Hormone Research in Paediatrics

Review Article

Horm Res Paediatr 2025;98(suppl 2):163–186
DOI: 10.1159/000549151

Published online: November 27, 2025

EndoCompass Project: Environmental Endocrinology

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Significance

Endocrinology is underrepresented in European Union research programmes despite the fundamental role of hormones for human health. Environmental endocrinology, which increases our understanding of how environmental factors and chemicals affect hormone systems, is a rather new discipline supported by only limited resources. The EndoCompass project, a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, identifies environmental endocrinology as one of its top strategic research priorities. This comprehensive article is based on expert analysis by leading researchers in environmental endocrinology, integrating literature review, epidemiological evidence, and emerging research priorities to identify key challenges and opportunities across endocrine systems.

Keywords
EndoCompass · Environment · Endocrine-disrupting chemical · Roadmap

Abstract
Background: Endocrine science remains underrepresented in European Union research programmes despite the fundamental role of hormone health in human well-being. Analysis

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of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At national funding level, endocrine societies report limited or little attention of national research funding towards endocrinology. The EndoCompass project – a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges. ***Methods:*** Research priorities were established through a comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014–2020). An expert analysis was conducted by leading researchers in environmental endocrinology, integrating literature review, epidemiological evidence, and emerging research priorities to identify key challenges and opportunities across endocrine systems. ***Results:*** Research priorities span 5 critical domains: mechanisms and biomarkers of endocrine-disrupting chemical (EDC) actions; environmental pharmaceutical contamination; climate change effects on endocrine function; endocrine consequences of air and water pollution; and mechanisms linking environmental stress to hormone disruption. Special emphasis is placed on understanding developmental programming, transgenerational effects, and implications for public health policy. ***Conclusions:*** This component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. The analysis demonstrates that environmental factors like EDCs fundamentally impact multiple endocrine systems, requiring coordinated research approaches. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact in endocrine health.

Introduction

The incidence rates of several non-communicable diseases are increasing globally. These include hormone-related metabolic, immunological and neurological conditions, reproductive disorders, and certain cancers. Adverse secular trends in hormone-regulated biological processes, such as the timing of pubertal onset [1, 2], semen quality [3], and body composition [4, 5], have also been documented.

These secular changes have occurred over just a few generations, a time frame much too short to imply genetic changes. This rather indicates that environmental and/or lifestyle factors are involved. Indeed, over the same period, significant environmental and lifestyle changes have occurred, which have largely been driven by increased use of fossil resources as fuels and also as building blocks of modern chemicals.

Thus, over the last 100 years, it is estimated that more than 350,000 new manufactured chemicals have been developed, of which thousands are, today, produced and marketed on a large scale [6]. This chemical expansion has contributed to significant economic growth and prosperity in developed countries, streamlined food production, and the development of new medicines. However, many of the compounds that are used often end up in our bodies [7, 8]. This concerns not only chemicals but also anthropogenic air particles, nanoparticles, and microplastics – several of which have been shown to be carcinogenic or to affect our hormone and immune systems, metabolism, or brain development [9].

The health consequences of these fundamental changes to our environment have become increasingly apparent, but the full extent is far from being properly elucidated. The "One Health theory" describes the interconnections among human, animal, and environmental health and the exposome (i.e., the overall exposure to the environment in a lifespan). It helps us understand how, among other factors, climate change, air, water, and food pollution, and endocrine-disrupting chemicals (EDCs) influence endocrine health from conception to death, as well as the well-being of future generations [10, 11].

Importantly, since the causes are anthropogenic, there is also great potential to reduce the health consequences of environmental influences through increased awareness, regulation, and prevention [12]. In 2020, the European Union launched the ambitious "Chemicals Strategy for Sustainability towards a Non-Toxic Environment" [13]. If the strategy's ambitions to protect the population from the most harmful environmental impacts are to be realized, there is a need to strengthen research. Targeted, preventive efforts require knowledge of how different environmental factors impact human health. Considering the endocrine aspects of many non-communicable diseases, this includes an increased understanding of how environmental factors affect hormone systems.

Endocrine Disruption by Chemicals

Over the second half of the 20th century, increasing numbers of reports emerged describing the impact of environmental chemicals on wildlife and human health. These early reports particularly involved reproductive and developmental functions and pointed to disturbed hormonal regulation. Accordingly, the term "endocrine disruptors" was proposed at an international workshop in 1992 [14]. Even so, the impact of EDCs on wildlife and human health was largely underestimated until several reports were published around the turn of the century, which extended awareness of the problem beyond the scientific community [15–17]. A decade later, the World Health Organization (WHO)/UN Environment Programme and the Endocrine Society published pioneering scientific statements on EDCs [18, 19]. Recently, the European Society of Endocrinology also raised concern regarding the endocrine health consequences of human exposures to EDCs in a position paper [20].

A first definition of an EDC was provided by the WHO and the International Programme on Chemical Safety (IPCS) in a report in 2002: "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" [15]. This definition has more recently been adopted by the European Commission [21]. The IPCS also proposed a definition for a potential endocrine disruptor requiring a lower level of evidence: "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" [15].

Causation versus Correlation: From Epidemiology to Translational Medicine

There is robust evidence showing the detrimental effects of EDCs in different wildlife species. A large amount of data from experimental cellular and animal models confirms that several environmental chemicals have a disrupting action on multiple endocrine systems.

Since the beginning, however, the evidence supporting a cause-effect relationship in humans was considered weak and inconclusive, largely because most human data derive from epidemiological/association studies, which cannot demonstrate cause-effect relationships. Furthermore, some factors complicate the advancement of knowledge in humans: (1) human exposure is generally to a mixture of many EDCs rather than to single substances; (2) exposures may vary throughout life; (3) effects of EDCs are often sex-dependent and developmental stage-dependent (age-dependent); (4) EDCs often do not exert their biological effects in a clear linear dose-response relationship; and (5) EDCs may have transgenerational effects. However, it is most likely that EDCs will adversely affect humans, as demonstrated in many other species, considering the high evolutionary conservation of basic components and mechanisms of hormone actions across species.

Notably, the rapid increase in the incidence of certain hormone-related diseases in specific geographical areas has indicated that environmental factors play a key role in the pathogenesis. Epidemiology has, indeed, played a major role in showing the close relationship between exposure to EDCs and certain diseases and malformations [22, 23]. The pioneering work of Skakkebæk et al. [24, 25] led to the definition of testicular dysgenesis syndrome, which includes cryptorchidism, hypospadias, impaired spermatogenesis, and testicular cancer caused by endocrine disruption in utero, potentially as a consequence of prenatal exposure to EDCs, such as pesticides and phthalates. A major breakthrough in this field has recently come from the publication of a longitudinal study reporting adverse neurodevelopmental outcomes in a large mother-child cohort exposed to a mixture of EDCs [26]. This study, for the first time, integrated experimental and epidemiological evidence, demonstrating a clear risk of language delay, a hallmark of neurodevelopmental delay, in the offspring of mothers exposed to EDCs during pregnancy.

