.74 trillion. Alternatively, using the United States EPA 2006 value of mortality risk reduction at US$ 7.4 million (United States Environmental Protection Agency [US EPA] 2025), the estimated cost would be US$ 2.6 trillion.

In addition to health-related costs, EDCs and other persistent contaminants may impose significant ecological harms through impacts on water resources, biodiversity, wildlife, and ecosystem services. While these ecological damages are difficult to monetize, the costs of remediation provide an indication of the scale of the burden. As an example, one study estimated that the current costs to remove perfluoroalkyl acids, a subclass of PFAS, from the environment at the same rate they are being added would be 20 to 7000 trillion USD per year (Ling 2024). The costs of cleaning up all PFAS from contaminated sites were more recently estimated to be €2 trillion across the United States of America and Europe over a 20-year period (Forever Pollution Project 2026).

Table 5.1 shows the disease burden and economic cost of exposure to EDCs over the life course in the United States of America, Canada and the European Union.

Table 5.1 Disease burden and economic cost of outcomes associated with exposure to endocrine-disrupting chemicals over the life course

EDC	Life stage of exposure	Outcome	United States of America (Attina *et al*. 2016; Obsekov, Kahn and Trasande 2023; Goldenman *et al*. 2019; Trasande *et al*. 2024)		Canada (Malits, Naidu and Trasande 2022)		European Union (Bellanger *et al*. 2015; Hauser *et al*. 2015; Hunt *et al*. 2016; Legler *et al*. 2015)	
			Disease burden	Economic cost (US$)	Disease burden	Economic cost (US$)	Disease burden	Economic cost (US$)
PBDE-47	Prenatal	Loss of IQ points and intellectual disability	11 million IQ points lost; 43,000 intellectual disability cases	266 billion	374,395 IQ points lost; 1,610 intellectual disability cases	11.4 billion	873,000 IQ points lost; 3,290 intellectual disability cases	12.6 billion
	Prenatal	Cryptorchism	4,300 cases	35.7 million	567 cases	7.3 million	4,615 cases	172.6 million
Organophosphates	Prenatal	Loss of IQ points and intellectual disability	1.8 million IQ points lost; 7,500 intellectual disability cases	44.7 billion	152,922 IQ points lost; 377 intellectual disability cases	4.2 billion	13 million IQ points lost; 59,300 intellectual disability cases	194.0 billion
DDE	Prenatal	Childhood obesity	857 cases	29.6 million	114 cases	2.5 million	1,555 cases	32.7 million
	Prenatal	Type 2 diabetes mellitus	24,900 cases	1.8 billion	3,270 cases	385.2 million	28,200 cases	1.1 billion
	Adulthood (female)	Fibroids	37,000 cases	259 million	2,254 cases	4.2 million	56,700 cases	216.8 million
DEHP	Adulthood	Obesity	5,900 cases	1.7 billion	2,093 cases	684.8 million	53,900 cases	20.8 billion
	Adulthood	Type 2 diabetes mellitus	1,300 cases	91.4 million	225 cases	25.8 million	20,500 cases	807.2 million
	Adulthood (female)	Endometriosis	86,000 cases	47.0 billion	10,151 cases	5.7 billion	145,000 cases	1.7 billion
BPA	Prenatal	Childhood obesity	33,000 cases	2.4 billion	1,023 cases	59 million	42,400 cases	2.0 billion
Phthalates	Adulthood (male)	Male infertility	240,100 cases	2.5 billion	1,395 cases	17 million	618,000 cases	6.3 billion
	Adulthood	Cardiovascular mortality	50,900 cases	23.8 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
PFOA, PFOS	Prenatal	Low birth weight	10,053 cases	1.4 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Prenatal	Childhood obesity	127,362 cases	2.7 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Childhood	Pneumonia	447–6,759 cases	1.5–22.5 million	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Pregnancy	Gestational diabetes	6,061 cases	414–852 million	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood	Obesity	4,294,379 cases	17 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood	Kidney cancer	142 cases	184 million	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood	Couple infertility	593–26,160 cases	37.6 million–1.7 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood (female)	Hypothyroidism	14,572 cases	1.3–5.2 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood (female)	Type 2 diabetes mellitus	1,728 cases	140 million	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood (female)	Endometriosis	696–18,062 cases	397 million–10.2 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood (female)	Polycystic ovarian syndrome	7,209–7,505 cases	10.5–10.9 million	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated
	Adulthood (female)	Breast cancer	421–3,095 cases	555 million–4.1 billion	Not yet calculated	Not yet calculated	Not yet calculated	Not yet calculated

Note: All estimates are from 2010, except for PFAS, for which United States of America estimates are from 2018.

5.2 Overview of existing policy instruments and actions

Over the past decades, efforts to better understand EDCs and their characteristics have increased. As the scientific evidence base has matured, it has revealed not only the health and environmental risks posed by EDCs but also their substantial socioeconomic costs (Kassotis *et al*. 2020).

Driven by the growing international concern about EDCs, a number of governments and stakeholders have initiated a range of instruments and actions aimed at minimizing the human health and environmental impacts of EDCs. Some of these efforts are directly linked to EDCs, while others are wider efforts to regulate larger groups of chemicals that include EDCs and their associated components. These efforts have yielded a diverse global policy landscape comprising internationally and nationally legally binding instruments, also referred to as hard law, as well as non-binding instruments, referred to as soft law, and voluntary initiatives. As the complexity of the policy landscape grows, and given the costs of inaction, it has become increasingly important to evaluate the consistency and effectiveness of existing instruments, binding and voluntary, in order to provide a clear picture of the regulatory systems in which EDCs are being addressed at the national, supranational and international levels. An analysis of current instruments and actions offers a benchmark for assessing the state of global progress in EDC policy. Such an analysis can also help identify opportunities for international cooperation and policy harmonization. Therefore, this section investigates the question of how well existing instruments and actions comprehensively address the relevant aspects of EDC risk management in different parts of the world and at different levels of governance systems.

To answer this question, the analysis focuses on two main aspects. First, from a policy design perspective, the chapter evaluates the effectiveness of different types of instruments in addressing the policy issue of EDCs. Second, it examines the global distribution and coverage of these instruments in various jurisdictions. By taking this approach, the section provides an overview of existing policy measures, highlights major regulatory gaps, and offers actionable recommendations for policymakers and stakeholders to inform a more comprehensive response to EDCs.

5.2.1 Legally binding instruments

A range of legally binding instruments have been implemented to regulate EDCs. This section identifies three main types of regulatory approaches to EDCs: (a) regulations that specifically refer to EDCs; (b) implicit frameworks; and (c) chemical-specific regulations.

A. Regulations with specific references to EDCs

To address EDCs at national and regional levels, several countries and regions have introduced new chemicals regulations or revised existing ones to explicitly reference EDCs, providing guidance on how these substances should be addressed. Typically, such regulatory measures are embedded within sector-specific legislation, such as those for pesticides or cosmetic products, as well as media-specific legislation, such as those on water or drinking water. They may also fall under broader regulations for industrial chemicals, such as the European REACH regulation (Regulation (EC) 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals), which is also mirrored in the laws and regulations used in the United Kingdom of Great Britain and Northern Ireland, the Republic of Korea and other countries. Across all these different types of legislation, the identification of a substance as an EDC can trigger specific risk management actions, such as restrictions, prohibitions or reporting requirements. However, because the EDC-specific provisions and risk management options differ between regulatory frameworks, regulatory responses to EDCs are highly variable. To gain an understanding of the global response to EDCs, this section reviews the provisions and risk management actions available under existing chemicals regulations.

Sector-specific regulations

Pesticides and biocides represent a sector where EDC-specific regulations are widely established. In the European Union, pesticides and biocides are regulated via the Plant Protection Products

Regulation (EC) 1107/2009 and the Biocidal Products Regulation (EU) 528/2012 (European Parliament and Council 2009; European Parliament and Council 2012). Both regulations have been amended to include criteria for the identification of EDCs, providing a consistent foundation for regulatory decision-making (EC 2017; EC 2018a). The regulations follow a clear management logic for EDCs, under which an active substance, safener or synergist can only be approved if it is not considered to have endocrine-disrupting properties that cause adverse effects in humans (Kassotis and Trasande 2021). Exemptions can be granted under specific conditions, for example, when human exposure is considered negligible or when a substance is deemed essential for controlling a serious danger. Despite the existence of these exemptions, the overall regulatory approach remains largely aligned with a hazard-based approach, which can be effective in minimizing human exposure, provided that EDCs are successfully identified (Kassotis *et al*. 2020). In the Swiss regulations relating to pesticides and biocidal agents that have been classified as EDCs, there are possibilities for limited-use authorizations in a professional use situation, provided that the benefits to society outweigh the harms, that the use is tightly time limited and that there are consistent frameworks in place to assess the potential and actual toxicity occurring in the allowed use.

Beyond the European Union, the United States of America and Canada have also implemented pesticide regulations that specifically reference endocrine-disrupting properties. In contrast to the European Union, pesticide regulations in the United States of America and Canada rely more heavily on traditional risk-based approaches (Cook *et al*. 2026). In the United States of America, for example, EDCs in pesticides are addressed via the Food Quality Protection Act, which amends the Federal Food, Drug, and Cosmetic Act, and requires the United States EPA to ensure that a pesticide poses a "reasonable certainty of no harm" before it can be registered for use. However, the Federal Food, Drug, and Cosmetic Act does not define specific criteria for identifying EDCs; instead, endocrine-disrupting properties are to be assessed through the United States EPA's Endocrine Disruptor Screening Program. Notably, in more than 25 years of existence, the Endocrine Disruptor Screening Program has not led to the formal identification of a single EDC (Maffini and Vandenberg 2022). Reliance on the Endocrine Disruptor Screening Program, therefore, significantly reduces the clarity and precision of the regulatory response to EDCs in the United States of America pesticide sector. Available risk management actions under the Federal Food, Drug, and Cosmetic Act include the approval or denial of pesticide registration for a specific use, imposing conditions on the use of a pesticide and setting maximum residue levels for crops. Similar risk management options exist under the Canadian Pest Control Products Act, under which registration is granted or denied based on a risk assessment, and maximum residue levels for crops can also be established. Brazil's old pesticide regulation (Federal Law No. 7802) followed a regulatory logic similar to the European Union approach and also incorporated elements of hazard-based identification and approval processes for EDCs. However, in 2023, Brazil introduced a new regulation for pesticide registration (Law 14.785), which mandated pesticide risk assessments as an integral part of the dossier submission process and removed any specific references to EDCs (Cione *et al*. 2024).

For sectors other than pesticides, regulations with specific references to EDCs are less common. One example is cosmetics in the European Union, which are governed by the Cosmetic Products Regulation (EC) 1223/2009. The Cosmetic Products Regulation aims to protect human health by ensuring the safety of cosmetic products placed on the European Union market and includes a system of restrictions and bans of certain substances in cosmetics. Restrictions are based on risk assessments conducted by the Scientific Committee on Consumer Safety, which also considers endocrine-disrupting properties of substances used in cosmetics (EC 2025). Although the Cosmetic Products Regulation does not include a general provision for or definition of EDCs, Article 15(4) requires the European Commission to review the Cosmetic Products Regulation with regard to substances with endocrine-disrupting properties. In 2018, the European Commission adopted the review of Regulation (EC) 1223/2009 on cosmetic products containing EDCs, which assessed

how potential EDCs were handled under the Cosmetic Products Regulation and, specifically, which ones were banned or restricted following safety assessments (EC 2018c). The review concluded that existing regulatory tools were sufficient to manage health risks from EDCs in cosmetics. Following the review, a priority list for risk assessment of 28 substances was developed in collaboration with European Union Member States and stakeholders, and the risk assessment of the first 14 chemicals is currently under way. Unlike substances that are carcinogenic, mutagenic or toxic to reproduction, which are banned in cosmetics in the European Union, EDCs are addressed on a case-by-case basis.

In the United States of America, drug approval also includes considerations for EDCs. If endocrine effects are identified during the evaluation of drugs intended for human use, other factors related to exposure will determine whether additional non-clinical testing or clinical monitoring is necessary (US FDA 2015). The FDA may approve a drug if it can be demonstrated that it is safe and effective for its proposed use and that its benefits outweigh the risks; otherwise, approval may be denied. Notably, pharmaceuticals for human use hold a special place in the regulatory landscape of chemicals. While the environmental impacts of a chemical are often recognized, drug approval is never conditional on such effects (Fumagalli 2024).

Beyond pesticides, cosmetics and pharmaceuticals, food and food packaging materials have come to reflect a growing understanding of the presence of EDCs and the associated need for regulation. Several States have begun updating their laws and rules to specifically address concerns regarding current and future chemical substances used in food packaging, including EDCs and associated substances.

Children's toys and related products have also come to be a focus of EDC-related regulation in several national systems, including the United States of America, the European Union, and others. For example, in Argentina endocrine impacts are cited as a particular threat to children stemming from chemicals and substances in toys, and legislation has been passed to establish and update restrictions on the composition of toys available on national markets.

Media-specific regulations

Media-specific regulations that explicitly address EDCs are primarily associated with water and drinking water. In the United States of America, the Food Quality Protection Act also amended the Safe Drinking Water Act, which mandates the United States EPA to test drinking water contaminants for endocrine-disrupting effects when it determines that a substantial population is exposed to such a contaminant (US EPA 2024). If the EPA decides to regulate a contaminant, it can either establish non-enforceable health goals or set enforceable standards in the form of maximum levels of contaminant allowed in any public drinking water system. Testing and identification of possible endocrine-disrupting effects are conducted within the Endocrine Disruptor Screening Program.

In the European Union, EDCs are recognized as "main pollutants" under the Water Framework Directive (UNEP 2017a). They may be included on the list of priority substances based on an assessment of their risk to and via aquatic environments. However, the Water Framework Directive does not contain any provisions for identification or risk assessment of EDCs, but relies on other relevant legislation, such as the REACH regulation. Under the Water Framework Directive, risk management measures include setting environmental quality standards for priority substances, either at the European Union level or by individual Member States. Based on these standards, Member States are required to implement measures to control and progressively reduce the release of these pollutants into water bodies.

Industrial chemicals regulations

Chemicals that are not subject to sector-specific regulations are usually governed by broader regulatory frameworks on industrial chemicals. A growing number of countries and regions, including Australia, Brazil, Canada, the European Union and the Republic of Korea, have regulations on industrial chemicals in place that explicitly reference EDCs. For example, the Canadian


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Environmental Protection Act, updated in 2023, includes "the ability of the substance to disrupt the reproductive system or endocrine system of an organism" as an element of information that is to be gathered regarding substances that are or have the potential to be classified as toxic for the purposes of regulation under the act. In the European Union, EDCs are addressed under the REACH regulation, which includes a provision for the authorization and restriction of substances with endocrine-disrupting properties. This provision is introduced in Article 57(f), which states that EDCs may be identified as substances of very high concern if they show adverse effects that are of equivalent level of concern to substances classified as carcinogenic, mutagenic or toxic to reproduction. REACH does not lay out explicit criteria for the identification of EDCs, and the identification is currently conducted on a case-by-case basis following the WHO/IPCS definition and OECD test guidelines. The European Union's classification, labelling and packaging (CLP) regulation contains two hazard categories for endocrine disruption, one for human health and one for the environment (EC 2023).

In the Republic of Korea, industrial chemicals are governed by the Act on the Registration and Evaluation of Chemicals (commonly referred to as K-REACH). Similarly to the European REACH regulation, chemicals that are likely to cause endocrine-disrupting effects can be designated as substances subject to authorization. Additionally, EDCs may be subject to restrictions or prohibitions.

The Australian National Industrial Chemicals Notification and Assessment Scheme, on the basis of risk assessment, contains provisions to make recommendations for measures for regulators in individual states and territories (UNEP 2017a).

Türkiye, having ratified the Stockholm and Rotterdam Conventions, adopted an approach based on the European Union REACH with its national regulation put into effect in 2017 and CLP regulation in 2013. In addition, monitoring efforts by the former Ministry of Forestry and Water Affairs (2016–2019) enabled investigation of EDCs in surface water bodies, their sources and treatment technologies so that environmental quality standards were established for selected specific pollutants, some of which are EDCs (Regulation on Surface Water Quality 2016; Gursoy-Haksevenler 2021). Although a dedicated mechanism for identification or regulation of EDCs is not present in Türkiye, numerous regulations have been put into effect since 2012 to reduce exposure to harmful chemicals that include a number of EDCs (see annex III): (a) a total of 11 EDCs, including alkylphenols, phthalates, pesticides and BPA, have environmental quality standards established under the Regulation on Surface Water Quality (2016); (b) three phthalates (DEHP, DBP and BBP) are regulated under the By-law on Control of Soil Pollution and Sites Contaminated by Point Sources (2013), as well as those included in the European Union harmonized regulations; (c) 22 EDCs present in the CLP regulation (2013); (d) 21 EDCs under the Regulation on Cosmetic Products (2023); (e) two pesticides banned under the active ingredients list in the Plant Protection Products Regulation; and (f) a variety of EDCs as part of Commission Regulation (EU) 10/2011 on plastic materials and articles intended to come into contact with food (2024).

Similarly, in 2024 Brazil adopted Federal Law No. 15.022/2024, which is considered to be the REACH equivalent, and which establishes the National Inventory of Chemical Substances.

This law prioritizes EDCs for risk assessment and also contains, among other risk management measures, provisions for restriction, authorization and prohibition. Two areas of particular regulatory concern are chemicals that have potential for negative impacts on humans and the environment as well as those having carcinogenic and reproductive effects. The implementation of this law was still being crafted at the time of writing of this report.

In Norway, ministerial and governmental efforts to focus on the regulation and reduction of risk from EDCs began in 2000, when a new spate of laws and rules entered into effect. Since that time, there have been progressive efforts to increase the scope of regulatory systems relating to EDCs and their use at the national level, including product-specific measures (such as those relating to BPA), as well as coordination with the European Union REACH regulation.

In India, a series of draft chemicals (management and safety) rules are being developed. The fifth draft, which is the last draft available in the public domain from the Basic Chemicals, Cosmetics and Dyes Export Promotion Council (CHEMEXCIL), was released in 2020 (Chemexcil 2020). This draft identified "priority substances", and included evaluation of substances with respect to the hazard classifications falling under the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS Rev 8), namely, carcinogenicity, germ cell mutagenicity or reproductive toxicity; and substances fulfilling criteria related to their persistent, bioaccumulative, and toxic (PBT) or very persistent (vP) or very bioaccumulative (vB) characteristics, and having "endocrine-disrupting properties". There were no further details on which tests should be reported to assess endocrine-disrupting properties. Schedule II explicitly listed three compounds – 20-(4-nonylphenoxy)-3,6,9,12,15,18-hexaoxaicosan-1-ol; 4-nonylphenol, branched, ethoxylated; and 26-(nonylphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-ol –for their endocrine-disrupting properties, over and above other compounds that were listed as being carcinogenic or toxic for reproduction. However, no subsequent drafts have been made for comments, and as of July 2026 the government Gazette notification (the authorized legal document of the Government of India) had also not yet arrived.

Key observations on EDC-specific regulations

Overall, regulations that contain specific references to EDCs are important policy instruments containing risk management mechanisms that have the potential to limit exposure or facilitate the replacement of EDCs. However, the effectiveness of these regulations critically depends on the accurate and efficient identification of EDCs (Duh-Leong *et al*. 2023). Regulations with clear identification criteria, such as the Plant Protection Products Regulation and Biocidal Products Regulation of the European Union, provide greater precision and transparency in achieving policy objectives. The key message is the general lack of horizontal approaches for the identification of EDCs, both within and across jurisdictions (Duh-Leong *et al*. 2023). This causes concerns about inconsistent assessment outcomes across countries and agencies and can lead to inefficiencies through duplication of efforts.

The overview of regulatory instruments above reveals that existing EDC-specific regulations are fragmented, with the type and scope of regulatory responses varying significantly by sector and jurisdiction. For instance, regulations on industrial chemicals tend to be wider in scope compared to those targeting smaller sectors or product categories. While some regulations have general provisions for EDCs in place, others such as the European Cosmetic Products Regulation address endocrine-disrupting properties on a case-by-case basis (Kassotis and Trasande 2021). Risk management options also differ across regulatory frameworks, varying by country and regulatory domain. These differences can lead to policy inconsistencies, whereby an EDC is regulated in one sector but is managed differently or is not regulated at all in another (Duh-Leong *et al*. 2023). For example, while pesticides in the United States of America are regulated under the Food Quality Protection Act, the Toxic Substances Control Act, which governs industrial chemicals, does not contain EDC-specific provisions. Addressing this issue will require greater

international harmonization and cooperation and a review of the coherence of the existing national or regional policy landscape regarding EDCs.

Another finding is that most regulatory frameworks rely on risk assessment procedures to justify regulatory action. In the scientific community, the application of risk-based approaches to EDCs has been criticized because the necessary data for most EDCs to support risk assessments are lacking (Vandenberg *et al*. 2017). Furthermore, EDC-specific characteristics, such as the existence of non-monotonic dose–response relationships and age-related vulnerability, further complicate the application of traditional risk-based approaches (Duh-Leong *et al*. 2023). Fully or partly hazard-based approaches, such as in the Plant Protection Products Regulation and Biocidal Products Regulation of the European Union, are thought to be more aligned with the precautionary principle (Kassotis *et al*. 2020).

At the time of writing of this report, existing regulations with specific provisions for EDCs remain concentrated in developed countries, but there are ongoing efforts by developing countries to adopt REACH and associated legal and regulatory frameworks. One contributing factor is that EDC pollution is a highly specific and technical issue that requires substantial technical and financial resources, which are capacities that are often lacking in developing countries (Sharma *et al*. 2023). These countries could therefore benefit significantly from increased international harmonization and cooperation (Kassotis *et al*. 2020). To better support developing countries in managing EDCs, more international measures are needed that recognize EDC pollution as a global policy issue (Blumenthal *et al*. 2022).

B. Implicit frameworks

In addition to regulations that specifically refer to EDCs, other legally binding instruments address these substances only implicitly. Such implicit frameworks typically consider or regulate substances based on their adverse effects, without requiring a causal understanding of those effects (UNEP 2017a). As a result, substances that are addressed due to their toxicity or potential to cause harm might be EDCs, but they may not be explicitly identified as such.

Internationally, arguably the most important of these implicit frameworks is the Stockholm Convention on Persistent Organic Pollutants, since many of the persistent organic pollutants regulated under the Stockholm Convention have also been found to possess EDC properties. Thus, while the Stockholm Convention text is silent on EDCs per se, in its implementation it has a considerable impact on the use, status and reporting of these chemicals. Additionally, the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal may be relevant where EDCs are present in wastes falling within the scope of the Convention. In such cases, the Convention provides a framework for controlling transboundary movements of those wastes and for ensuring their environmentally sound management. The International Labour Organization (ILO) Chemicals Convention, 1990 (No. 170), establishes a framework for the safe use of chemicals at work by requiring the assessment, classification, labelling and communication of chemical hazards, as well as measures to protect workers from exposure. It does not make direct reference to EDCs but they are covered indirectly, as the Convention refers to hazardous chemicals, established by competent authority.

At national level, with the example of Latin American countries and with a focus on water regulations, Mexico has no specific EDC identification, but current drinking water regulations (NOM-127-SSA1-202) set concentration limits for certain EDCs, including carbamates and organochlorine and organophosphate pesticides. Similar legislation can be found in Colombia's Decree 1594/1984, Paraguay's Resolution 222/02 of 2002, and the Bolivarian Republic of Venezuela's Decree 883 of 1995. Regarding occupational health and safety, Mexico has legislation to inform workers of occupational exposure to hazardous chemicals including EDCs (NOM-018-STPS-2015) and has set the basis to legislate maximum pesticide concentrations in agricultural products for human consumption (Gobierno de México 2017).

Implicit frameworks are often simpler as they only consider adverse effects and do not require

a causal link between endocrine disruption and those effects. As a result, implicit frameworks may offer an efficient and effective means of limiting human and environmental exposure to EDCs, particularly for substances already recognized as substances of potential concern. However, implicit frameworks are often limited by their failure to take account of the specific characteristics of many EDCs (UNEP 2017a). For example, standardized regulatory endpoints and assessments do not necessarily reflect non-monotonic responses, low-dose effects or sensitive exposure time windows. Because implicit frameworks are not directly intended to regulate EDCs, they tend to be less precise in managing endocrine-specific toxicity.

Despite these limitations, implicit frameworks can serve as valuable complements to explicit EDC regulations (UNEP 2017a). Their broader applicability and relative ease of implementation can help extend regulatory reach. This is particularly important in low- and middle-income countries, where regulatory capacity and tailored frameworks are often lacking. In such contexts, multilateral environmental agreements, such as the Stockholm Convention, offer a pragmatic starting point for chemical control, even if they do not directly address endocrine disruption.

C. Substance-specific regulations

While broad regulatory frameworks address many chemicals simultaneously, certain EDCs are also subject to substance-specific regulations. These typically involve the restriction or prohibition of particular substances in specific applications or are intended to facilitate their replacement. For instance, many countries have prohibited or restricted the use of BPA in baby bottles and other applications with high exposure potential for young children (UNEP 2017a). Although such targeted regulations are effective instruments for phasing out substances of known concern, they have given rise to regrettable substitution. This phenomenon is a common limitation of chemical-by-chemical regulatory approaches and has been well documented in the context of chemical-specific EDC regulations (Duh-Leong *et al*. 2023). A well-known example is the replacement of BPA with BPS and many other structurally similar alternatives in plastic products, which were later found to exhibit similar or even stronger effects than BPA (Chen, Ike and Fujita 2002; Kuruto-Niwa *et al*. 2005).

It cannot be generally assumed that the chemicals replacing EDCs are better or safer. Bans and restrictions of specific EDCs should therefore always be accompanied by a sound mechanism for assessing alternatives (Duh-Leong *et al*. 2023). In this context, concepts such as functional substitution and chemical grouping approaches are gaining traction (Cousins *et al*. 2020; Tickner *et al*. 2015). However, despite these developments, EDC-specific regulations remain relatively unambitious in terms of their overall scope and potential to minimize EDC exposure. They are also ill suited to address cumulative exposure to multiple EDCs from different sources, which is a central challenge in current chemical risk assessment (Duh-Leong *et al*. 2023).

Unlike broader regulatory frameworks, substance-specific measures may require less regulatory capacity. However, to be truly effective, EDC-specific regulations must be supported by complementary policy instruments that enable the comprehensive evaluation of alternatives and the management of substitution-related risks.

5.2.2 Soft law instruments

Soft law refers to legally non-binding instruments, such as declarations, resolutions and guidelines. These instruments are widely used to promote international cooperation and to guide national and regional policy development. Despite their non-binding nature, soft law instruments also play an important role in shaping the policy landscape of EDCs.

At the international level, soft law has been used to raise awareness and coordinate action on EDCs. A key development was the recognition of EDCs as an emerging policy issue under the Strategic Approach to International Chemicals Management, a global multi-stakeholder and multisectoral policy framework. This recognition was established through resolutions adopted at the third session of the International Conference on Chemicals Management in 2012 and reaffirmed at its fourth session in 2015 (Strategic Approach to


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International Chemicals Management [SAICM] 2012; SAICM 2015). These resolutions called upon governments, intergovernmental bodies and other stakeholders to undertake cooperative action on EDCs, with particular emphasis on work coordinated by the Inter-Organization Programme for the Sound Management of Chemicals. The resolutions adopted at the third and fourth sessions of the International Conference on Chemicals Management played a key role in elevating EDCs on the global policy agenda. They highlighted the health and environmental risks associated with EDC exposure and promoted the dissemination of scientific knowledge, expert guidance and science-based information exchange among relevant actors.

In 2023, the fifth session of the International Conference on Chemicals Management adopted the Global Framework on Chemicals – for a Planet Free of Harm from Chemicals and Waste, as a successor to the Strategic Approach to International Chemicals Management. The Conference also decided that EDCs, along with all existing emerging policy issues and other issues of concern, would transition into "issues of concern" under the Global Framework on Chemicals on an interim basis, pending consideration at the first International Conference. In addition, several targets of the Global Framework on Chemicals are of relevance to addressing EDCs, notably highly hazardous pesticides in agriculture (Target A7), export of chemicals prohibited nationally (Target A5), support to safer and more sustainable agricultural practices, including agroecology, integrated pest management and the use of non-chemical alternatives, as appropriate (Target D5), and national mainstreaming of the sound management of chemicals and waste through implementation in all relevant sectoral plans, budgets and development plans and development assistance policies and programmes (Target E1).

The Globally Harmonized System of Classification and Labelling of Chemicals was outlined in the 1990s and has been regularly updated since its first edition of 2003 (GHS 2025). Currently, the 11th edition is in force. The Globally Harmonized System preceded the European Union CLP regulation, but since its enactment in the European Union, the CLP regulation has been a driver of further development of the Globally Harmonized System. Criteria for EDCs were included in the European Union's CLP regulation in 2024 (Food Packaging Forum 2024) but have not yet been adopted in the Globally Harmonized System.

EDCs are mentioned in several United Nations documents pointing out the need to protect humans from the impacts of toxic chemicals, including United Nations Human Rights Council resolution 45/30 on the rights of the child and a healthy environment (UN HRC 2020), and three reports by the United Nations Special Rapporteur on toxics and human rights on gender and hazardous substances, the plastics cycle and human rights, and the right to science in the context of toxic substances (United Nations Special Rapporteur 2021a; United Nations Special Rapporteur 2021b; United Nations Special Rapporteur 2024).

At national and regional levels, soft law instruments related to EDCs have often taken the form of action plans or strategic policy communications. These documents typically outline overarching goals, set timelines and

engage stakeholders. While non-binding, they reflect political intent and often help build regulatory and institutional capacity.

In the European Union, the European Commission issued the 2018 communication Towards a comprehensive European Union framework on endocrine disruptors, updating its Community Strategy for Endocrine Disrupters of 1999 (European Commission 2018b). The strategy outlines several activities, many of which further contribute to building regulatory and societal capacity for addressing EDCs. These include, for example, a fitness check of existing legislation to assess whether the European Union delivers on its overall policy objective of protecting human health and the environment by identifying and minimizing exposure to EDCs. Additional measures included a pledge to continued research support through Horizon Europe, the organization of an annual European Union forum on EDCs, the creation of a central web portal, and increased engagement with international classification systems. The strategy also encourages European Union Member States to implement public awareness and education campaigns.