Characteristics and Actions of EDCs

The US Environment Protection Agency has identified more than 1,800 chemicals that can affect endocrine and non-endocrine pathways [27]. In the European Union, around 100 chemicals have been identified and legally classified as endocrine disruptors [28]. Most known EDCs are organic compounds, often composed of cyclic structures, which they have in common with natural steroid and thyroid hormones. This may explain why some EDCs can mimic the interaction of natural hormones with steroid or thyroid hormone receptors.

However, many EDCs have different molecular structures. For instance, per- and polyfluoroalkyl substances (PFASs), a large class of more than 15,000 synthetic chemicals, consist of a fully or partially fluorinated carbon chain (which makes it stable and difficult to degrade) carrying diverse functional groups, such as carboxyl and sulphonate groups.

Ultimately, depending on the chemical, endocrine-disrupting action may be exerted via a wide selection of pathways that are highly conserved in wildlife and humans. These include receptor and signalling systems for small-molecule hormones (comprising nuclear and non-nuclear hormone receptors and orphan receptors), as well as enzymatic pathways and proteins involved in hormone biosynthesis, transport or metabolism, and also neurotransmitter receptors and numerous other mechanisms involved in the regulation and signalling of the endocrine system [29]. Endocrine-disrupting chemicals that exert their action through binding to hormone receptors can act as agonists, partial agonists, or antagonists of hormonal action and thereby disrupt homoeostasis.

The major EDC families include:

1. Pharmaceuticals, such as trenbolone acetate, ethinyloestradiol, dexamethasone, levonorgestrel, rosiglitazone, and metformin.
2. Cosmetics and personal care products, such as phthalates, benzophenones, parabens, triclosan, and diethyl(meta)toluamide (widely known as DEET).
3. Pesticides, herbicides, and fungicides, such as chlorpyrifos, glyphosate, pyraclostrobin, dichlorodiphenyltrichloroethane (DDT), and atrazine.
4. Industrial chemicals, such as bisphenols, polychlorinated biphenyls (PCBs), triphenyl phosphate, PFASs (including perfluorooctanesulfonic acid [PFOS] and perfluorooctanoic acid [PFOA]), polybrominated diphenyl ethers (PBDEs), and organotins.
5. Metals such as lead, cadmium, mercury, and arsenic.

These chemicals can be subdivided into persistent and non-persistent substances, with persistent compounds having long elimination half-lives (possibly several years or decades), resulting in bioaccumulation, while non-persistent substances can be cleared within hours or days. However, even exposure to non-persistent substances may be (semi-) persistent if the exposure (and thereby uptake) is frequent/constant. Exposure occurs through food, drinking water, air, soil, food packaging, cosmetics, toys, furniture, and household products. Endocrine-disrupting chemicals may be transferred from the mother to her child across the placenta and through breast milk.

Exposure to EDCs and Child Health

Exposure to EDCs can affect multiple organs and systems in experimental models and wildlife. In humans, the list of diseases linked to EDC exposure is rapidly growing. Exposure to EDCs during critical developmental windows (i.e., foetal life, early postnatal life, and puberty) may permanently affect organ development and function, with long-term consequences for health.

Exposure to PBDEs has been related to reduced IQ and intellectual disability, altered timing of puberty, cryptorchidism, and testicular cancer. Pesticide exposure has been linked to reduced IQ, intellectual disability, obesity, type 2 diabetes mellitus, prostate cancer, cryptorchidism, and hypospadias. Bisphenol A may induce obesity, impaired semen quality, and testicular dysgenesis syndrome. Exposure to PFASs has been associated with obesity, increased cholesterol levels, polycystic ovary syndrome (PCOS), impaired semen quality, breast cancer, impaired antibody response to immunization, reduced birth weight, and kidney, testicular, and prostate cancer. Phthalates are involved in early/precocious puberty in girls, male infertility, testicular dysgenesis syndrome, and childhood growth failure. Finally, the exposure to EDC mixtures may lead to attention deficit disorder, autism spectrum disorder, impaired neurodevelopment, and cryptorchidism.

Hypothalamic and Pituitary Function and EDC Exposure

Few data, mainly derived from cell and animal models, exist on the hypothalamic and pituitary effects of EDCs. There is evidence showing that EDCs affect the hypothalamic expression of gonadotrophin-releasing hormone (GnRH) and kisspeptin, influence the pulsatile release of GnRH, and alter pituitary gonadotrophins [30]. In particular, GnRH neurones in the preoptic area are targeted by PCBs, DDT (and its metabolites), PBDEs, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Kisspeptin neurones in the anteroventral periventricular nucleus are targeted by PCBs and PFASs/PFOA. KNDy neurones in the arcuate nucleus are targeted by organophosphate flame retardants, PBDEs, PFASs, and TCDD. Pituitary gonadotrophs are targeted by PCBs, DDT (and its metabolites), methoxychlor, PCBs, PFASs, and TCDD.

The detrimental effects of EDCs in the hypothalamus occur at low concentrations and ultimately lead to disruption of steroidogenesis, oestrous cyclicity, and the onset of puberty. These data, mainly derived from rodents, prompt us to investigate whether chronic exposure to EDCs in humans affects fertility with significant implications for public health.

The hypothalamic-pituitary-adrenal axis is another target of EDCs. Studies in rodents show an effect of bisphenol A, PFOS, tributyltin, and phthalates on the

production of corticotrophin-releasing hormone (CRH) and adrenocorticotrophin (ACTH) [31–33]. Endocrine-disrupting chemicals may also exert epigenetic effects in the hypothalamus.

The exposure of mice to a mixture of phthalates, pesticides, and bisphenol A increases active coping during swimming stress in both sexes, increases locomotion, and reduces social interaction in male progeny. This exposure is able to modify the expression of corticosterone receptors, their regulator Fkbp5, CRH and its receptor, oxytocin and its receptor, oestrogen receptor-β (ERβ), serotonin receptors (Htr1a, Htr2a), and glutamate receptor subunit Grin2b, in the limbic system of adult animals [34]. In rats, the exposure to bisphenol A increases DNA methylation of *Fkbp5* and reduces the protein levels in the hippocampus [35]. The effect of bisphenol A on *Fkbp5* is abolished upon knockdown of ERβ, suggesting a role for this receptor in mediating this effect. Finally, by targeting basal and stress-reactive hypothalamic-pituitary-adrenal activity, EDC exposure has been associated with the development of stress-related disorders [36].

Growth hormone (GH) and prolactin secretion may be affected by exposure to EDCs. Dichlorodiphenyltrichloroethane affects the expression of GH and prolactin genes in the rainbow trout pituitary [37]. Dichlorodiphenyltrichloroethane acts as a xeno-oestrogen, although its potency is much lower than that of oestradiol; it is able to increase GH and prolactin mRNA at concentrations about 500-fold higher than that of oestradiol.