At the national level, many countries have adopted policies, guidelines and similar measures that recognize the importance of addressing EDCs and the regulation of their uses across a spectrum of sectors and topics. China has demonstrated strategic intent to act on EDCs through its 13th Five-Year Plan for National Environmental Protection, released in 2016 (People's Republic of China State Council 2016). The plan explicitly addresses EDCs, calling for strict control of pollution from these substances through measures such as phase-out, restriction and substitution by 2017. New Zealand has recognized the need for future measures to be adopted in order to address the threats to human and environmental health stemming from EDCs. Sweden has tasked the Swedish Chemicals Agency with implementing a "non-toxic environment" as part of its national environmental quality objectives, including measures relating to EDCs and specific chemicals of concern. Japan, through its Ministry of the Environment, extensively contributed to the development of OECD test guidelines for EDCs (Organisation for Economic Co-operation and Development [OECD] 2009a; OECD 2009b; OECD 2023; OECD 2024). Furthermore, Japan employs a two-tiered approach (tier 1 to assess actions to endocrine systems by reliability assessment of the literature, in vitro assays, and in vivo short-term screening assays; tier 2 to characterize adverse effects by long-term assays) for testing of EDCs (Ministry of the Environment of Japan 2016). An updated programme (Ministry of the Environment of Japan 2022), structured as the previous one, has been implemented and is in use currently.

These are only some of the many examples where soft law elements, including those tied to the Sustainable Development Goals, have directly intersected with EDC regulation.

The overall effectiveness of soft law initiatives is variable and depends on the nature of the initiative and the perceived urgency of the policy issue. In the case of EDCs, soft law instruments have played a critical role in raising awareness and elevating EDCs as a global policy issue. In the European Union, soft law has yielded several practical outcomes and has helped to increase regulatory efficiency and policy coherence in a highly fragmented policy landscape. However, due to their non-binding nature, soft law instruments are inherently vulnerable to shifts in political momentum. The absence of enforcement mechanisms means that consistent follow-through is not guaranteed, which can limit their long-term impact and effectiveness. On the other hand, voluntary initiatives led by governmental, societal and industry actors complement regulation and often address dimensions of the EDC issue that regulatory frameworks may overlook.

5.2.3 Voluntary efforts

Intergovernmental organizations have played an important role in coordinating voluntary efforts on EDCs. In 2012, WHO and UNEP released the second report on the state of the science on EDCs, which pointed out important knowledge gaps and called for more research to better understand the risks posed by EDCs (UNEP and WHO 2013). In 2017, UNEP published a series of overview reports reviewing efforts to identify EDCs,

current scientific knowledge on their life cycles, environmental exposures and effects, and existing regulatory frameworks at the national, regional and global levels (UNEP 2017a).

Civil society organizations have also made key contributions. In 2009, the Endocrine Society issued its first scientific statement to alert the scientific community to the effects of environmental EDCs on health and disease (Diamanti-Kandarakis *et al*. 2009). Efforts to improve access to scientific data have further advanced the field. The Endocrine Disruption Exchange, for instance, maintains a publicly accessible database of potential endocrine disruptors that identifies chemicals with at least one study demonstrating endocrine-disrupting activity (The Endocrine Disruption Exchange 2018). The list was closed in 2019, but will remain available. Collectively, these knowledge-sharing initiatives have been instrumental in consolidating EDCs as a global policy issue and in supporting informed decision-making.

Despite the increasing scientific and regulatory attention to EDCs, public awareness remains limited. A general lack of knowledge about the risks posed by EDCs, their sources and associated effects hinders individuals, including those in vulnerable populations, from taking protective measures to minimize their exposure (Kelly *et al*. 2020; Okman and Yalçın 2024). Several organizations have responded to this gap by conducting awareness-raising activities. In 2017, UNEP published a series of infographics and a brochure on EDCs that included practical steps to reduce exposure (UNEP 2017b; UNEP 2017c). In 2014, the Endocrine Society and the International Pollutants Elimination Network (IPEN) published a guide for public interest organizations and policymakers, which presented a global picture of EDC exposure and health risks (Gore *et al*. 2014). Nonetheless, recent studies indicate that public understanding of EDCs remains low, underscoring the need for more targeted and sustained outreach (Kelly *et al*. 2020; Okman and Yalçın 2024). Awareness campaigns involving health care professionals, schools and the media are seen as promising strategies to enhance public knowledge. Additional awareness-raising campaigns might be particularly important in developing countries, where EDC management is often overshadowed by other pressing public health and environmental emergencies (Sharma *et al*. 2023).

5.2.4 Gaps and actionable recommendations

In summary, progress on EDC-related instruments has been highly uneven, with most existing instruments and actions concentrated in developed countries or those with economies in transition. Legally binding measures with specific provisions for EDCs are fragmented, resulting in considerable variation in regulatory responses across sectors, environmental media and jurisdictions. This fragmentation contributes to policy inconsistencies and can undermine the overall effectiveness and coherence of regulatory efforts. The effectiveness of regulations explicitly addressing EDCs critically depends on the reliable and efficient identification of these substances. However, internationally harmonized criteria for the regulatory identification of EDCs are lacking.

Moreover, most EDC-specific regulations rely heavily on traditional risk assessment and chemical-by-chemical procedures as the basis for regulatory action. To overcome EDC-specific limitations and make regulatory decision-making more effective, greater emphasis on hazard-based approaches is needed.

Implicit regulatory frameworks can offer an effective and efficient means of regulating EDCs based solely on their adverse effects; however, established and standardized regulatory endpoints and toxicity criteria may not adequately capture EDC-specific characteristics. In the absence of robust mechanisms for assessing alternatives, many chemical-specific regulations that ban or restrict EDCs have historically led to regrettable substitution, whereby hazardous substances are replaced with alternatives that pose similar or even greater risks.

Aside from regulatory action, international soft law and collaborative efforts to share and synthesize information have played important roles in elevating EDCs as a global policy issue. Although many governments and stakeholders have responded to these efforts, public awareness

and knowledge about EDCs – particularly among vulnerable populations – remain low. In developing countries, the EDC issue is often overshadowed by more pressing public health and environmental emergencies, limiting the capacity of governments and individuals to take preventive measures. Overall, a stronger emphasis on the global nature of the EDC policy issue is needed.

Actionable recommendations are as follows.

- Strengthen information-sharing capacity to facilitate the exchange of data and assessment outcomes between jurisdictions.
- Assess feasibility to incorporate hazard-based approaches into decision-making processes under regulations with EDC-specific provisions.
- Review and update current standardized toxicity criteria to better capture EDC-specific toxicities.
- Strengthen global measures on EDCs through greater international coordination and harmonized approaches.
- Build capacity in low- and middle-income countries through technical assistance, training, and laboratory infrastructure.
- Expand monitoring and economic assessments to better quantify the health, environmental, and societal costs of EDC exposure.

6 Implications for decision makers

Lead authors

Laura N. Vandenberg (University of Massachusetts, United States of America), Henrik Holbech (University of Southern Denmark, Denmark), Juliette Legler (Utrecht University, Kingdom of the Netherlands), Martin Scheringer (ETH Zurich, Switzerland; Masaryk University, Czech Republic), Leonardo Trasande (New York University, United States of America) and R. Thomas Zoeller (University of Massachusetts, United States of America)

This 2026 state of the science report assesses key scientific advances since the 2012 assessment on EDCs. It is intended to inform policymakers and other stakeholders about EDCs, their risks to human and wildlife health, and the actions needed to mitigate those risks.

This chapter synthesizes key messages from chapters 1–5, identifies gaps and challenges, and translates their implications into a call to action for decision makers at national and international levels.

6.1 Summary of the state of the science and key messages

1. Evidence showing that EDC exposure results in serious adverse effects in humans and wildlife is strong across multiple health domains

Exposure to EDCs is widespread in both humans and wildlife. Since 2012, evidence linking EDC exposure to adverse outcomes has continued to strengthen, and the mechanistic evidence is established well enough in many cases to conclude causality. Rates of several endocrine-related disorders, including low semen quality, neurobehavioural disorders, early puberty, obesity, type 2 diabetes and some cancers, have increased worldwide. Because these changes are occurring rapidly, they are unlikely to be explained primarily by genetic change. Human and wildlife studies continue to report associations between chemical exposure and health effects, consistent with evidence from laboratory studies. Many of the mechanisms by which EDCs interfere with hormone systems are well understood, though the endocrine system's complexity means that some effects, mechanisms and pathways remain to be characterized.

Systematic analysis of the literature identifies several health domains in humans and wildlife that are affected by EDC exposure: male and female reproduction, the thyroid hormone system, neurobehaviour and neurodevelopment, metabolism, the immune system and the cardiovascular system. Each of these health domains is complex and the evidence for adverse effects is strong for some exposure–outcome relationships (figure 6.1).

Human studies increasingly report associations between EDC exposure and a wide range of adverse health outcomes across the lifespan. Epidemiological studies indicate that EDC exposure during sensitive developmental periods is associated with adverse birth outcomes, including low birth weight, reduced head circumference, preterm birth and neurodevelopmental delays (box 6.1). Early-life exposure, particularly prenatal development and early childhood, has also been associated with neurobehavioural disorders such as attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety and cognitive impairment.

FIGURE 6.1

WEIGHT OF EVIDENCE FOR EDC-ASSOCIATED EFFECTS, BY HEALTH DOMAIN

	Humans	Animals
Male reproduction	Strong	Strong
Female reproduction	Strong	Strong
Thyroid	Strong	Strong
Neurodevelopment and behavior	Strong	Strong
Metabolism	Moderate	Strong
Immune	Moderate	Strong
Cardiovascular	Emerging	Emerging
Cancer	Moderate	Moderate*

Shading indicates the strength of evidence for an association in humans and in animals. Animal ratings reflect vertebrate (laboratory and wildlife) evidence; invertebrate evidence is weaker.
*Cancer: animal evidence is strong in laboratory mammals but sparse and confounded in wildlife.

Substantial evidence also connects EDC exposure to reproductive health disorders. In women, associations have been reported with endometriosis, polycystic ovarian syndrome (recently renamed "polyendocrine metabolic ovarian syndrome"), altered pubertal timing, and reduced breastfeeding duration. In men, EDC exposure has been linked to declining semen quantity and quality, hormonal disruption, increased infertility risk, and congenital reproductive abnormalities such as cryptorchidism and hypospadias.

EDCs are further associated with metabolic disorders including obesity, type 2 diabetes mellitus, and metabolic dysfunction-associated steatotic liver disease (MASLD), as well as cardiovascular disease. EDC exposure can also disrupt thyroid hormone regulation, leading to altered circulating hormone levels that may affect both metabolism and neurodevelopment.

Growing epidemiological evidence links EDC exposure to immune dysfunction, including increased risk of allergic and autoimmune conditions, and to hormonally related cancers such as breast, prostate, thyroid and endometrial cancer. Taken together, the expanding body of human research suggests that EDC exposure contributes to a broad spectrum of endocrine-related diseases and disorders.

In wildlife, the effects of EDCs extend to both vertebrates and invertebrates. In vertebrates, documented effects include diminished egg quality and sperm counts in fish, impaired

Box 6.1 Critical developmental windows are especially sensitive to EDCs

Hormones play essential roles at all stages of life, from conception to death, across all organisms. However, during specific periods of development (for example, embryonic, fetal and pubertal stages), hormonal signals are "organizational", meaning they permanently shape tissues, organs and physiological systems (for example, sex determination and differentiation). Hormonal disruptions that occur during these windows can be irreversible. EDCs that interfere with hormone signals during these critical periods of development, therefore, carry particular concern.

In adults, these same hormones regulate different kinds of events (such as the female menstrual cycle or male spermatogenesis). Thus, EDC exposure during adulthood can still have measurable adverse effects on health and physiological functions. However, in adults, these effects are often, but not always, reversible if EDC exposure ceases.

Children are especially vulnerable to EDCs not only because of the sensitive developmental processes that occur in early life, but also because they consume more food and water and breathe more air per unit of body weight than adults, resulting in proportionally higher chemical exposure. Early life EDC exposure occurring in utero or during puberty can also have latent effects: outcomes such as cancer, metabolic syndrome and infertility may not manifest until decades after an exposure, consistent with the developmental origins of health and disease framework.

In non-mammalian vertebrates such as fish and amphibians, sex determination is more environmentally flexible than in mammals. EDC exposure during critical developmental periods can create intersex phenotypes or reverse phenotypic sex entirely. Similar effects of EDCs are also observed in some invertebrate species.

spermatogenesis in frogs, reduced reproductive success in reptiles, neurobehavioural disruption in birds, altered sex ratios in fish and amphibians, and disrupted immune responses across multiple taxa. In invertebrates, a large, diverse and important group whose endocrine systems are increasingly better understood, effects of EDCs include changed sex ratios in crustaceans, disrupted moulting in arthropods, abnormal shell development in molluscs, inhibition of spermatogenesis in earthworms and echinoderms, and disrupted immune responses in bees and molluscs.

Policy implications

Exposure to EDCs has been linked to a range of diseases and health conditions in humans, as well as widespread effects on wildlife populations. These findings suggest that current measures to protect public and environmental health do not fully address the issue. Because of the complexity of the endocrine system, the effects of EDC exposure span multiple health domains rather than a single system or endpoint, requiring broad assessment. The evidence highlights the importance for accounting for critical periods of development, when individuals are especially vulnerable, in regulatory frameworks. Experience indicates that the 10-fold uncertainty factor often used in risk assessment to account for exposures in developing individuals is not always sufficient to account for the increased susceptibility to EDCs observed during critical periods of development. In addition, some health effects may not appear until many years after exposure, by which time the chemical or chemical mixture may already be in widespread use. As a result, delays in reducing exposures could lead to continued risks for people, wildlife and ecosystems.

2. Widespread and ubiquitous human and wildlife exposure to EDCs is increasingly documented

Globally, humans and wildlife are exposed to a wide range of chemical classes identified as EDCs, through many pathways of exposure. These include bisphenols, phthalates, polychlorinated and polybrominated biphenyls, certain PFAS, alkylphenols, parabens, many organophosphate pesticides, and others. Human exposure occurs in the everyday environment, including homes, schools, playgrounds, cars, workplaces and specialized settings such as medical environments. EDCs are present in virtually every environmental matrix, including soil, water (including drinking water),

air, food and dust and are incorporated in a wide range of consumer products including many plastics, personal care products, pharmaceuticals, toys, household goods, and electronics as well as pesticides. The aquatic environment receives a large quantity and variety of EDCs, where they remain in circulation, and food chains serve as a key route of exposure for both humans and wildlife. Wastewater treatment plants are significant emission sources; monitoring of effluents from those plants provides important data on chemical releases to water bodies.

Exposures have been measured in regions where these chemicals are neither manufactured nor used, with some EDCs reaching the Arctic and Antarctic through environmental long-range transport. Some persist in the environment for decades, while others are produced at such high volumes that their levels remain high although the chemicals are degradable.

Human and environmental (bio)monitoring provides three essential pieces of information: the magnitude and distribution of exposure to EDCs within populations and wildlife; spatial patterns that help identify exposure hotspots; and trends over time that allow evaluation of whether regulatory interventions or changes in consumer use patterns are effective. These functions make biomonitoring a cornerstone of EDC management.