Overall, the available data, generated by studies in experimental models, support the concept that the hypothalamus and pituitary are potential targets for the disrupting action of EDCs, especially if exposure occurs in early life. Intrauterine programming of the hypothalamus and pituitary is regulated by different environmental influences, such as maternal nutrition, oxygenation, and stress. There is now compelling experimental evidence that foetal exposure to EDCs plays a role in programming and affects the development of these structures, leading to a spectrum of endocrine disorders throughout life. The evidence in humans is still scant due to the objective difficulties of obtaining long-term epidemiological data and setting up controlled studies, but the available experimental data prompt us to intensify research on the effects of the environment on hypothalamic and pituitary organogenesis and function.

Puberty and EDC Exposure

Age at breast development or thelarche represents the first clinical marker of female puberty. Herman-Giddens documented, for the first time, that age at breast development had been decreasing between the 1970s and the 1990s in a large American cohort [38]. Since then, age at breast development has continued to decrease worldwide [2]. The obesity epidemic undoubtedly contributes to this trend as age of puberty in girls is negatively correlated with body mass index (BMI) [39]. However, studies in the lean population have reported a similar secular trend in earlier puberty [40], pointing to environmental factors, including EDCs [41–43].

While age at thelarche keeps decreasing, it appears that age at menarche – which had decreased between 1890 and 1960 – has stabilized in the USA and most European countries [43]. However, it continues to decrease in other parts of the world [44–46]. Such a difference in evolution when looking at the beginning and end of female puberty suggests that different environmental mechanisms influence the 2 milestones. Although it is less documented, pubertal timing in boys appears to follow a similar trend towards an earlier beginning [47, 48].

In addition to the secular trend regarding pubertal timing in the general population, recent studies have documented an increase in the number of girls who have premature thelarche or are treated for central precocious puberty [49–51]. Notably, the trend appears even stronger in first- and second-generation immigrants. An increase in incidence of central precocious puberty in boys has been reported by large studies [49, 52] and seems to be driven by an increase in so-called idiopathic precocious puberty, rather than an increase in organic causes [53].

Both the secular trend in pubertal timing and the increase in incidence of precocious puberty are too fast to be explained by genetic factors. Several, but not all, human studies have identified a link between prenatal or early postnatal exposure to EDCs, such as phthalates, bisphenol A, or pesticides, and differences in the timing of thelarche and menarche [43, 53–55]. Such studies highlight surprising but important observations. Firstly, exposure to so-called oestrogenic compounds is not systematically linked to early puberty. Secondly, female pubertal timing in girls might also be sensitive to anti-androgenic compounds. Although it is less studied, the link between male puberty and EDC exposure has also been documented [55, 56]. Epidemiological studies face major methodological challenges, such as a long delay between exposure and effects, and the evaluation of

exposure to non-persistent chemicals or mixtures. Large longitudinal studies need to confirm the link between early exposure to EDCs and pubertal timing, particularly in boys and need to explore the effects of EDC mixtures.

Puberty results from the reactivation of GnRH neurones after a period of quiescence. Gonadotrophin-releasing hormone secretion is controlled by a complex neuronal and glial network within the hypothalamus. It is classically accepted that a loss of trans-synaptic inhibition, together with a rise in excitatory inputs, is responsible for the activation of GnRH release. Compelling data indicate that the pulse generator is not intrinsic to GnRH neurones but, rather, extrinsic and located within the arcuate nucleus and mediobasal hypothalamus [57]. This network is extremely sensitive to environmental factors, as illustrated by animal models of early exposure to changes in energy availability, stress, or endocrine disruptors [58].

Many animal studies have documented the high sensitivity of the components of the GnRH pulse generator to endocrine disruption. The hypothalamic targets include kisspeptin, oxytocin, glutamate, gamma aminobutyric acid, and others [42, 59–62]. When comparing different time windows of sensitivity, it appears that the periods of gestation and lactation are critical and may lead to pubertal disruption of GnRH secretion and activity. More recent studies have shown that the programming of pubertal activation can be affected by exposure to EDCs through epigenetic mechanisms and can have transgenerational effects [63]. The mechanisms by which EDCs might reprogramme the GnRH network in humans, however, remain to be elucidated. Since epigenetic changes are known to be involved in the reawakening of GnRH secretion at puberty [64], the methylome might play a role in EDC-induced changes in puberty onset.

In summary, it is now accepted that age at onset of puberty has been decreasing for several decades in girls and boys. In addition, the incidence of precocious thelarche and precocious central puberty has been increasing over the last 2 decades. This fact will need to be confirmed by large multicentre studies internationally. Epidemiological studies indicate that prenatal or early postnatal exposure to EDCs plays a role in the changes in pubertal timing. These epidemiological associations are supported by laboratory studies showing that EDCs alter the maturation of the GnRH network. Future studies need to define whether altered pubertal timing caused by EDCs is a marker of impaired reproductive health later in life. Recent advances in high-throughput approaches have identified new molecular pathways targeted by EDCs in the hypothalamus, pituitary, and ovaries. Moving forward, single-cell and spatial transcriptomics or proteomics approaches will help characterize cell-specific responses to EDCs. Studies should also be aimed at differentiating effects of EDCs at the level of the hypothalamus-pituitary, direct effects on breast development in girls, and alteration of gonadal steroidogenesis. Considering the interplay between reproduction and energy balance, the combined impact of dietary changes, microbiome alterations, and EDCs on puberty requires further exploration.

Female Reproduction and EDC Exposure

The effects of EDC exposure on the female reproductive system strongly depend on the life stage when exposure occurs [65]. Over recent decades, the incidence of female reproductive disorders has been increasing. This includes an increased incidence of idiopathic central precocious puberty, PCOS, endometriosis, and premature ovarian insufficiency [66–68]. This trend coincides with the increase in declining human fertility rate [69, 70].

The aetiology of these diseases is highly multifactorial and involves both genetic and environmental factors. Recent epidemiological data, together with results from experimental models, suggest a causal role of EDCs in the rapid increase in incidence of the alterations of female reproductive system. Exposure to EDCs starts very early during development as numerous exogenous chemicals are found in follicular fluid [71, 72], amniotic fluid [73], placenta [74], and cord blood [75].

The first evidence of endocrine disruption of female reproductive health was illustrated by diethylstilboestrol (DES), a synthetic oestrogen, which was prescribed to pregnant women at risk of miscarriage during the 1960s and 1970s. Decades later, studies have shown that the daughters of women who were exposed to DES during pregnancy had a higher incidence of various reproductive disorders, including infertility, miscarriage, early menopause, and premalignant and malignant diseases [76]. Furthermore, their granddaughters have reported menstrual cycle alterations and ovarian carcinoma [77, 78], illustrating the multigenerational effects of this EDC.

Epidemiological evidence supports a causal link between EDC exposures and disrupted ovarian reserve. Parabens, for instance, are found in cosmetics and personal care products. They are known to have both anti-androgenic and oestrogenic properties [79, 80] and bind to ERα and ERβ [81, 82]. Higher urinary levels of parabens have been found to be associated with lower

antral follicle count in women undergoing fertility treatment [83, 84]. Moreover, a recent cross-sectional study in Japanese female students showed that urinary levels of parabens are associated with shortening of menstrual cycle length [85], another marker of ovarian reserve impairment [86, 87].

Similarly, urinary levels of bisphenol A have been associated with fewer oocytes retrieved [88] and lower antral follicle count [89] in women undergoing fertility treatment. This could be attributed to the potential effect of bisphenol A on follicular development and steroidogenesis [90, 91]. Per- and polyfluoroalkyl substances have been found in follicular fluid [71, 72] and are associated with impaired quantity [92] and quality of oocytes [93]. Experimental models have revealed that EDCs disrupt meiosis, impair follicular growth and induce atresia, although a knowledge gap regarding mechanisms of action persists [94].

Polycystic ovary syndrome is the most common reproductive disease in women, with a prevalence of up to 21% [95]. The disease involves reproductive, cardiometabolic, and mental health disturbances [96]. Four studies identified exposure to PFASs as a risk factor for PCOS [97–100]. Bisphenol A was also identified as a risk factor for PCOS. Fifteen case-control and 7 cross-sectional studies showed that patients with PCOS had higher levels of bisphenol A when compared with controls [101]. Some studies have also found higher levels of DDT, PCBs, pesticides, or polycyclic aromatic hydrocarbons in women with PCOS [102–107]. These studies are often limited by small sample sizes and single EDC measurements.

Endometriosis is a chronic inflammatory disease, characterized by the presence of endometrium-like tissue outside the uterus, with a prevalence of up to 10% in women of reproductive age [108]. Higher levels of PFASs (i.e., PFOA and perfluorononanoic acid) have been found in women with endometriosis in large American cohorts [109, 110]. In vitro studies suggest that phthalates promote growth and invasiveness of endometrial cells by enhancing activity of certain matrix metalloproteinases, extracellular signal-regulated kinase, and p21-activated kinase 4. These findings were supported by a subsequent in vivo study, showing that mice that had transplanted endometrial foci after being given phthalates exhibited an increased volume of the lesion [111].

To elucidate the real impact of EDCs on the female reproductive system, in vitro and in vivo studies are needed to investigate:

1. Environmentally relevant doses of EDCs,
2. The more susceptible time windows during development,
3. The effects of EDC mixtures,
4. The interplay between endocrine disruption and the role of other factors, such as diet, stress, and microbiome,
5. The potential transgenerational effects,
6. The trends of exposure and the incidence of female reproductive diseases,
7. The risk of exposure in vulnerable groups (e.g., children, pregnant women, the elderly, and professionals exposed to EDCs),

Male Reproduction and EDC Exposure

Cryptorchidism, hypospadias, testicular germ cell cancer, and poor semen quality have a common origin in foetal life [112]. This hypothesis of a testicular dysgenesis syndrome has now been extended to include short anogenital distance and impaired testosterone production. Exposure to EDCs, especially during foetal life, may disturb testicular development with lifelong consequences as early reproductive development is linked to adult testis function [113]. Some EDCs also result in foetal growth restriction, which itself is a risk factor for male reproductive disorders. Overall, small study sizes, the large biological variability in reproductive health measures, differences in matrices used for measurement of EDCs, and, in particular, the difficulty in assessing exposure mixtures often complicate human studies.

Some, but not all, studies have shown associations between cryptorchidism or hypospadias and local use of pesticides, parental occupation in farming or gardening, or parental occupational exposure to pesticides [114–117], as well as significant differences in exposure levels between cases and controls (i.e., to pesticides, dioxins, flame retardants, phthalates, and other EDCs). Others have not found this.

The prevalence of testicular cancer, the most common cancer in young men, is increasing in many countries [118]. Association studies with EDC exposure measurements suggest overall a stronger correlation to maternal exposure [119] (i.e., exposure of the young man in foetal life) than to concurrent exposure levels in the young man himself [115, 120]. This is in line with the testicular dysgenesis syndrome hypothesis.

The decline of semen quality observed in many countries [3] has stimulated research into potential environmental causes. Studies of prenatal and early-life exposures to EDCs are rare, but suggest associations of some persistent and non-persistent EDCs with semen quality [117, 121]. Meta-analyses of adult exposures to

non-persistent chemicals (i.e., phthalates, parabens, bisphenol A, or benzophenones) or to persistent chemicals (i.e., PCBs, PFASs, and organochlorine pesticides) have shown conflicting results [121].

Anogenital distance (i.e., the distance between the anus and scrotum or ventral base of the penis) is considered a read-out of androgen action in utero [122]. Studies with individual chemicals, such as PCBs, dioxins, PBDEs, pesticides, parabens, phenols, and PFASs, have shown negative associations with anogenital length in male offspring [117], and a meta-analysis reported a significant reduction in anogenital distance with prenatal phthalate exposure [123]. Interestingly, in several studies, adult male anogenital distance is positively associated with sperm parameters [124–126].

Very few studies exist exploring the effect of EDCs on reproductive hormone levels. Maternal exposure to phthalates, PFOA, and dioxins, as well as adult exposure to some EDCs, has shown effects on the Leydig cell or Sertoli cell axis [117], but more studies are needed.

Thyroid Hormone Function and EDC Exposure

The thyroid gland and the complex thyroid hormone feedback system are among the known relevant target structures for adverse effects of EDCs. Thyroid hormones regulate human development, growth, and anabolic and catabolic processes, as well as maintenance of metabolic homoeostasis throughout all life phases.

Adequate maternal thyroid hormone supply is crucial for the healthy development of the human offspring, especially during the first trimester of pregnancy, when the foetal thyroid hormone system has not yet developed, but also later on during further pregnancy, foetal development, and lactation. Thus, ubiquitous EDC exposure [127] during these and subsequent sensitive windows of development, especially of the central nervous system, jeopardizes health in later life.

Yet, more than half of the global population, especially females of reproductive age, have an insufficient nutritional iodide intake [128]. However, this is essential for maintaining adequate thyroid hormone synthesis during pregnancy, where demands for the maternal-foetal unit increase. Additional nutritional and environmental exposure to EDC mixtures, targeting the thyroid hormone system during this sensitive period when it is already challenged by iodide deficiency, may trigger or even amplify adverse developmental outcomes [129, 130].

Recent progress in thyroid hormone research has revealed that EDC exposure does not only affect the thyroid hormone-producing gland and its key proteins involved in iodide uptake, oxidation, thyroid hormone biosynthesis, storage, and secretion – which have been the focus of classical (embryo-)toxicology. Rather, the systemic aspects of thyroid hormone distribution, cellular uptake and metabolism, as well as receptor-mediated tri-iodothyronine (T3) action at the local target organ levels (especially in the brain), play a more important role than the gland itself as target structures for EDC interference.

Various classes of known and suspected EDC are known to adversely interfere with the thyroid hormone system, especially during pregnancy and adolescence. However, observational and epidemiological evidence provided by regional and international investigations remains controversial. Studies have been performed mainly on single EDC compounds (e.g., bisphenol A) or chemical groups (e.g., PFASs, phthalates), rarely covering complex EDC mixtures, which represent realistic exposure scenarios throughout life. Furthermore, single time-point analyses of EDC exposure and/or endpoint/outcome/biomarker parameters have mainly been performed. Only a few larger epidemiologic studies include multiple time-point analyses of exposure associated with outcome parameters. The majority of publications report (retrospective, observational) studies with small case numbers or monitoring and follow-up periods that are too short.