Despite progress, monitoring coverage remains uneven globally. Even in high-income countries, biomonitoring data are incomplete and exposure to many chemicals is not routinely assessed in representative human populations. These gaps are more evident in low- and middle-income countries, in many occupational settings, and within vulnerable population groups. Moreover, environmental and biomonitoring data are also lacking for many ecosystems and wildlife populations. As a result, it is difficult to accurately assess exposures, identify populations at risk, and evaluate whether regulatory and risk management measures are effective. In addition, gender and other social determinants can influence exposure and vulnerability to EDCs, highlighting the need to strengthen biomonitoring efforts, including sex-disaggregated data and increased attention to vulnerable populations.

Policy implications

Gaps in exposure data, particularly in low- and middle-income countries and for wildlife populations, can limit assessment, policy evaluation and the development of effective interventions. The widespread use of EDCs in consumer products and their presence across environmental media means that exposure is widespread and continuous, and occurs through multiple pathways for both humans and wildlife. As evidence on EDC-related health effects continues to grow, biomonitoring is an important source of information on exposure patterns among consumers, workers and other potentially vulnerable groups.

3. An increasing number of chemicals have been identified as EDCs as testing programmes have advanced, yet most chemicals remain untested and major gaps persist

The number of chemicals identified as EDCs continues to grow, in large part due to the significant investment in the development of assays and testing programmes as well as interest from the scientific community at large. Evidence from laboratory studies continues to expand the list of identified EDCs (see, for example, the European Chemicals Agency EDC assessment database and the European Food Safety Authority pesticide active substance assessments) (ECHA 2026; EFSA 2026). Major international investments have expanded the ability to test chemicals for endocrine-disrupting properties. Studies using laboratory animals and new approach methodologies based on cell and computer models (see box 6.2) and developed specifically to identify mechanisms and adverse effects, such as the OECD test guidelines, have been especially critical in identifying EDCs. National and international EDC testing programmes have grown significantly over the past decade, and many new validated and standardized screens, tests, assays and guidance documents are now available.

Box 6.2 Testing for EDCs continues to advance

New approach methodologies, including computer simulations and cell-based assays, offer promising gains in the speed and cost of EDC safety testing. Additionally, new approach methods can characterize intrinsic hazardous properties and provide increased mechanistic insights, which are especially important for the lesser-studied endocrine-mediated health effects and endpoints.

The transition from validated animal-based studies to validated new approach methods is under way but will require substantial time and resources. Authoritative bodies and the broader scientific community have determined that new approach methods are not yet sufficient to replace animal models. These same authorities have concluded that the absence of effects in new approach methods cannot be used to draw conclusions about the absence of hazards. They also note that available new approach methods are missing important modes of action, especially for endocrine-mediated outcomes, which are often complex and involve interactions among hormone systems and across organs that are not fully understood. Demonstrating the reproducibility, reliability and whole organism relevance of new approach methods is essential before they can be accepted as replacements in regulatory contexts.

Commitments to animal-free testing are ethically important and logistically desirable but must be supported with adequate resources and adopted carefully. At present, evidence from animal studies, combined with other laboratory approaches, remains critical to protect human and wildlife populations from EDCs.

Despite these advances, human and environmental exposures to EDCs are incompletely documented. And because there are critical gaps in the available assays and implementation of testing programmes has been limited, the total universe of EDCs remains unknown. More than 350,000 chemicals and chemical mixtures have been registered for production and use globally, but the vast majority have never been evaluated for endocrine-disrupting properties, and there is little to no formal testing beyond the estrogen, androgen, thyroid and steroidogenic pathways.

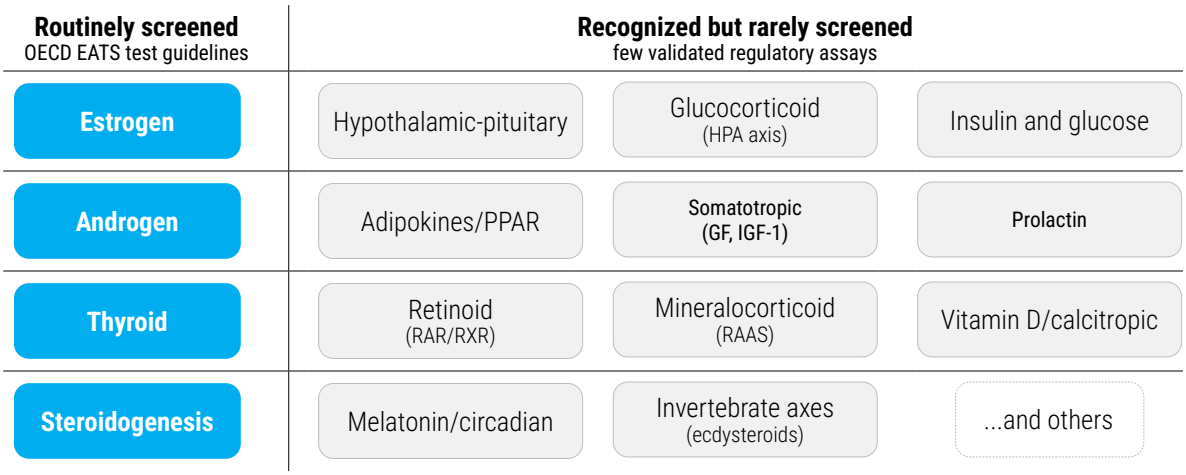
Most testing efforts indeed remain focused on estrogen, androgen, thyroid and steroidogenic modalities and often centre around endpoints that are relatively easy to evaluate but are less sensitive than other outcomes (see figure 6.2). Tests to identify EDCs acting on other hormonal systems, including neurohormones, pituitary hormones, corticosteroids, metabolic hormones and renal hormones, are also still lacking. Consequently, chemicals not covered by current testing frameworks likely cause harm in human and wildlife populations that is not yet fully appreciated. Testing strategies that are sustainable by design would prevent regrettable substitutions but have not received the attention needed. Finally, current tests leave many species without sufficient protection; for example, the unique aspects of invertebrate endocrine systems are poorly represented in testing programmes.

Approaches that examine one chemical, one receptor or one outcome at a time do not adequately account for the complexity of hormone systems and endocrine disruption and are likely to underestimate the full impact of EDC exposure on human, animal and ecosystem health. Most EDC studies examine one chemical at a time, while real-world exposures involve complex mixtures whose constituents can change throughout the chemical lifespan and over time. Studies also typically assess a limited range of outcomes and rarely account for interactions with other stressors such as temperature, nutrient insufficiency or excess, circadian disruption, or chemical carcinogens that EDC exposures can amplify.

These limitations are particularly significant given that an adverse effect extends beyond direct harm to include a reduction in an organism's capacity to respond to additional stressors. An EDC exposure that appears benign in isolation may, therefore, compromise human and wildlife health in ways that only become apparent when a second challenge is introduced. A classic example is that of blocking one of the thyroid hormone receptors:

FIGURE 6.2

ENDOCRINE PATHWAY COVERAGE IN REGULATORY TESTING



Internationally harmonized (OECD) test guidelines focus on the estrogen, androgen, thyroid and steroidogenic pathways, although even these are not included in all regulations. Few, if any, of the other recognized endocrine pathways have validated regulatory assays, so many potential mechanisms of disruption are not routinely screened for. Independent scientists have nonetheless characterized these pathways and developed research methods for them – the gap is in regulatory validation, not scientific knowledge. Pathways shown are representative, not exhaustive.

under standard conditions, the animals are almost normal, but at reduced temperature, they die. This feature of EDCs has been poorly evaluated in validated test guidelines and will be challenging for new approach methods to address.

Policy implications

The absence of data on a chemical should not be interpreted as the absence of EDC properties. Existing testing frameworks provide a foundation for the identification and evaluation of EDCs, but they do not provide comprehensive coverage of all relevant elements. Remaining knowledge gaps include limited testing methods beyond estrogen, androgen, thyroid and steroidogenic pathways, an insufficient number of validated assays for invertebrate species, and challenges in accounting for real-world exposures to chemical mixtures and other stressors. The available evidence also indicates limitations of single chemical hazard and risk assessments for capturing the cumulative and combined effects of EDC exposure on human health and wildlife. These findings highlight the relevance of complementary approaches, including grouping- and read-across-based evaluations and regulations, to avoid regrettable substitution. They also highlight the importance of generating information on endocrine-disrupting properties before substances are placed on the market or released into the environment, across jurisdictions and chemical uses, while also evaluating existing chemicals already in use to protect public health, wildlife and ecosystem services. Because EDCs are often selected and incorporated into products for specific functions or performance characteristics, a sector-based approach can focus on the functional uses of chemicals and identify safer, sustainable alternatives that deliver equivalent performance or function.

4. The estimated health, environmental and economic burden of EDCs is large and likely underestimated, with global health-related costs alone estimated to exceed US$ 1.1 trillion annually.

In recent years, it has been recognized that exposure to EDCs can result in significant health costs that should be considered in economic assessments, with global health-related costs. These EDC-attributable health costs are considered externalities because they are borne by

individuals and the health care system rather than by the industries that profit from EDC-containing products (figure 6.3).

Quantitative estimates of the health-related costs associated with EDC exposure are available and are methodologically robust. Studies developed for the European Union identified a conservative estimate of 163 billion euros (1.2% of GDP) in annual costs attributed to just 15 health conditions associated with EDC exposure. Comparable United States of America estimates reached US$ 340 billion (2.3% of GDP). As global exposure assessments have advanced, extrapolation from estimates for the European Union, the United States of America and Canada shows that the costs of diseases linked to EDCs could amount to 1 percent or more of global GDP, equivalent to approximately US$1.1 trillion in 2025. This figure is almost certainly an underestimate because it reflects only a subset of diseases and chemicals for which causal attribution has been established. These estimates also do not include ecological costs.

The economic argument for action is therefore strong. For decision makers, the assessment of policy action may include the costs of interventions as well as the health, environmental and economic costs associated with continued exposure.

Policy implications

Current estimates of the health and economic burden associated with EDC exposure are likely to represent lower-bound estimates and therefore underestimate the costs of inaction. Global health-related costs have been estimated to exceed US$ 1.1 trillion annually, highlighting the substantial economic benefit of action. These findings are relevant to the application of the polluter pays principle and to discussions on how the health and environmental costs associated with EDC exposure are reflected in economic decision-making. Approaches that account for these external costs will contribute to a more comprehensive assessment of the societal impacts of chemical production and use.

FIGURE 6.3

ECONOMIC COST OF INACTION

Economic cost of inaction

1.2–2.3% of GDP

EDC-attributable disease costs per year, wherever they have been estimated

Economic cost by jurisdiction (disease and disability)

United States
US$340 bn
2.3% of GDP

European Union
€340 bn
1.2% of GDP

Canada
CA$24.6 bn
1.3% of GDP

EDC-attributable costs of disease and disability, estimated by the cost-of-illness method for a 2010 population. These are lower bounds: they cover only a subset of EDCs and health effects, assess single chemicals rather than mixtures, and exclude PFAS. Ecological and ecosystem service costs (biodiversity, clean water, wildlife) are not included and are separately estimated to be far larger but highly uncertain. Comparable estimates for low- and middle-income countries are largely unavailable.

5. Policy and governance frameworks have evolved since 2012 but remain fragmented and insufficient to transform products and sectors causing widespread EDC exposure.

A global definition of EDCs has existed since 2002. This definition has, in some regions of the world, been used as a foundation for the development of scientific regulatory criteria for EDCs requiring three elements: (a) an adverse health effect; (b) an endocrine mode of action; and (c) a plausible link between the two. Lists of EDCs identified on this basis (see, for example, the European Chemicals Agency EDC assessment database and the European Food Safety Authority pesticide active substance assessments) continue to expand. Global implementation of these criteria as hazard classes in the Globally Harmonized System of Classification and Labelling of Chemicals is needed to ensure uniform identification of EDCs across the globe. There is also a need for two distinct categories with a clear distinction between identified and potential EDCs. Such designations should be based on transparent evaluations using all available evidence. Importantly, identifying chemicals as EDCs is a critical aspect of hazard identification which should be kept separate from later risk management decisions.

EDCs are addressed through a wide range of binding and non-binding legal instruments as well as voluntary initiatives located at the national, regional and international levels. Several of these instruments and initiatives are specific to EDCs, for example in the context of pesticides, pharmaceuticals or cosmetics. Others, such as the Stockholm Convention on Persistent Organic Pollutants, cover larger groups of chemicals and include EDCs only implicitly. In recent years, the regulatory landscape has become strengthened with an increasing number of legal instruments and voluntary initiatives, including non-binding instruments, such as the Global Framework on Chemicals.

The way in which EDCs are addressed varies between instruments and jurisdictions, which leads to inconsistencies and gaps in the protection of human and environmental health. Many regulatory instruments still rely on risk assessment approaches to justify regulation of EDCs, which creates obstacles to effective EDC regulation. Considerable gaps and inconsistencies remain and EDC regulation is not sufficiently effective.

Coordinated international actions, adopting a One Health approach and accounting for the abilities and incentives needed in lower-resourced countries, are necessary to achieve meaningful reductions in EDC exposure worldwide (box 6.3 and figure 6.4). The One Health approach indicates that evidence from laboratory animals and wildlife can inform human health determinations, and vice versa. Furthermore, evidence from laboratory studies can provide a sufficient basis to support regulatory action, particularly where human and wildlife data are limited.