It is only recently that the first well-controlled, sufficiently well-populated, prospective, and long-term monitoring and assessment studies have been published, with statistical power that allows plausible interpretations and strong conclusions. These reports can directly relate epidemiological observations in humans to clear cause-effect analyses from meaningful, unequivocal animal model and cellular mechanistic in vitro studies.

Extensive results are now available on the effects of pre- and postnatal EDC exposure of the thyroid hormone system (recently reviewed in several meta-analyses [131, 132]). Prenatally elevated PFAS (and organochlorine compound) exposure was negatively associated with decreased blood concentrations of foetal total thyroxine (T4) [131]. In an adult population, PFAS elevations in the blood were negatively associated with total T4, while PFOS concentration was positively associated with free T4 and thyrotrophin (TSH) and negatively associated with total T3, in a subgroup of the populations studied. Not all studies evaluated in these meta-analyses revealed congruent results. Increasing exposure to PFASs has also been shown to increase plasma T4 concentration and to result in altered amino acid and lipid metabolism in exposed adolescent and

young individuals in a recent metabolomic study [133]. Specific exposure dose-response relationships between some PFAS species and thyroid hormone concentration patterns were observed in various subpopulations [127].

Prenatal exposure to pesticides (e.g., β-hexachlorocyclohexane and mecarbam) was associated with disruption of the thyroid hormone system and intermediary metabolism, as well as with adverse outcome, such as decreased birth weight [134]. Studies on widely abundant classical and novel phthalate species report associations between exposure to several phthalates and their metabolites and disturbed function of the hypothalamus-pituitary-thyroid axis during various life phases [135]. Reported data on associations of prenatal exposure to triclosan, an antimicrobial EDC contained in many consumer products for daily body care, and the maternal-foetal thyroid hormone system remain inconclusive [136].

These recent surveys complement previous scenarios [137]. They support data suggesting that exposure to various persistent organic pollutants and EDCs during early pregnancy and the perinatal phase perturb the foetal thyroid hormone system, as indicated by altered serum free T4 or total T4, irrespective of an adequate TSH change, which is expected but not observed. The consequences are a negative impact on foetal brain development, IQ, and intellectual functions.

These comprehensive assessments for multiple EDC species also complement early data sets on the adverse effects of increased exposure during pregnancy to perchlorate, nitrate, or thiocyanate. These are known antithyroid agents contained in nutritive components, including drinking water or tobacco smoke [138]. Similarly, heavy metals (mercury, lead, and cadmium) are well known to adversely interfere with the thyroid gland and the thyroid hormone system in the general population. However, crucial measures to control and reduce heavy metal exposure, which adversely affects the thyroid hormone system [139], are already in force and effective. These may result in better protection of the thyroid, especially if nutritional supply with iodide is improved in combination with selenium compounds, which inactivate heavy metals [140].

Overall, reported data on the impact of maternal and prenatal EDC exposure on the thyroid hormone system of the offspring are still inconclusive. However, they strongly indicate adverse effects of EDCs on maternal and foetal thyroid hormone status during pregnancy and on brain development in the womb and later in life, with consequences for intellectual, behavioural, and locomotor functions in the affected offspring [141, 142].

Whether chemicals found in amniotic fluid, (cord) blood, foetal tissues, or the urine and blood of pregnant women and their offspring exert their adverse effects as EDCs, neurotoxins, or immunotoxic agents (e.g., bisphenol A), or via a combination of these mechanistic modalities, remains to be studied in more detail. This will require (prospective) mother-child cohorts of sufficient group size, longitudinal assessment of (pre-, peri-, and postnatal) EDC exposure and (non-invasive) monitoring of meaningful parameters, biomarkers, and endpoints that are sufficiently specific for selected health impact and underlying mechanisms. Notably, studies also need to take into account sexual dimorphic patterns of sensitivity, affectedness, and outcome of exposure to EDC and their mixtures. Divergent sensitivities, affectedness, and outcomes have been reported for prenatal exposure to specific EDCs and endpoints monitored in female and male offspring of exposed mothers.

Furthermore, efforts to improve the global iodide supply are of eminent importance in strengthening the protection of the thyroid gland, and the entire fine-tuned and closely regulated thyroid hormone system, against additional adverse EDC effects. This will require the absolute guarantee of an adequate nutritional supply of iodide, which is the essential trace component of the thyroid hormone system, especially during pregnancy and lactation, and the development and growth of newborns, children and adolescents, as well as during all later life phases. An optimal iodide supply (together with an adapted selenium and iron intake) will protect the thyroid gland and its lifelong hormone production and possibly mitigate – or even prevent – the adverse effects of maternal-foetal and adult EDC exposure.

Metabolic Functions and EDC Exposure

Besides the robust data from in vitro and animal models that show a clear effect of EDCs on adiposity, there is increasing epidemiological evidence in humans of an association between the exposure to specific EDCs and the risk of obesity [143]. Some EDCs are able to alter regulation of energy balance and promote adiposity ("obesogens"), exerting their action by disrupting peroxisome pro-liferator-activated receptors (PPARs), retinoic acid receptors, ERs, thyroid hormone receptors, adipocyte proliferation and differentiation, and central regulation of appetite and satiety [144].

According to the hypothesis regarding the developmental origins of health and disease, exposure to EDCs in foetal and early postnatal life may increase the risk of obesity and associated non-communicable diseases in adulthood. Obesogen exposures during development can

induce epigenetic changes that persist across generations through the process of transgenerational epigenetic inheritance. One of the most well-characterized obesogens is the organotin tributyltin. Organotins are widely used in industry and, to some extent, in agriculture. Human exposure to organotins can occur via the diet, such as in seafood contaminated by tributyltin used in marine shipping applications, or as fungicides for paper mills and industrial water systems. Tributyltin binds to and activates PPARγ and the retinoid X receptor, promoting adipogenesis and lipid accumulation. Several other pesticides and biocides (e.g., DDT [145] and chlorpyrifos [146, 147]) also have obesogenic effects. Other EDC families closely associated with obesity risk include PFASs, phthalates, and bisphenols [148]. The exposure to both long- and short-chain PFASs is associated with childhood obesity, though with sexual dimorphism [149].

Prenatal and childhood exposure to phthalates has also been associated with weight and BMI in girls [150, 151]. With regard to bisphenols, conflicting data are available [152, 153]. Recently, a case-control study has shown that a higher exposure to bisphenol A is associated with the risk of obesity in girls [154]. This finding is consistent with the results of a survey on 1,860 children aged 8–19 years who participated in the 2003–2006 National Health and Nutrition Examination Survey (NHANES). This study had complete data on both urinary bisphenol A concentration and body composition measured by dual-energy X-ray absorptiometry. It showed that higher bisphenol A levels were associated with increased fat mass in girls, but not in boys [155].

In exploring the impact of EDCs on obesity risk, there is a need to evaluate the mixture effect in addition to the effects induced by single compounds as humans are exposed to many different EDCs. However, data on EDC mixtures are still scant [156].

The overall effect size of the obesogenic action of EDCs is not negligible: it is comparable with familial and dietary influences [157]. However, compared with sugar-sweetened beverages or snack foods, EDCs are invisible, and potentially obesogenic in relatively small quantities, particularly in specific time windows of development. Therefore, minimization of EDC exposure should be included in obesity prevention policies, and policy-makers are urged to pay greater attention to EDCs in the development of strategies to reduce obesity prevalence. Furthermore, the transgenerational effects of most EDCs also predispose future generations to undesirable phenotypic traits and diseases, including obesity and related metabolic disorders. Finally, longitudinal observational studies from conception to young adulthood are needed to investigate the long-term effects of exposure to single chemicals or to a mixture of EDCs on obesity risk. These studies should be actively promoted and supported by health and research agencies as the incidence of obesity is increasing worldwide in both childhood and adulthood, with the consequent increase in comorbidities, including metabolic disorders, cardiovascular disease, and cancer.

Bone Metabolism and EDC Exposure

The available scientific evidence shows that exposure to EDCs can negatively affect both bone growth and composition as this is largely a hormone-dependent process. Findings are currently often preliminary; in-depth and consolidator studies, and complete understanding, are still lacking. Gender effects are suggested, with some data being contradictory [158]. Studies have addressed the effects of single EDCs through in vitro and in vivo studies, and overall skeletal growth and remodelling processes are affected [159]. Interstitial epiphyseal growth (bone elongation) and appositional growth (bone remodelling) are both required for bone growth [160], and any disruption of these processes leads to changes in bone strength, plasticity, bending force, architecture, mineral density (BMD), and mineral content [158].

Epidemiological studies in humans remain scarce and have limitations. However, exposure to DDTs and phthalates has been shown to be associated with changes in the methylation status of both the *H19* and *IGF2* genes. These are well known for being related to Silver-Russell and Beckwith-Wiedemann syndromes, which are characterized by reduced and over-growth, respectively [161]. Similar findings were reported in relation to phthalate exposure, in the ELEMENT study [162]. The CHECK study found a positive association between exposure to the DDT metabolite *p,p′*-DDE, PCBs, and Σ19-organochlorine pesticides and *IGF2* methylation status in the placenta, but no association with another placental marker of methylation, *LINE-1*, and reduced birth length [161]. Levels of exposure to polychlorinated dibenzo-*p*-dioxins/dibenzofurans (PCDD/Fs) at 2 and 5 years of age have different effects on height in males with respect to females, with a reduced height at 2 years of age in females only, and an association of exposure levels with increased T3 and insulin-like growth factor-1 (IGF-1) levels, again more evident in females than in males [163]. However, these effects of dioxin exposure on growth were not confirmed by a later study [164]. With regard to the effects of exposure to phthalates, it is generally recognized that the effect of mixtures is worse

than that of a single metabolite and that some of the negative effects on longitudinal growth are mediated by a reduction in IGF-1 and IGF-binding protein-3 in the circulation [165]. A 20-year study described weak relationships between exposure to phthalates and height *z*-score during childhood [166]. Like other EDCs, some of the effects of phthalates on longitudinal growth are mediated through changes in BMI [167].

Bisphenol A exposure was described as being associated with downregulation of IGF-1 and *IGF-1* mRNA expression in the embryo, with subsequent changes in foetal weight [168]. Other effects would be mediated indirectly by changes in BMI, due to the negative effects of bisphenol A on bone marrow adipose tissue, with a subsequent increase in adiposity. This latter is associated with significant clinical effects on bone density and strength [169]. One study reported that high maternal urine concentrations of bisphenol S were associated with an increased head circumference and higher birth weight, if exposure occurred mainly during the first trimester of pregnancy [170]. Furthermore, reduced BMD was reported at 10 years of age following exposure during pregnancy [171].

A cross-sectional study in 2292 children, aged 6–9 years, found that exposure to PFASs was associated with lower levels of IGF-1 and sex hormones, thus probably affecting growth [172]. One of the most recent studies, the HOME study, reported that exposure to PFASs was related to a lower birth weight but, at 2 years of age, increased growth was observed [173], and it was hypothesized that PFASs induced rapid growth [174]. The NHANES Project Viva and other studies have reported that prenatal and early postnatal serum levels of PFAS are associated with reduced BMD in adolescents [175–178]. Polycyclic aromatic hydrocarbons also have negative effects on foetal growth [179–181].

In summary, the available studies in humans indicate that exposure to EDCs contributes to growth retardation, delayed ossification, and changes in bone length, size, and geometry, with subsequent reduction of BMD and quality. Finally, a good number of in vitro and in vivo studies have identified the affected molecular pathways that disrupt bone homoeostasis and architecture, including negative effects on the ERs, disruption of androgen action, induction of apoptosis, and modification of differentiation pathways, reduction in IGF-1 type 1 receptor gene expression, changes in the IGF system peptides, and changes in epigenetics in bone cells [158].

Adrenal Function and EDC Exposure

The adrenal gland belongs to the hypothalamic-pituitary-adrenal axis and plays a key role in electrolyte homoeostasis, the stress response, and steroidogenesis. It has long been known that the adrenal gland, particularly the cortex, is highly susceptible to exogenous noxae [182], owing to anatomical and histological features [182, 183] such as increased vascularization, which allows prompt distribution of produced hormones. This makes the adrenal gland available to exogenous substances present in the bloodstream, including EDCs. Furthermore, the lipophilic nature of the cortical cells and the well-developed apparatus for uptake of lipid components constitutes an ideal pool for lipid chemical accumulation. Indeed, studies in animal models (i.e., rats and mice) showed that certain chemicals accumulate in the adrenal cortex and can cause toxicity [184].

The cortex is also an environment for steroidogenesis, during which hydroxylation reactions produce reactive oxidative species (ROS), inducing oxidative stress. Some EDCs, including bisphenol A [185], phthalates [186], and parabens [187], have been described as inducing oxidative stress. Exposure to these could potentially further increase ROS, hence disrupting the redox balance and negatively affecting adrenal function. In one study in Wistar rats, bisphenol A was confirmed to increase oxidative stress and cause other structural changes, with a final increase in corticosterone and ACTH levels [188].

In addition, some EDCs have been shown to interfere with hormone distribution and binding to the receptors of target cells. For instance, in the first of 2 studies conducted in silico, it was demonstrated that alternative plasticizers di(2-ethylhexyl) terephthalate, tris(2-ethylhexyl) trimellitate, and di-isononyl hexahydrophthalate can bind to sex hormone-binding globulin (SHBG) [189]. In the second study, phthalates were predicted to bind to corticosteroid-binding globulin [190], suggesting possible changes in physiological distribution of hormones secreted by the adrenal cortex. In a cross-sectional study using data from NHANES, exposure to the pesticide *p,p′*-DDT was associated with lower levels of SHBG [191]. Additionally, it was found that hexaconazole, a fungicide, could also bind SHBG [192].