Policy implications

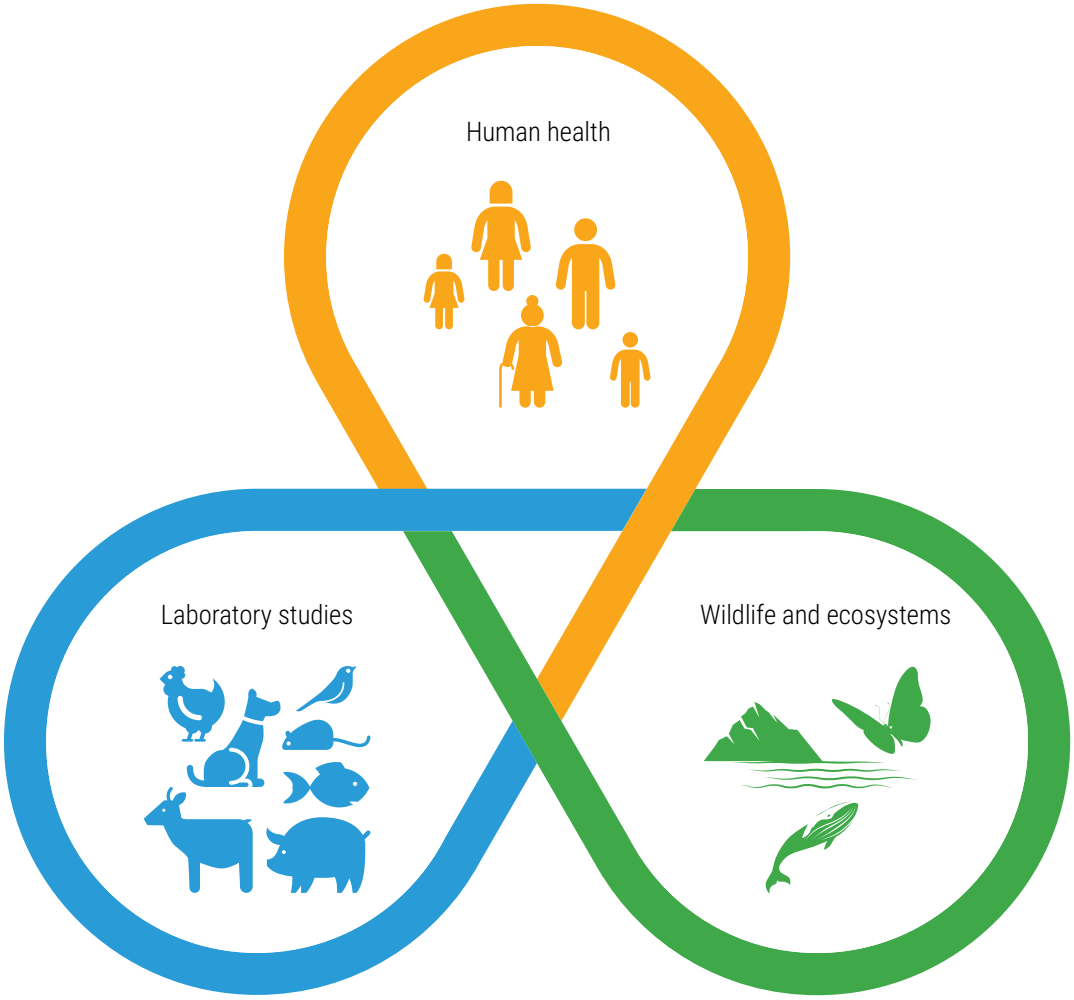
The transboundary nature of EDC contamination means that no country can address this problem in isolation, which highlights the importance of international frameworks, harmonized standards and data sharing. Available evidence suggests that important gaps remain in current regulatory approaches, calling for enhanced national and international actions. Implementation of internationally harmonized hazard classes for EDCs within the Globally Harmonized System of Classification and Labelling of Chemicals can support consistent identification, classification and labelling of EDCs worldwide.

The growing evidence on EDCs highlights the importance of strengthening and aligning existing binding and non-binding instruments, as well as voluntary initiatives, to support more systematic, comprehensive and effective protection of human health, wildlife and ecosystems. Evidence is already sufficient to support action, particularly in a number of sectors known to be significant sources of exposure to EDCs.

A sector- and value-chain-based perspective can complement traditional chemical-by-chemical approaches and help identify practical opportunities to prevent exposure at source through phase-out, and to promote substitution, innovation and the adoption of safer alternatives. Successful approaches generally combine

FIGURE 6.4

INTERCONNECTEDNESS OF THE ONE HEALTH APPROACH



The One Health approach recognizes the interconnectedness and interrelatedness of human, laboratory animal and environmental health. Studying features of one of the three domains can shed light on the other two. However, a holistic evaluation acknowledges the close connection between the health of humans, animals and the environment (including ecosystems), finding ways to study the effects of EDCs on all three domains.

Box 6.3 One Health approach and EDCs

The One Health approach recognizes that the health of humans, animals and the environment are closely linked and interdependent. Data from laboratory animals, domesticated animals and wildlife populations can inform human health assessments, and vice versa. This integrated approach also acknowledges that hormones and endocrine systems are structurally and functionally very similar across vertebrate species. Therefore, the value of cross-species evidence in establishing the plausibility of effects in humans is very high.

For decision makers, the One Health approach offers a practical tool: it allows evidence from multiple sectors and species to be integrated in the assessment of EDC hazards, and it identifies interventions that deliver co-benefits for human health, animal welfare and biodiversity.

science, regulation, innovation, financing, capacity-building and international cooperation. Coordinated international action and related capacity building are particularly important for developing countries.

6.2 Key implications for decision makers: a call to action to address key gaps and needs

The scientific evidence is clear: EDCs are a global and growing threat to human and environmental health. The economic costs of EDC exposures, and resulting human health and environmental effects, are large, underestimated and unevenly distributed. Despite advances in science, testing and governance, current approaches to identify EDCs and regulate these chemicals remain uneven and insufficient.

At the same time, growing consumer demand for safer products is creating incentives for innovation in green and sustainable chemistry. Investment in chemicals and products that are safe and sustainable by design can reduce exposure at source and help prevent regrettable substitutions. Increasing awareness of EDC-related risks may also increase the potential for reputational and liability risks for producers that continue to rely on EDCs in their processes and products. Countries are also increasingly adopting policies and regulations that address product design and chemicals in products, providing additional opportunities to reduce exposure to EDCs at source and across the product life cycle.

Drawing on the evidence presented in this report, six priority needs or areas for action emerge that reflect the major scientific findings and challenges associated with EDCs:

- Protect vulnerable populations from EDC exposure, particularly during critical development and life stages, such as pregnancy, infancy and childhood.
- Improve monitoring and understanding of EDC exposure.
- Advance EDC identification, testing and assessment.
- Account for the health, environmental and economic costs of EDC exposure.
- Strengthen governance, partnerships, and regulations and transform products and sectors driving exposures to EDCs.
- Use the One Health approach to characterize the impact of EDCs on understudied species, health outcomes and responses to additional stressors.

The actions presented in table 6.1 are organized according to the level at which implementation is most appropriately undertaken.

- **International and multilateral action.** EDCs do not respect national borders. Many of the most harmful EDCs are persistent, long-range pollutants; others are present at high levels due to continuous production in large volumes. Beyond environmental transboundary movement, EDCs can also move across borders through trade in products and materials. Effective governance requires internationally coordinated solutions, complementing national and regional measures to address identified and potential EDCs. Countries with fewer resources must be supported.
- **National regulatory and policy action.** National governments hold primary responsibility for chemical regulation, environmental monitoring and health protection. Interventions at national or regional levels also play a key role in addressing exposure to identified and potential EDCs, particularly in sectors with high exposure such as food contact materials, packaging, toys, cosmetics or pesticides. Actions presented are within the authority of national environmental, health and trade ministries.
- **Testing, research and science policy.** Decision makers who fund research and set science policy can significantly accelerate progress in EDC identification, hazard assessment and the development of safer alternatives.

Table 6.1 Priority needs and areas for action for EDCs, by level of implementation

International and multilateral action	National regulatory and policy action	Testing, research and science policy
Protect vulnerable populations from EDC exposures, particularly during critical development and life stages, such as pregnancy, infancy and childhood		
Strengthen regulatory infrastructure and monitoring programmes. Efforts are especially needed in resource-limited countries, recognizing that weaker national systems create the potential for global exposure and associated health hazards.	Design equitable policies that address the disproportionate EDC exposure burdens borne by vulnerable groups, including communities living near industrial facilities, indigenous populations, pregnant women, children and high-exposure occupational groups. Take into account broader factors, including gender norms, occupational roles, and socioeconomic conditions in prevention measures. Improve wastewater treatment infrastructure when monitoring indicates significant EDC emissions from treatment plants.	Conduct controlled laboratory studies to continue building mechanistic understanding for how EDC exposures contribute to adverse health outcomes. Develop new approach methods that account for differences in biological vulnerability during critical windows of development. Support biomonitoring studies to quantify EDC exposures during critical windows of development. Design studies that recognize and evaluate the long latency anticipated between early life EDC exposures and later-life disease outcomes. Include both sex differences and gender factors in future studies to better understand and account for the differential impacts of EDC exposure
Improve monitoring and understanding of EDC exposure		
Improve characterization of exposure sources globally, including chemical use patterns and emission data, especially in low- and middle-income countries where commercial databases are largely absent. Expand and coordinate EDC biomonitoring programmes globally, with priority investment in low- and middle-income countries where data gaps are most severe, but also additional investment in high-income countries where biomonitoring data are also lacking. Create transparent, internationally accessible data portals for EDC effects across species, usage, exposure, and monitoring data. Address inconsistent chemical identifier systems that currently impede data sharing.	Continue and expand national human biomonitoring programmes, including under the Global Monitoring Plan of the Stockholm Convention, and secure long-term funding for their operation. Continue and expand non-invasive EDC monitoring programmes in wildlife, including for sensitive indicator species such as marine mammals. Develop global environmental surveillance and wildlife sentinel programmes to detect emerging effects on wildlife species and ecosystems. Conduct cradle-to-grave assessments of EDC exposure across the chemical and product life cycle, with particular attention to chemical and product design, as well as occupational exposure (for example, exposure to bisphenols and phthalates during plastic manufacture, pesticide applicator exposures) and safe disposal.	Conduct longitudinal human cohort studies, with biomonitoring across the life span. Improve exposure assessments for emerging chemical replacements and transformation products.

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Table 6.1 continued

International and multilateral action	National regulatory and policy action	Testing, research and science policy
Advance EDC identification, testing and assessment		
Adopt harmonized international criteria for EDC identification, including recognition of EDC hazard classes under the Globally Harmonized System of Classification and Labelling of Chemicals, to create a consistent global tool for identification, classification and labelling. Promote mutual acceptance of data and coordinated testing standards through OECD and other intergovernmental organizations, reducing redundant testing and improving regulatory efficiency across jurisdictions. Recognize that new approach methods are designed to identify intrinsic hazardous properties of chemicals and mixtures, and support efforts to validate these methods.	Require premarket testing of new chemicals for endocrine-disrupting properties before they enter commerce, regardless of sector (industrial applications, food safety, occupational safety or agriculture). The absence of data must not be treated as evidence of safety. Implement scientific criteria for EDC identification in relevant pieces of legislation. Implement hazard-based regulatory approaches for identified EDCs wherever possible. Develop regulations that complement single-chemical approaches with mixture-based assessment methods, acknowledging that chemicals can act differently in a mixture than they do individually. One pragmatic approach in case of lack of data is to include a mixture assessment factor in risk assessments. Use read-across methods to apply evidence from single chemicals to support group-based or function-based regulations (for example, class bans or functional substitution). Class-based regulations can prevent regrettable substitution, in which one harmful chemical is replaced by another harmful chemical that simply has less information available. Expand research programmes investigating effects of EDCs and their underlying mechanisms. Continue supporting work on estrogen, androgen, thyroid and steroidogenic modalities, and expand work on non-estrogen, androgen, thyroid and steroidogenic pathways. Vast knowledge gaps must be addressed to develop adequate test methods, including during the transition from animal to non-animal testing.	Expand research and develop tests and assays beyond estrogen, androgen, thyroid and steroidogenic modalities to include neurohormones, pituitary hormones, corticosteroids, retinoid, metabolic and renal hormones, and invertebrate-specific endocrine systems (juvenile and moulting hormones), among others. Develop and validate new approach methods that are reproducible, reliable and relevant at the organismal level. Ensure that validation demonstrates their ability to support regulatory decision-making before they are accepted as substitutes for animal-based test guidelines. Continue to improve validated animal-based test guidelines. Replacements for animal-based testing must be sufficiently comprehensive, accounting for the complexity of the endocrine system but also the different hormone responsive cells, tissues and organs within the domains that have been shown to be associated with EDCs (for example, male and female reproductive systems; thyroid; brain, neurobehaviour and neurodevelopment; metabolic organs; the immune system; and the cardiovascular system). Incorporate academically generated and publicly funded evidence into formal hazard and risk evaluations, alongside data from standardized test guidelines. Guidance documents are available to support this integration. Academic researchers should use reporting frameworks that best support the use of their data by regulators. Adopt systems biology approaches to capture interactions among hormonal networks, moving beyond single-receptor and single-pathway models. Incorporate mixtures into scientific studies and testing design, reflecting the reality of how humans and wildlife are actually exposed.

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Table 6.1 continued

International and multilateral action	National regulatory and policy action	Testing, research and science policy
Account for the health, environmental and economic costs of EDC exposure		
Improve quantification of health, environmental and economic outcomes to support more informed decision-making and assess the potential gains from actions aimed at reducing EDC exposure.	Use socioeconomic analyses to quantify the benefits of regulatory action (for example, health care costs averted, decreased disability-adjusted life-years, productivity gains) and use these data to build the political and fiscal case for intervention. Internalize the health and environmental costs of EDC exposure into economic and regulatory decision-making, including through fiscal mechanisms that incorporate these costs into the price of a product.	Quantify the costs of EDCs on ecosystem services and biodiversity loss to provide the evidence base needed to support environmental protection policies alongside human health ones.
Strengthen governance, partnerships, and regulations and transform products and sectors driving exposures to EDCs		
Support global legally binding instruments and equivalent frameworks that address major sources of EDC exposure, including plastics or pesticides, as these instruments can provide effective means of reducing widespread global exposure. Review, strengthen, harmonize and, where necessary, update binding and non-binding regulatory instruments and voluntary initiatives to make EDC governance more systematic, comprehensive and consistent. Support implementation of the Global Framework on Chemicals by accelerating sectoral transformation towards safer products, sustainable value chains and reduced exposure to EDCs.	Accelerate regulatory action on known EDCs, particularly in high-exposure sectors such as food contact materials, toys, and cosmetics. Support implementation and, where available, uptake of already existing safer alternatives, product redesign, safe and sustainable chemistry, sustainable procurement and group-based approaches to prevent regrettable substitutions and eliminate EDC exposures at source. Maintain research funding for legacy chemicals that are no longer manufactured but for which exposures continue to be documented. Prioritize phasing out of chemicals already restricted internationally and consider the "essential use" approach to uses where safe and sustainable alternatives are not yet available. Require industries to develop and disclose chemical substitutions, transparently demonstrating that chemical alternatives do not share the same EDC properties.	Strengthen international capacity-building in laboratories through established and new funding mechanisms and collaborative research approaches. Create mechanisms for academic-regulatory partnerships to continue modernizing approaches used in hazard identification and risk assessment.

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Table 6.1 continued

International and multilateral action	National regulatory and policy action	Testing, research and science policy
Use the One Health approach to characterize the impact of EDCs on understudied species, health outcomes and responses to additional stressors.		
Mainstream the One Health approach in EDC policy and regulation, recognizing the interconnectedness of human, animal and environmental health and the value of evidence across different systems and evidence streams.	Recognize that regulatory frameworks should not require epidemiological evidence of harm before action can be taken, acknowledging that once epidemiological evidence is available, populations have already been exposed and harmed.	Adopt or strengthen the One Health approach in research design and regulatory assessment, integrating evidence from humans, laboratory animals and wildlife to achieve more robust and efficient hazard characterization. Prioritize research on real-world mixture exposures, multiple stressors (including climate change, high temperatures, social and nutritional stresses, and exposure to chemical carcinogens), sex-specific effects, transgenerational impacts, and the critical periods of development most relevant to health-protective regulatory decision-making.

The evidence reviewed in this report highlights the importance of immediate, coordinated and equitable action on EDCs. Actions can occur at multiple points across product systems, sectors and value chains. While uptake may differ according to national circumstances and available capacities, there is an expanding body of evidence on practical approaches for reducing exposure, supporting safer alternatives and strengthening EDC management. The costs of delay – in terms of adverse health effects, lost productivity, ecological damage and economic loss – far exceed the costs of prevention and effective regulation. The evidence is sufficiently strong to support policy action. To protect humans and ecosystems from the harms of EDC exposure, sustained political commitment, adequate resources and international cooperation are required. In the meantime, the effective use and strengthening of already existing policy tools is needed without delay.