Furthermore, the hypothalamic-pituitary-adrenal axis can be impaired by factors affecting both the hypothalamus and pituitary gland. In vivo studies in pregnant rats showed that exposure to bisphenol A led to increased corticosterone, ACTH, and CRH secretion, with subsequent depression-like symptoms in the female offspring [193]. Additionally, in a randomized, double-blind, crossover trial in humans, it was shown that

exposure to particulate matter with a diameter ≤2.5 μm ($PM_{2.5}$) led to a substantial rise in cortisol, cortisone, and catecholamine levels [194]. In contrast, PFOS (another EDC) led to suppression of glucocorticoid levels [195]. This could be attributed to the blocking effect of this EDC on specific enzymes required for steroid hormone production [196]. Interestingly, PFOS was also associated with elevated dehydroepiandrosterone (DHEA), particularly in female rats, in addition to a decreased cortisol/DHEA ratio, indicating that PFOS favours androgen production [195]. These changes suggest a crosstalk between EDC-mediated impaired adrenocortical function and potential female reproductive disorders, such as PCOS, which is associated with increased DHEA levels [197].

Pharmaceutical drugs represent a major EDC family, having the potential to disrupt adrenal function by directly affecting the adrenal glands and by dysregulating the hypothalamus and pituitary gland, inducing adrenal insufficiency [198], which is a life-threatening condition. In Europe, an increased prevalence and a trend towards a higher incidence of adrenal insufficiency have been observed [199, 200]. Finally, many in vivo studies have shown that prenatal exposure to DDT can impair organogenesis of the adrenal cortex [201, 202] and medulla [203].

Endocrine Cancers and EDC Exposure

Evidence suggesting a role of EDCs in the aetiology and progression of endocrine cancers encompasses mechanistic studies, epidemiological findings, and experimental research [204, 205]. Endocrine-disrupting chemicals interact with hormonal pathways and disrupt hormone homoeostasis, which may promote hyperplasia of hormone-producing cells and activation of tumourigenic pathways. They can alter gene expression, induce epigenetic changes [206], and disrupt cellular and immune function [207], thereby contributing to the development and progression of cancers. Endocrine-disrupting chemicals can also influence the tumour microenvironment [208] by affecting immune response, inflammation, and angiogenesis [209], all of which are critical for cancer development and progression.

Thyroid cancer, which is the most common endocrine malignancy, has seen a global increase in incidence. While this increase is largely due to better diagnosis, it also raises concerns about environmental factors such as EDCs [210]. In a recent meta-analysis to elucidate the relationship between EDCs and thyroid cancer, exposures to PBDEs, phthalates, and heavy metals were associated with an increased risk of thyroid cancer, while no significant association was found for bisphenol A [211]. However, this might reflect the innate challenge in epidemiological studies of a high risk of exposure misclassification and low statistical power when studying exposures to non-persistent chemicals with a high day-to-day variation, such as bisphenol A.

Only 2 studies to date have assessed associations between EDC exposure and adrenal tumours in humans. One of these found elevated specific persistent organic pollutants in patients with aldosteronoma [212]. The second reported increased levels of bisphenol A in patients with non-functioning adrenal incidentalomas, particularly in women [213]. However, these studies lack data on specific exposure, including time and doses, highlighting the need for further investigation.

For some endocrine cancers, the malignancy may arise secondary to gland dysfunction in which EDCs may play a role (e.g., as in pancreatic neuroendocrine tumours). Pancreatic neuroendocrine tumours are rare, but incidence rates are increasing [214], and known risk factors include smoking and type 2 diabetes. Several EDCs have been associated with increased risk of developing type 2 diabetes [215]. Agents involved in the initiation phase of pancreatic cancers in general include organ-chlorinated compounds and heavy metals, many of which are EDCs [216].

Cancers of hormone-sensitive tissues, such as breast, endometrial, prostate, and testicular germ cell cancers, have also been associated with exposure to EDCs. This suggests that EDCs may be a risk factor in the development of these tumours [119, 204, 217–219].

Future Research Priorities

There is now robust evidence indicating EDCs to be one of the leading environmental risks globally. Such evidence should be further strengthened.

- In vitro and in vivo mechanistic studies are still needed to uncover or validate new modes of EDC action and biomarkers of endocrine-disrupting effects using state-of-the-art methodologies (e.g., transcriptomics and epigenetics).
- Epidemiological studies remain crucial to identify/monitor certain hormone-related diseases and conditions in relation to the degree of exposure in different subpopulations or different geographical areas, including a need for:
  - Follow-up studies to study long-term and transgenerational adverse effects and elucidate underlying pathophysiological mechanisms.

- Longitudinal or repeated cross-sectional population studies to assess trends in exposure and the incidence of specific diseases over time, as well as pre- and post-intervention/regulation to monitor the effects of preventive measures.
- Integrating more comprehensive exposure estimates, such as human biomonitoring, by suspect screening/non-targeted analyses and use of (real-time) spatial exposure measures.
- Integrating omics methodologies; for example, trans-criptome-wide association studies can aid in dissecting environmental chemical-gene interactions and exposure-associated changes in the metabolome can unveil pathways involved.

Pharmaceuticals

Epidemiology, Societal Impact, and Research State of the Art

Modern medicine is characterized by a tremendous increase in the number of medications for the treatment of diseases or prevention of long-term disease consequences. Today, there are thousands of products on the market, and pharmaceutical development of novel targeted medications for humans and animals is a large-scale business [220]. Physicians and pharmacists are traditionally trained in the appropriate application of drugs for specific indications. Information about potential side effects and interactions of medications is also readily available, and their documentation is a legal requirement. However, very few healthcare professionals know that some, even rather common and widely used, medications may have endocrine-disrupting effects. This may occur through the same pathway as the drug's therapeutic application, and sometimes through additives, capsules, or medical devices such as intravenous tubes [221, 222]. Growing concern also surrounds pharmaceuticals and their derivatives found in the environment, which can lead to unintended exposure [223, 224]. There are still few data on the extent and health effects of this unintentional exposure [225].

Worldwide, the production and consumption of prescription medicines and over-the-counter drugs increases [220]. One example of this development is the use of mild analgesics [226]. Epidemiological human studies, as well as experimental studies, indicate that paracetamol and non-steroidal anti-inflammatory drugs (i.e., aspirin, diclofenac, and indomethacin) have adverse effects on testicular and ovarian development and reproductive function [227–229], especially in the offspring if taken during pregnancy [230]. Another example is metformin, a common drug for type 2 diabetes mellitus; wildlife and human studies have raised concerns about its broad environmental distribution and anti-androgenic effects on the male reproductive tract [231]. Anti-fungal medications, such as the widely used azole compounds, affect steroidogenesis [232, 233], which may be of particular concern when taken during sensitive developmental windows, including pregnancy. Immune checkpoint inhibitors, which have emerged as new effective treatments for several types of cancer, can cause both reversible and irreversible endocrine effects [234]. These pharmaceuticals are the most recent example of the importance of understanding common pathways of action in living organisms from the holistic perspective of systems biology.