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Chapter 4

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Chapter 5

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Annex I. Brief history of EDC research and policy responses

The 1991 Wingspread Conference on Endocrine-Disrupting Chemicals brought together experts from multiple disciplines and resulted in a consensus statement stating that many chemicals could harm wildlife and humans by affecting endocrine systems (Wingspread 1991). Books such as *Our Stolen Future* (Colborn, Dumanoski and Myers 1996) further raised public awareness, prompting countries to develop research programmes and methods to investigate the endocrine-disrupting potential of anthropogenic chemicals.

At the international level, the Fiftieth World Health Assembly adopted resolution WHA50.13 in 1997 (World Health Assembly 1997), which called upon the World Health Organization (WHO) to "take the necessary steps to reinforce WHO leadership in undertaking risk assessment as a basis for tackling high priority problems as they emerge, and in promoting and coordinating related research, for example, on potential endocrine-related health effects of exposure to chemicals".

In 2002, the International Programme on Chemicals Safety (IPCS), a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and WHO, conducted the first Global assessment of the state-of-the-science of endocrine disruptors (IPCS 2002). This assessment provided a clear definition of EDCs which has now been widely accepted by governments and stakeholders worldwide. The 2002 assessment also highlighted extensive evidence of their adverse effects on wildlife, while calling for more rigorous studies on their impact on humans. It called for broad, collaborative and international research initiatives, with a list of critical research needs.

To capture the wealth of knowledge generated, WHO and UNEP conducted a second assessment, *State of the Science of Endocrine Disrupting Chemicals – 2012* (UNEP and WHO 2013). That 2012 assessment focused on consolidating scientific evidence on the environmental and health effects of EDCs, as well as EDC exposure, that had been generated since the first assessment. The assessment further highlighted unique characteristics of EDCs that need to be carefully considered when testing, assessing and managing their risks.

Importantly, the 2012 assessment sparked policy development at all levels. Internationally, informed by the 2012 assessment, the International Conference on Chemicals Management (ICCM) recognized EDCs as an emerging policy issue of concern under the Strategic Approach to International Chemicals Management during its third session in 2012 (ICCM resolution III/2) (Strategic Approach to International Chemicals Management [SAICM] 2012). The ICCM acknowledged the potential adverse effects of EDCs on human health and the environment, emphasizing the need to protect vulnerable populations, particularly in developing countries and economies in transition. In 2015, at its fourth session, the ICCM invited UNEP and WHO to address these needs by generating and disseminating information on EDCs (ICCM resolution IV/2) (SAICM 2015).

Subsequently, UNEP commissioned the International Panel on Chemical Pollution to develop three overview reports on EDCs, complementing the 2012 assessment. These reports included a review of worldwide initiatives to identify EDCs and potential EDCs; an overview of current scientific knowledge on the life cycles, environmental exposures and environmental effects of selected EDCs and potential EDCs; and existing national, regional and global regulatory frameworks (International Panel on Chemical Pollution [IPCP] 2017a; IPCP 2017b;

IPCP 2017c). In 2020, UNEP conducted another assessment on issues of concern, including EDCs. This assessment analysed existing regulatory instruments and voluntary actions, highlighting major gaps, challenges and opportunities for future sound management actions (UNEP 2020).

During this period, research on EDCs continued rapidly, advancing scientific knowledge on many fronts, including identifying new end-points that are sensitive to EDCs and health consequences that are associated with EDC exposure (see chapter 2), developing testing and assessment methods to identify and make decisions about EDCs (see chapter 3), quantifying exposures to EDCs and developing substitutions and replacements for known and suspected EDCs (see chapter 4), and understanding socioeconomic impacts and environmental justice issues (see chapter 5).

At its resumed fifth session in March 2022, the United Nations Environment Assembly requested UNEP, in cooperation with WHO, to update the 2012 assessment (resolution 5/7) (United Nations Environment Assembly 2021). One year later, the World Health Assembly adopted resolution WHA76.17 requesting WHO to work jointly with UNEP on the update (World Health Assembly 2023). This new state of the science assessment is a direct response to these resolutions.

Annex II. Chapter 2 search methodologies and general overview of retrieved literature

Notes on the literature search and literature inclusion parameters

The research reported here is based entirely on scientific literature (journal articles, book chapters, reports, government reports and web pages). The sources were found via Google Scholar, Web of Science and Scopus. To minimize knowledge gaps, all three search engines were used simultaneously and with the same pattern of search inputs. Undermind AI was explored as a search tool but eventually did not contribute to the search.

The search began with the terms "endocrine disrupting chemicals" and "EDC(s)". It was then deepened to the relevant topic by adding "exposure" to the search terms. For each individual chemical and class, a search was conducted for just the name of the chemical (for example, "bisphenol A") or their abbreviation (for example, "PCBs"), and then deepened by adding "endocrine disruption" or "endocrine disruptor" to the search term. Following this, "biomonitoring", "human biomonitoring", and "wildlife biomonitoring" were added to the chemical name or abbreviation to find relevant sources. Results were collected for all available dates, and then limited to the 2012–2025 time frame, in order to look for sources that were specifically not included in the 2012 report *State of the science of endocrine disrupting chemicals – 2012*, and more recently published sources, to provide an update on the state of the science.

Strong indicators for the inclusion of sources were high citation count, and inclusion and publication in a reputable journal. As this review aims to provide a current overview, more recent as well as comprehensive studies were prioritized, particularly when it came to biomonitoring studies, even if they may still have a low citation count. Where possible, open-access publications were favoured and included to ensure that the information retrieved may also be accessible to readers not affiliated with an institution that subscribes to a certain journal.

It was important to include studies that approached the topic of EDC exposure from different perspectives, different disciplines (including medicine, chemistry, ecology and biology) and different magnitudes: both the search for papers that looked generally at EDCs and those looking at either classes or individual chemicals are referenced here. It was also important to include contradictory sources to highlight that, although abundant, knowledge on EDCs is not uniform. Despite this, the report aims to reflect a majority consensus found in the literature. This report is not meant as an exhaustive review of all available sources.

It was not the intention to compile an exhaustive review of each chemical class: as illustrated in chapter 2, there are over 60 reviews for BPA alone, with countless more primary studies. Therefore, there is no guarantee that all "relevant" sources have been included in each section. This report aims to provide a concise, balanced, comprehensible overview of the current state of the science, painting a picture of what the current understanding is, to inform how science and legislation could proceed.

Methodology used to review and synthesize literature for Chapter 2

1. Human Health

Umbrella review

Background

An "umbrella review" which is also referred to as a "scoping metareview" or scoping "review of reviews" was performed (World Health Organization 2022). As indicated in the WHO Quality Assurance handbook for normative and

standard-setting products, an umbrella review is warranted "in topics with good reason to believe that many reviews already exist in the topic. It aims to summarise evidence from multiple systematic reviews at diverse levels, including the combination of different interventions, different outcomes, different conditions, problems or populations." The overview of reviews had as a main goal to map main health outcomes and compounds studied in the EDC body of literature using high-quality evidence from the literature. It also served to evaluate the quality of the evidence on specific topics where multiple primary studies have been performed, and for which meta-analysis has been conducted.

Methodology

The following protocol was adapted based on the WHO Quality Assurance Handbook guidelines for rapid review (World Health Organization 2014) and reviewed by colleagues from WHO's Methods and Standards Unit. The methodology is described in more detail in a manuscript submitted for publication (Contreras Berecochea *et al.* 2026a). The flowchart of the steps followed in the protocol, and the resulting numbers of publications, are shown below (figure A1).

1. Define research questions in Population, Exposure, Comparator, Outcome (PECO) format (table A1)

To determine what the body of evidence of scoping reviews, systematic reviews and systematic evidence maps related to endocrine disruptors is, the following two questions will be answered:

Q1. Which endocrine disruptor-related health outcomes have been reviewed in systematic reviews, scoping reviews and systematic evidence maps?

Q2. What is the relationship between EDC exposure and the health outcomes?

2. Study inclusion and exclusion criteria

The following inclusion and exclusion criteria were applied while scanning the abstract and title:

Table A1 PECO statement, adapted from Pelch *et al.* (2019)

PECO element	Evidence
Populations	Any human, animal (whole organism including experimental and observational studies), or ex vivo/in vitro models utilizing organs, tissues, cell lines, or cellular components (e.g. cell-free receptor binding assays).
Exposure	Exposure to at least one endocrine disruptor. Exposures may include, for example: biomarkers of exposure, modelling of potential exposures, and/or administered exposures. No restrictions were placed on exposure route, dose, frequency, or assessment approach.
Comparators	Humans, animals, organs, tissues, cell lines, or cellular components exposed to no or a lower level of an endocrine disruptor than the more highly exposed subjects or treatment groups, or vehicle-only treatment.
Outcomes	Any health outcome or type of biological response measured in the exposed population.

Inclusion:

- Must be a systematic review, scoping review, or systematic evidence map.
- Must be related to endocrine disruptor exposure.

Exclusion:

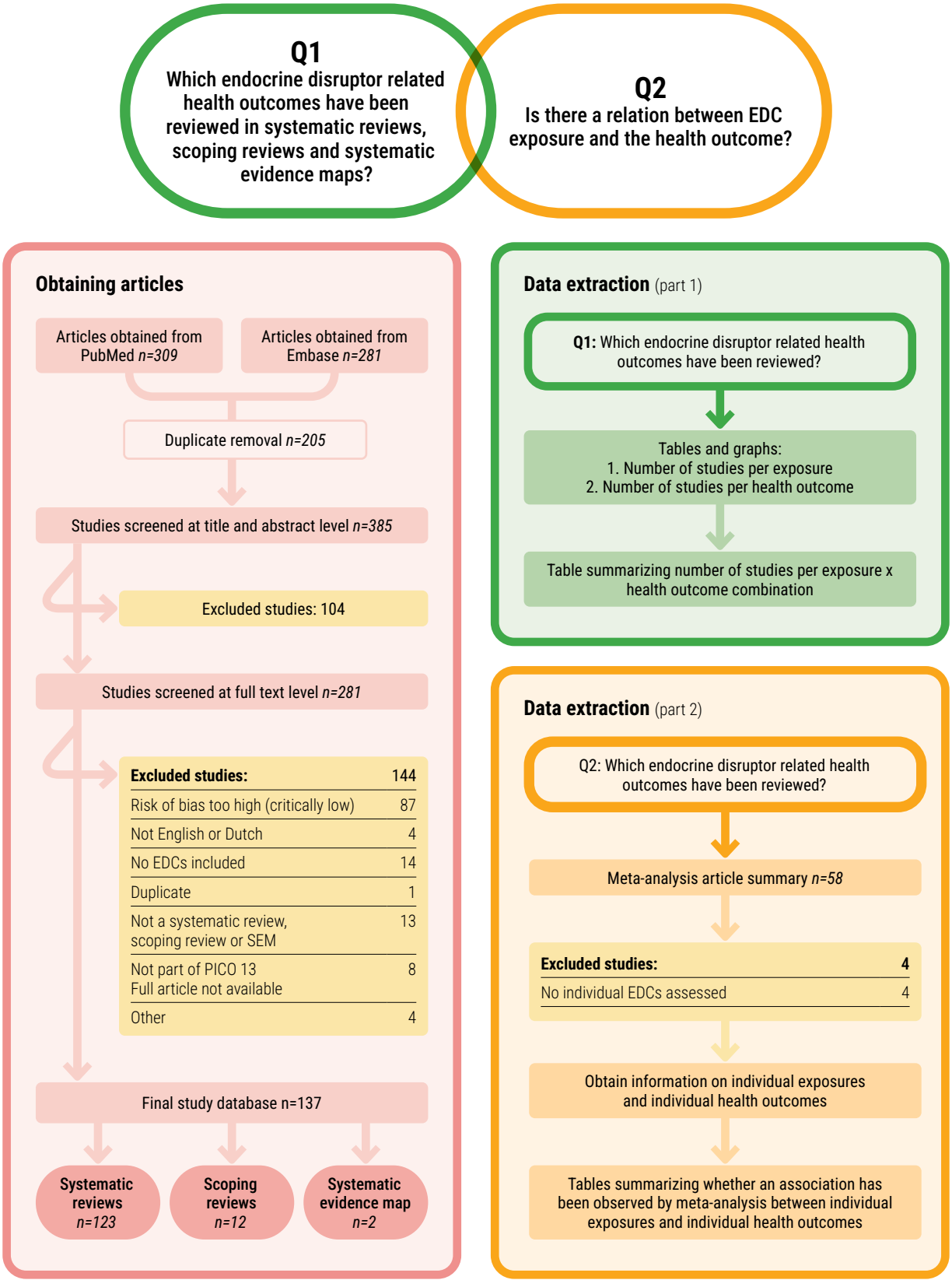
- Studies that are not looking at populations, interventions, comparators and outcomes of interest (as defined in step 1).
- Reviews with a high risk of bias.
- Non-English and Dutch articles.
- No full text available.

3. Define search databases and search terms

Only systematic review, scoping reviews and systematic evidence maps related to the term "endocrine disruptor" will be searched in the scientific literature. It should be noted that the search terms will not pick up all possible reviews of endocrine-disrupting compounds (i.e. reviews of specific compounds which may be known (potential) endocrine disruptors,

FIGURE A1

METHODOLOGY



but do not mention endocrine in the title, abstract or keywords). The search will also not include government reports or grey literature. The initial search was performed on 11 January 2023, and updated on 15 July 2024, with the following search terms shown in table A2.

Table A2 Search strategies

PubMed	(("Endocrine Disruptors"[Mesh]) OR (endocrine disr*[Title/Abstract]) OR ("endocrine disruptor"[Title/Abstract:~3])) AND ((systematic[Title/Abstract] AND review[Title/Abstract]) OR (scoping[Title/Abstract] AND review[Title/Abstract]) OR (systematic[Title/Abstract] AND evidence[Title/Abstract] AND map[Title/Abstract]))
EMBASE	("endocrine disruptor"/exp OR ((endocri* NEAR/3 disrupt*):ti,ab,kw)) AND ((systematic:ti,ab,kw AND review:ti,ab,kw) OR (scoping:ti,ab,kw AND review:ti,ab,kw) OR (systematic:ti,ab,kw AND evidence:ti,ab,kw AND mapping:ti,ab,kw)) NOT "conference abstract"/it

4. Study flow diagram

Figure A1 above.

5. Obtain articles and scan abstract and title

The search queries were performed as indicated in step 3, and the title and abstract of all articles were scanned and included or excluded following the criteria described in step 2. One person reviewed all titles and abstracts, and a second person independently reviewed the publications that were proposed for exclusion by the first reviewer.

6. Assess the risk of bias and conflict of interest

Individual studies were assessed based on the AMSTAR 2 checklist, the most widely used systematic review quality control checklist (Ma *et al*. 2020). The overall confidence in the results of the reviews was rated either high, moderate, low or critically low according to the criteria defined in Contreras Berecochea *et al*. (2026a).

7. Data extraction process

Full text screening was carried out to extract data from categories such as type of article, general information, types of studies (including animal, epidemiological, exposure, in vitro), compounds studied and health outcomes. The health outcome categories, as well as the layout of the data extraction table, are described in Contreras Contreras Berecochea *et al*. (2026a).

Scoping review

Background

A scoping review was conducted to explore the association between EDC exposure and cardiometabolic health outcomes not previously covered (or not covered in detail) in the 2012 report (Contreras Berecochea, Moreira Farnezi, and Legler 2026b). We prioritized 1) cardiovascular disease (CVD), 2) Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and 3) Metabolic Syndrome (MetS) for scoping review, as these outcomes were not covered in 2012. The methodology described below applies for these three outcomes.

Methodology

1. Protocol

The aim of the scoping review was to map evidence from primary sources, the evidence associating health outcomes (CVD, MASLD, MetS) with exposure to EDCs and identify research gaps. We selected a scoping review because it provides a comprehensive approach to summarise and disseminate research findings, identify research gaps, and provide an overview of the existing evidence base, irrespective of quality (Peters *et al*. 2015). This scoping review was based on the guidelines provided in the WHO Quality Assurance Handbook (World Health Organization 2022), and adhered to the PRISMA-ScR guidelines (Tricco *et al*. 2018).

2. Eligibility criteria

Inclusive criteria were employed to examine as many relevant studies as possible. One person reviewed all titles and abstracts, while a second person examined only the citations that were proposed for exclusion by the first reviewer. Studies eligible for consideration had to be available in English, Spanish, French or another accessible language for translation. We did not set restrictions on the year of publication. Our literature search was systematic, but the inclusion and review were pragmatic. This pragmatic approach means that we did not assess the quality of studies or exclude any

based on the certainty of the evidence. With this strategy, we aimed to broadly include published literature to approximate saturation on the most frequently explored aspects of EDC exposure and the health outcomes.

Our research question was formulated using a PECO framework (table A3). We ask the following question: What is the evidence linking exposure to EDCs to the risk of the specific health outcome in humans, compared to individuals with lower or no exposure to EDCs?

Table A3 PECO framework

Population	Humans of all ages, sexes, and socio-demographic backgrounds.
Exposure	Exposure to at least one EDC. Exposures may include biomarkers of exposure, modelled exposure estimate, and/or administered exposures.
Comparators	Different levels of exposure (e.g., high vs. low) or no exposure to EDCs.
Outcome	Cardiovascular diseases (CVDs) including any subcategory of CVD, CVD mortality or surrogate markers directly related to CVD risk. Metabolic Dysfunction-Associated Steatotic Liver Disease, including previous terminologies such as NAFLD, MAFLD, and steatotic liver disease. Metabolic syndrome, including surrogate biomarkers directly related to MetS.

The following inclusion and exclusion criteria were used:

Inclusion:

- Original human epidemiological studies of any design investigating the association between EDC exposure and the health outcomes, providing dose-response relationships such as (but not limited to) relative risks, hazard ratios or odds ratios.

Exclusion:

- Any reviews, commentaries, opinion pieces, animal studies, laboratory experiments.
- No full text is available.
- Studies not looking at populations, exposures, comparators, and outcomes of interest as defined in table A4.

3. Information Sources and Search Strategy

We systematically searched EMBASE and Web of Science for studies matching the PECO question for each health outcome. The literature search strategies are detailed in table A4. We defined our search string only using the term "endocrine disruptor" and included studies where the authors explicitly refer to these chemicals as EDCs. However, we will not verify whether the chemicals mentioned are officially classified as EDCs by recognised entities as it is out of the scope of this review. Furthermore, it should be noted that the search terms will not retrieve all possible reviews of endocrine-disrupting compounds. For instance, reports of specific compounds that may be known (potential) as endocrine disruptors do not mention endocrine in the title, abstract, or keywords. Additionally, we searched for the specific health outcome terms (i.e. "cardiovascular diseases", "MASLD", "metabolic syndrome") rather than specific subcategories of each health outcome. We deemed it more pertinent to include a broader health outcome scope, as it provides a comprehensive view of cardiometabolic outcomes that is more informative for policymakers and the general public.

4. Selection of Sources of Evidence

Endnote (Clarivate 2024) was used to deduplicate the results from EMBASE and Web of Science. We screened the reports by title and abstract using ASReviewLab (Schoot and Bruin 2024). All potentially relevant articles were further investigated as full texts.

5. Data Charting Process

A data extraction form was drafted in Excel and piloted with a few example studies. The form was adapted based on this test. The following study characteristics were extracted:

A. General information: Authors, Year of publication, Journal, Title.

B. Type of article:
   1. Epidemiological study (yes/no)

Table A4 **Search strategies for the three health outcomes selected**

Health outcome / search strategy date	EMBASE	Web of Science
Cardiovascular diseases / January 21, 2025, and updated on 15 July, 2025	("endocri* disrupt*") AND ('cardiovascular disease*' OR "cvd*") NOT ("review*" OR "meta*analys*" OR "animal experiment*" OR "in*vitro" OR "ex*vivo") AND "article"/it	TS=("endocri* disrupt*") AND TS=("cardiovascular disease*" OR "CVD*") NOT TS=("in vitro" OR "ex vivo" OR "*review" OR "review*" OR "meta*analys*" OR "animal* stud*" OR "lab* stud*" OR "animal* experiment*") + applying the "Document type" filter only including "articles"
Metabolic Dysfunction-Associated Steatotic Liver Disease / 14 July, 2025	("endocri* disrupt*") AND ("MASLD" OR "non*alcoholic fatty liver disease*" OR "NAFLD" OR "hepatic steatosis"OR "steatotic liver disease" OR "MAFLD") NOT ("review*" OR "meta*analys*" OR "animal experiment*" OR "in*vitro" OR "ex*vivo") AND "article"/it	TS=("endocrin* disrupt*") AND TS=("MASLD*" OR "non alcoholic fatty liver disease*" OR "NAFLD*" OR "hepatic steatosis" OR "steatotic liver disease" OR "MAFLD") NOT TS=("in vitro" OR "ex vivo" OR review* OR "meta-analys*" OR "animal stud*" OR "lab stud*" OR "animal experiment*") AND DT=(Article)
Metabolic syndrome / 14 July, 2025	("endocri* disrupt*") AND ("Metabolic syndrome*" OR "MetS*") NOT ("review*" OR "meta*analys*" OR "animal experiment*" OR "in*vitro" OR "ex*vivo") AND "article"/it	TS=("endocrin* disrupt*") AND TS=("metabolic syndrome*" OR MetS*) NOT TS=("in vitro" OR "ex vivo" OR review* OR "meta-analys*" OR "animal stud*" OR "lab stud*" OR "animal experiment*") AND DT=(Article)

2. Study design (e.g. cohort studies, case-control, cross-sectional)

C. Region of study: Country, multi-country, regions, etc.

D. Study population: Children, adolescents, adults, etc.

E. Exposure assessment

   1. Type of markers used:
      a. Biological (i.e. serum, blood, urine, hair, breast milk, etc.)
      b. Environmental (i.e. water, wastewater, soil, sediments, air, etc.)

   2. EDC group. One of the following groups of compounds:
      a. Dioxins, Flame retardants, including polybrominated compounds (PBCs), Metals, Parabens, Per- and poly-fluoroalkyl substances (PFASs), Pesticides, including herbicides, fungicides, insecticides, Pharmaceuticals, Phenols, Phthalates, Phytoestrogens, Polychlorinated compounds, Polycyclic aromatic hydrocarbons (PAHs).

   3. Specific compounds described.

F. Health outcome

   1. Specific outcomes related to the health category.
   2. Surrogate measurements of the health outcome (explicitly mentioned in the article as risk factors, biomarkers or indicators of the health outcome or health outcome risk).

G. Quantitative data:

   1. Statistical methods and estimates are used to describe links or associations between EDCs and health outcomes.
   2. Estimates (only including statistically significant associations).
   3. Exposure levels.

H. Key findings: Conclusion reported by the authors; limitations and gaps highlighted by the authors.

6. Critical appraisal of individual sources of evidence

Given that scoping reviews aim to map the existing evidence base on a subject, we did not formally assess the included studies' risk of bias. However, as mentioned in the WHO Quality Assurance Handbook (World Health Organization 2022), *"... a scoping review that assesses "quality" typically does this (at the study type level) by enumerating how many of each type of study has been found without assessing whether each study*

represents a strong or weak example of that type. Scoping reviews do not usually examine the effects of bias at an individual study level. They may simply comment on unexpected absences of evidence that may represent the exclusion of particular perspectives or voices...". Hence, we interpreted the results in terms of presence or absence of evidence, different supporting study designs and gaps for future research.

7. Synthesis of results

The presentation of results followed a narrative format accompanied by the summarisation of study characteristics through diagrammatic and tabular forms. Data were stored and processed in MS Excel (Microsoft Corporation 2025).

2. Wildlife

To update the 2012 WHO-UNEP assessment of EDCs in animals including laboratory animals and wildlife animals, an evidence-mapping approach was used to identify and characterize review literature addressing EDC-related adverse effects in wildlife species. The objective was to provide an overview of the evidence available since 2012, identify major health outcomes and mechanisms investigated across taxonomic groups, and synthesize the current understanding of endocrine disruption in wildlife populations.

An initial search focusing exclusively on systematic reviews, scoping reviews and systematic evidence maps was undertaken following the approach used in the Human Health chapter. However, this strategy retrieved only a limited number of records for most animal taxa (table A5). To ensure adequate coverage of the available evidence, the search strategy was expanded to include all review literature published since 2012.

The final methodology combined systematic searching, screening, database curation, targeted supplementary searches, and expert-guided identification of relevant reviews.

PECO statement

The evidence mapping was guided by a PECO framework (table A6).

The evidence mapping addressed the following research questions:

Q1. Which animal health outcomes associated with endocrine-disrupting chemicals have been evaluated in the review literature published since 2012?

Q2. What evidence exists linking endocrine-disrupting chemicals to adverse effects in animal-taxa?

Eligibility criteria

The following inclusion and exclusion criteria were applied during title/abstract and full-text screening.

Table A5 The numbers of systematic reviews, scoping reviews and systematic evidence maps identified for animals, categorized according to animal phyla

Phyla	Systematic reviews	Scoping reviews	Systematic evidence map	Total
Fish (bony & Cartilaginous)	30	5	0	35
Amphibian	1	0	0	1
Bird	1	1	0	2
Reptile	1	0	0	1
Arthropod	4	0	0	4
Mollusc(k)	2	0	0	2
Annelid	0	0	0	0
Flatworm	0	0	0	0
Echinoderm	0	0	0	0
Cnidarian	0	0	0	0

Table A6 PECO (Population, Exposure, Comparator, Outcome) framework used to guide the evidence mapping and define the scope of the review

Population	Animal species, including mammals, fish, amphibians, reptiles, birds and invertebrates (divided into classes).
Exposure	Exposure to one or more endocrine-disrupting chemicals or endocrine-active substances.
Comparators	No formal comparator was required for inclusion due to the evidence-mapping nature of the review.
Outcome	Any adverse health outcome, biological response, endocrine pathway disruption, or mechanistic endpoint relevant to wildlife health or population-level impacts.

Inclusion criteria

- Published from 2012 onwards.
- Review article, including narrative reviews, systematic reviews, scoping reviews and evidence maps.
- Addressed endocrine-disrupting chemicals or endocrine disruption.
- Included one or more wildlife taxonomic groups of interest.
- Reported biological responses, health outcomes, mechanisms, or adverse effects relevant to wildlife.

Exclusion criteria

- Primary research articles.
- Human health-only reviews.
- Reviews without relevance to endocrine disruption.
- Non-English articles.
- Articles for which full text could not be obtained.
- Duplicates.
- Reviews considered outside the scope of wildlife endocrine disruption.

Information sources and search strategy

All literature searches were conducted in Web of Science (all databases) including:

- Web of Science Core Collection
- MEDLINE®
- Zoological Record
- ProQuest™ Dissertations & Thesis Citation Index
- SciELO Citation Index
- KCI-Korean Journal Database
- Grants Index

The search strategy included all review articles published since 2012 and search strings shown in table A7 were used. In February to April 2026, additional target searches were performed to identify reviews relevant to specific taxonomic groups, health outcomes, mechanisms, and chemical classes that appeared underrepresented in the primary search results. For example, inclusion of "metabolic* disrupt*" instead of "endocrin* disrupt*" or "cardiovascular* instead of "endocrin* disrupt*".

Study flow diagram

The literature search, screening, eligibility assessment, database curation and additional records identified through targeted searches and expert contributions are summarized in figure A2.

Selection of sources of evidence

Search results were imported into Covidence© (a systematic review software) for screening and management. Title and abstract screening were conducted using predefined eligibility criteria. Each record was categorized as:

- Include
- Exclude
- Maybe

Records marked as "Maybe" were retained for full-text assessment. Studies retained after title and abstract screening were exported to EndNote for full-text retrieval. Full-text PDF files were then imported into Covidence© for eligibility assessment. Articles that could not be retrieved automatically were obtained manually through institutional subscriptions and other available sources.

Full-text screening was subsequently performed using the predefined exclusion criteria. In addition to records identified through structured searches, supplementary records identified by chapter authors and domain experts during report development and expert commenting rounds, were included.

Table A7 **Overview of the search strategies used to identify review articles on endocrine-disrupting chemicals and endocrine-active substances across wildlife taxonomic groups. Broad taxon-specific search strings were applied during the primary search, followed by supplementary targeted searches to improve coverage of underrepresented health outcomes, mechanisms, chemical classes, and taxa**

Taxonomic group	Broad search terms	Date of search	Supplementary Targeted search terms
Fish	"endocrin* disrupt*" AND fish* AND review*[a]	25-02-26	Original search terms were supplemented with specific health outcomes
Amphibians	"endocrin* disrupt*" AND amphibian* AND review*[a]	28-02-26	Original search terms were supplemented with specific health outcomes
Reptiles	"endocrin* disrupt*" AND reptil* AND review*[a]	05-03-26	Original search terms were supplemented with specific health outcomes
Birds	"endocrin* disrupt*" AND (bird* OR avian*) AND review*[a]	03-03-26	Original search terms were supplemented with specific health outcomes
Laboratory Mammals **Wildlife mammals**	For mammals used in laboratory studies: "endocrin* disrupt*" AND (mammal* OR rodent* or mice or rat*) AND review*[a] For mammalian wildlife, a modified strategy was used to minimize retrieval of human health and laboratory animal literature: "endocrin* disrupt*" AND review*[a] AND mammal* with exclusion terms: human health, dog, rat, mice, rodent, pig, children	01-04-26	Original search terms were supplemented with specific health outcomes
Invertebrates	For invertebrates, the search terms were developed to cover all relevant classes: ["endocrin* disrupt*" " review*[a] " invertebrat*, mollusk* mollusc* arthropod* nematod* insect* crustacean* annelid* echinoderm* tunicate*]	01-04-26	Original search terms were supplemented with specific health outcomes

[a] Review* should appear in the abstract for inclusion.

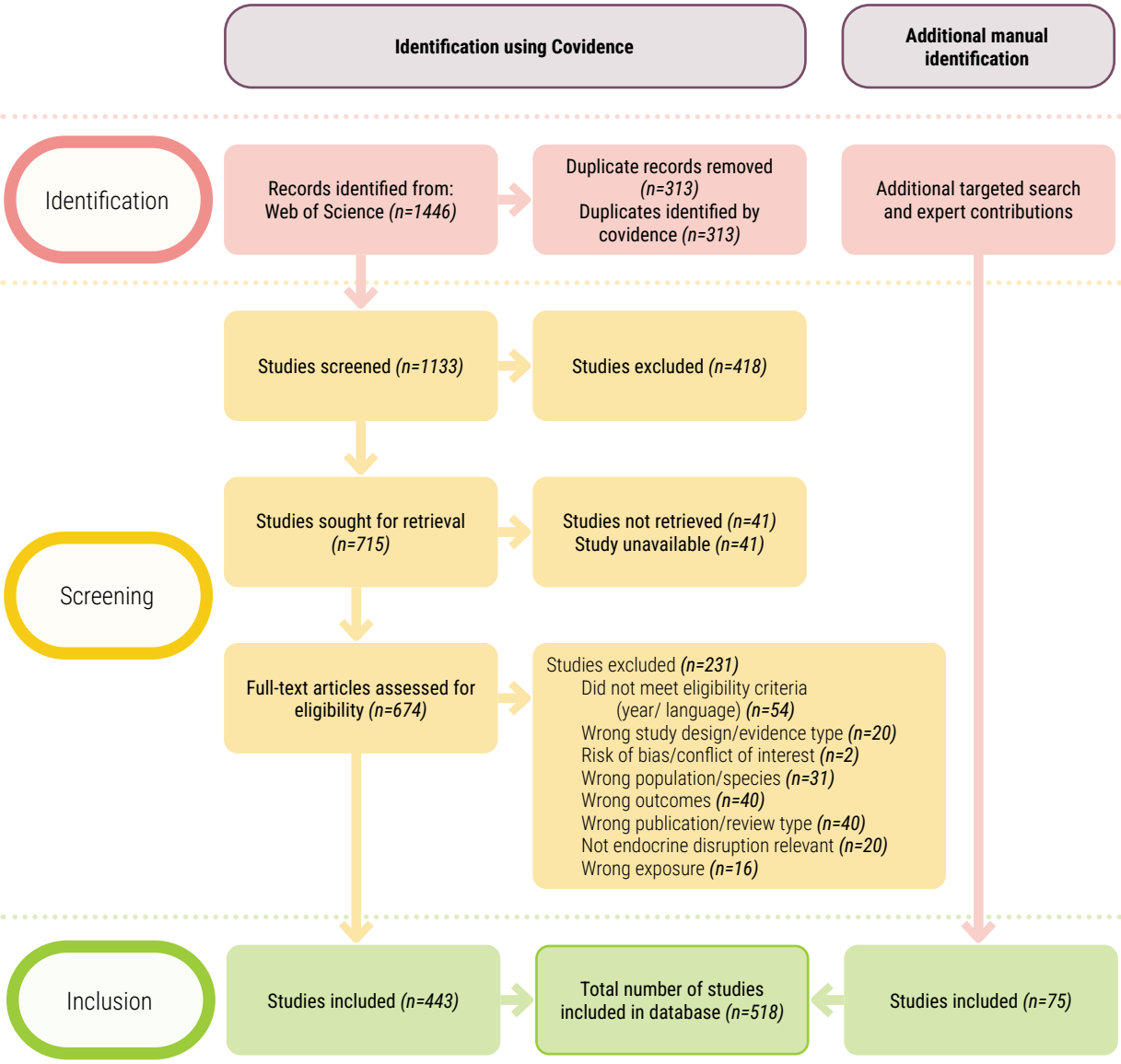
Data extraction and database curation

Data extraction was performed in Covidence© using a customized extraction template (table A8). Reviews could be assigned to multiple categories where relevant.

The curated database was continuously updated throughout report development. Additional references identified through targeted searches and expert contributions were incorporated into a master reference library and subjected to the same curation procedures before inclusion in the final synthesis.

FIGURE A2

PRISMA FLOW DIAGRAM



Evidence synthesis

Evidence was synthesized by grouping reviews according to taxonomic groups and health outcome category. Health outcome categories were aligned, where possible, with those used in the Human Health review to facilitate comparison and synthesis across Chapter 2.

The final synthesis focused on identifying major mechanisms of endocrine disruption, patterns across taxa, consistency of findings and implications for wildlife populations.
In total, 518 review articles were included in the evidence-mapping database, of which 189 addressed animal and wildlife health outcomes and were used in the synthesis presented in Chapter 2.

Table A8 **Variables included in the data extraction template used in Covidence© for the evidence mapping database**

Variable	Answer option
Citation	Text field
Title	Text field
Author(s)	Text field
Year of publication	Text field
Journal	Text field
Types of EDCs covered	Predefined options: • Plastic related chemicals • Persistent organic pollutants (POPs) • Per- and polyfluoroalkyl substances (PFASs) • Pesticides (including herbicides and insecticides) • Flame retardants • Pharmaceutical and personal care products • Heavy metals • Other chemicals
Sources of exposure	Predefined options: • Water • Sediment • Diet • Air • Injection • Not specified
Exposure settings	Predefined options: • Laboratory • Field • Both
Taxonomic groups covered	Predefined options: • Fish • Mammals • Amphibia • Reptiles • Birds
Health outcome category (select all that apply)	Predefined options: • Reproductive disorders • Developmental disorders • Neuro-behavioral disorders • Thyroid-related disorders • Metabolic disorders • Immune-related disorders • Behavioral disorders • Cancer-related disorders • Cardiovascular disorders • Other
Main findings/conclusions	Text field
Knowledge gaps identified by author(s)	Text field
Recommendations for future research by author(s)	Text field

Annex III. Chemicals currently identified as EDCs by the European Union

Table A9 **EDCs officially identified and classified by the European Union**

Name and abbreviation	CAS no.
(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2- (4-MBC)	36861-47-9
(1R,3E,4S)-1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (4-MBC)	95342-41-9
(1R,3Z,4S)-1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (4-MBC)	852541-21-0
(1R,4S)-1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (4-MBC)	741687-98-9
(1S,3E,4R)-1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (4-MBC)	852541-30-1
(1S,3Z,4R)-1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (4-MBC)	852541-25-4
(3E)-1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one (4-MBC)	1782069-81-1
1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one; 3-BC	15087-24-8
14-(nonylphenoxy)-3,6,9,12-tetraoxatetradecan-1-ol	26264-02-8
17-(4-nonylphenoxy)-3,6,9,12,15-pentaoxaheptadecan-1-ol	34166-38-6
2-(4-nonylphenoxy)ethanol	104-35-8
2-(isononylphenoxy)ethanol	85005-55-6
2-(nonylphenoxy)ethanol	27986-36-3
2-[2-(4-nonylphenoxy)ethoxy]ethanol	20427-84-3
2-[2-(nonylphenoxy)ethoxy]ethanol	27176-93-8
2-[2-[2-[2-(4-nonylphenoxy)ethoxy]ethoxy]ethoxy]ethanol	7311-27-5
2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethanol	2315-67-5
2-[4-(3,6-dimethylheptan-3-yl)phenoxy]ethanol	1119449-37-4
2-{2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethoxy}ethanol	2315-61-9
2-{2-[4-(3,6-dimethylheptan-3-yl)phenoxy]ethoxy}ethanol	1119449-38-5
2,2-dibromo-2-cyanoacetamide (DBNPA)	10222-01-2
20-(4-nonylphenoxy)-3,6,9,12,15,18-hexaoxaicosan-1-ol	27942-27-4
20-(isononylphenoxy)-3,6,9,12,15,18-hexaoxaicosan-1-ol	65455-69-8
20-(nonylphenoxy)-3,6,9,12,15,18-hexaoxaicosan-1-ol	27177-03-3
20-[4-(1,1,3,3-tetramethylbutyl)phenoxy]-3,6,9,12,15,18-hexaoxaicosan-1-ol	2497-59-8
23-(nonylphenoxy)-3,6,9,12,15,18,21-heptaoxatricosan-1-ol	27177-05-5
26-(4-nonylphenoxy)-3,6,9,12,15,18,21,24- octaoxahexacosan -1-ol	14409-72-4
26-(nonylphenoxy)-3,6,9,12,15,18,21,24-octaoxahexacosan-1-ol	26571-11-9
29-(nonylphenoxy)-3,6,9,12,15,18,21,24,27-nonaoxanonacosanol	27177-08-8
3,6,9,12-tetraoxatetradecan-1-ol, 14-(4-nonylphenoxy)-	20636-48-0
3,6,9,12-tetraoxatetradecan-1-ol, 14-(4-nonylphenoxy)-, branched	91648-64-5
3,6,9,12,15-pentaoxaheptadecan-1-ol, 17-(nonylphenoxy)-	27177-01-1
3,6,9,12,15,18,21,24,27-nonaoxanonacosan-1-ol, 29-(isononylphenoxy)-	65455-72-3
4-(1-ethyl-1-methylhexyl)phenol	52427-13-1
4-(1-ethyl-1,3-dimethylpentyl)phenol	186825-36-5
4-(1-ethyl-1,4-dimethylpentyl)phenol	142731-63-3

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Table A9 continued

Name and abbreviation	CAS no.
4-(1,1,3,3-tetramethylbutyl)phenol	140-66-9
4-(1,1,5-trimethylhexyl)phenol	521947-27-3
4-(2-methylhexan-2-yl)phenol	30784-31-7
4-(2,2-dimethylpentan-3-yl)phenol	861010-65-3
4-(2,3-dimethylpentan-2-yl)phenol	861011-60-1
4-(2,3,3-trimethylbutan-2-yl)phenol	72861-06-4
4-(2,4-dimethylpentan-2-yl)phenol	33104-11-9
4-(2,4-dimethylpentan-3-yl)phenol	1824346-00-0
4-(3-ethylheptan-2-yl)phenol	186825-39-8
4-(3-ethylpentan-3-yl)phenol	37872-24-5
4-(3-ethylpentyl)phenol	911370-98-4
4-(3-methylhexan-2-yl)phenol	854904-93-1
4-(3-methylhexan-3-yl)phenol	30784-32-8
4-(3-methylhexyl)phenol	102570-52-5
4-(3,3-dimethylpentan-2-yl)phenol	911371-06-7
4-(4-methylhexan-2-yl)phenol	71945-81-8
4-(4-methylhexyl)phenol	1139800-98-8
4-(4,4-dimethylpentan-2-yl)phenol	911371-07-8
4-(5-methylhexan-2-yl)phenol	857629-71-1
4-(5-methylhexan-3-yl)phenol	854904-92-0
4-(5-methylhexyl)phenol	100532-36-3
4-(heptan-2-yl)phenol	6863-24-7
4-(heptan-3-yl)phenol	6465-74-3
4-(heptan-4-yl)phenol	6465-71-0
4-heptylphenol	1987-50-4
4-isododecylphenol	27459-10-5
4-nonylphenol, branched, ethoxylated	127087-87-0
4-nonylphenol, branched, ethoxylated 1 - 2.5 moles ethoxylated	127087-87-0
4-nonylphenol, ethoxylated 1 - 2.5 moles ethoxylated	26027-38-3
4-t-nonylphenol-diethoxylate	156609-10-8
4-tert-butylphenol	98-54-4
4,4'-(1-methylpropylidene)bisphenol: Bisphenol B	77-40-7
4,4'-isopropylidenediphenol; Bisphenol A	80-05-7
4,4'-sulphonyldiphenol, Bisphenol S (BPS)	80-09-1
44-(nonylphenoxy)-3,6,9,12,15,18,21,24,27,30,33,36,39,42-tetradecaoxatetratetracontanol	57321-10-5
Asulam	3337-71-1
Benthiavalicarb	413615-35-7
Benzyl butyl phthalate (BBP)	85-68-7
Bis(2-ethylhexyl) phthalate (DEHP)	117-81-7
Butyl 4-hydroxybenzoate; Butylparaben	94-26-8
Cholecalciferol	67-97-0

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Table A9 continued

Name and abbreviation	CAS no.
Clofentezine	74115-24-5
Cyanamide	420-04-2
Dibutyl phthalate (DBP)	84-74-2
Dicyclohexyl phthalate (DCHP)	84-61-7
Diisobutyl phthalate	84-69-5
Dimethomorph	110488-70-5
Flufenacet	142459-58-3
Formaldehyde, reaction products with branched and linear heptylphenol, carbon disulfide and hydrazine	93925-00-9
Isobutyl 4-hydroxybenzoate; Isobutylparaben	4247-02-3
Isononylphenol	11066-49-2
Isononylphenol, ethoxylated	37205-87-1
Mancozeb	8018-01-7
Medetomidine	86347-14-0
Mepanipyrim	110235-47-7
Metiram	9006-42-2
Metribuzin	21087-64-9
Nonylphenol	25154-52-3
Nonylphenol, branched, ethoxylated 1 - 2.5 moles ethoxylated	68412-54-4
Nonylphenol, ethoxylated	9016-45-9
Nonylphenol, ethoxylated (10-EO)	9016-45-9
Nonylphenol, ethoxylated (15-EO)	9016-45-9
Nonylphenol, ethoxylated (6,5-EO)	9016-45-9
Nonylphenol, ethoxylated (8-EO)	9016-45-9
Nonylphenol, ethoxylated (EO = 10)	9016-45-9
Nonylphenol, ethoxylated (EO = 4)	127087-87-0
Nonylphenol, ethoxylated (polymer)	9016-45-9
Nonylphenolpolyglycolether	9016-45-9
p-(1-methyloctyl)phenol	17404-66-9
p-(1,1-dimethylheptyl)phenol	30784-30-6
p-(1,1-dimethylpropyl)phenol	80-46-6
p-isononylphenol	26543-97-5
p-nonylphenol	104-40-5
Phenol, (tetrapropenyl) derivatives	74499-35-7
Phenol, 4-(1-ethyl-1,2-dimethylpropyl)-	30784-27-1
Phenol, 4-dodecyl, branched	210555-94-5
Phenol, 4-isododecyl-	27147-75-7
Phenol, 4-nonyl-, branched	84852-15-3
Phenol, 4-nonyl-, phosphite (3:1)	3050-88-2
Phenol, 4-tert-heptyl-	288864-02-8
Phenol, dodecyl-, branched	121158-58-5

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Table A9 continued

Name and abbreviation	CAS no.
Phenol, heptyl derivs	72624-02-3
Phenol, nonyl-, branched	90481-04-2
Phenol, p-isononyl-, phosphite (3:1)	31631-13-7
Phenol, p-sec-nonyl-, phosphite	106599-06-8
Phenol, tetrapropylene-	57427-55-1
Poly (oxy-1,2-ethanediyl), alpha -(nonylphenyl)-omega-hydroxy-, branched	68412-54-4
Poly(oxy-1,2-ethanediyl), a-(nonylphenyl)-w-hydroxy-	9016-45-9
Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched	68412-53-3
Poly(oxy-1,2-ethanediyl), α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-	9036-19-5
Polyethylene glycol p-(1,1,3,3-tetramethylbutyl)phenyl ether	9002-93-1
Propiconazole	60207-90-1
Reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.	1471311-26-8
Triflusulfuron-methyl	126535-15-7
Triphenyl phosphate (TPP)	115-86-6
Tris (4-nonylphenol, branched) phosphite (TNPP)	26523-78-4
Tris(nonylphenyl) phosphite	26523-78-4

Note: Table includes EDCs included under Plant Protection Products Regulation, Biocidal Products Regulation, and REACH's Candidate List of substances of very high concern: https://edlists.org/the-ed-lists/list-i-substances-identified-as-endocrine-disruptors-by-the-eu.

UN environment programme

www.unep.org
unep-communication-director@un.org

World Health Organization

www.who.int
ipcsmail@who.int