Future Research Priorities

Research into the endocrine-disrupting effects of pharmaceuticals is only at its beginning. However, compared with environmental exposure levels, medications are administered at higher doses per body weight or body surface, and often over long periods.

- Research is needed into the environmental fate of pharmaceuticals and into methodologies to prevent environmental contamination due to human use of pharmaceuticals.
- Adverse (side) effects on the endocrine system, including transgenerational effects, should be determined as part of the safety testing for pharmaceuticals.

Climate

Epidemiology, Societal Impact, and Research State of the Art

The current climate change, driven by human activities such as burning fossil fuels and deforestation, has far-reaching consequences for health. Rising temperatures, extreme weather events, and changes in disease patterns are current direct and indirect threats. Children are vulnerable to heat-related illnesses due to their higher metabolic rates and lower ability to regulate body temperature. The elderly also represent a vulnerable population [235]. Heatwaves can lead to dehydration, heat exhaustion, and endocrine imbalance, besides heatstroke. In a large population study, seasonal climatic factors such as temperature, rainfall, aqueous vapour pressure, sunshine hours, and air pollution parameters showed differential effects on thyroid homoeostasis [236]. This indirectly has consequences for growth in

children and for metabolism and cognitive function in both children and adults. Global warming also causes evaporation of iodide from seawater and in regions distant from the coast, resulting in a depletion of iodide in plant foods and drinking water, ultimately affecting thyroid function [237, 238].

Nitrate competes with iodide uptake by the thyroid and has an impact on hormonal synthesis; in addition, some nitrosamines are known carcinogens [239]. Seasonal heavy rains wash away soil minerals, while temperature spikes contribute to elevated nitrate and nitrite concentrations, and cause moisture loss in fruits and vegetables, further increasing these levels [239]. Such effects may counteract the altered availability of iodide for thyroid hormone biosynthesis.

Higher outdoor temperatures can favour the obesity pandemic by decreasing the opportunity and motivation for outdoor physical activity. Climate change also has an effect on gene expression patterns, and higher temperatures would determine an overall reduced energy expenditure. This is associated with changes in the amounts of white and brown adipose tissue, with subsequent changes in adipocytokines, among other factors, and would favour the complications arising from obesity [240].

Future Research Priorities

A more comprehensive understanding of connections among endocrine diseases, climatic changes, pollution, biodiversity, and food is warranted to pursue the One Health approach.

- Understanding the impact of climatic factors on human health, including metabolism, thyroid function, and reproduction, is an issue of increasing importance.
- Understanding the impact of climate change on the quality of food products, including changes in micronutrients and contaminants and how this relates to health consequences, is a current need.

Air and Water Pollution

Epidemiology, Societal Impact, and Research State of the Art

Air pollution is largely driven by the combustion of fossil fuels, greenhouse gases, and industrial processes. Air pollutants such as particulate matter (PM), nitrogen dioxide (NO_2), and ozone (O_3) have many effects. Many air pollutants carry EDCs, such as polycyclic aromatic hydrocarbons, phthalates, mercury, and perchlorate [241, 242].

Fat-soluble airborne contaminants may accumulate in adipose tissue during pregnancy and contribute to preterm birth and low birth weight [243] and to the increase in non-communicable diseases later in life. Recent research suggests a link between neuroendocrine effects of air pollution and cognitive impairment in children [244]. Oxidative stress damage, inflammation, endocrine disruption, and epigenetic changes are all implicated. Airborne toxins can interfere with thyroid function. Higher exposures to $PM_{2.5}$-bound metals have been associated with lower maternal free T4 and free T3 levels, and preconception $PM_{2.5}$ and PM_{10} exposure increased the risk of hypothyroidism during pregnancy [245]. Furthermore, the elicited inflammatory response and oxidative stress can potentially trigger autoimmune responses against the thyroid gland and worsen asthma symptoms and respiratory conditions.

Moreover, some evidence suggests that $PM_{2.5}$ decreases the number of ovarian follicles in females [246]. Increased incidence and prevalence of type 2 diabetes mellitus have been associated with combined exposure to PM and NO_2 [247]. Bone strength seems to be affected too [248]. Overall, studies and epidemiological data have evidenced a clear association between PM exposure and hormone-related clinical symptoms, as well as a number of conditions of multifactorial origin.

Light pollution has also emerged as a health concern in modern societies, for its effects on hormonal circadian rhythms. The extensive use of electronic devices as well as artificial light is of concern as they disrupt the natural darkness required for melatonin production. The consequences extend beyond sleep disorders, potentially contributing to a range of health issues, such as mood and metabolic disorders [249]. The increase in central precocious puberty during the pandemic has also been related to the huge increase in screen time in children during that period [250, 251].

Drinking water sources can be polluted by heavy metals, environmentally persistent pharmaceutical pollutants and other endocrine disruptors (e.g., pesticides, pharmaceuticals, herbicides, and bisphenols). Most come from waste discharged from industrial activities, such as paper and textile mills and leather industries, and wastewater for agricultural purposes [224]. Perchlorate can interfere with iodide uptake by the thyroid gland, leading to thyroid dysfunction. Arsenic-contaminated water can favour diabetes, affecting insulin signal transduction, secretion and sensitivity, and adipocyte development [252]. Cadmium favours adipocyte

hyperplasia and hypertrophy, alters appetite and satiety regulation, and decreases insulin sensitivity [252].

In conclusion, water pollution also influences the endocrine system in a multifactorial fashion. Depending on the contaminants, several hormone-related conditions and multifactorial diseases are affected.

Future Research Priorities

Future research should evaluate the prolonged and transgenerational effects of environmental pollution on human health. Longitudinal studies will play a pivotal role in tracking the effects of exposures over time.

Mapping of pollution, identification of high-exposure locations ("hot-spots"), and linking to disease incidences are important, for example:

- Using geographic information systems for geospatial relationships between data on pollution and factors affecting pollution (e.g., traffic, industry, agriculture) and spatially dependent health data (e.g., from health data registries or medical reimbursement systems).
- Adopting human geo-sensing approaches to obtain individual exposure profiles for linking to health data.

Stressful Environments

Epidemiology, Societal Impact, and Research State of the Art

Diseases characterized by a very steep and recent increase in incidence, such as obesity, cardiovascular pathologies, fatigue syndrome, anxiety, and autoimmunity, are all associated with a dysregulated stress response.

Stress happens when the homoeostasis of an organism is threatened. Targets of the stress effectors include the cognitive, reward, and fear systems, growth, the hypothalamic-pituitary-adrenal, gonadal, and thyroid hormone axes, and the control of energy balance [253]. For that reason, any excessive, prolonged, or maladaptive stress response acts as an endocrine disruptor and can impact growth, adiposity, appetite, neurodevelopment, reproduction, or cognitive functions. Stress may also act as a mediator for adverse effects of EDCs, such as phthalates [254].

Stress encompasses several forms, including natural and anthropogenic disasters, social or economic difficulties, and malnutrition. Hence, its epidemiology is extremely difficult to estimate and varies widely with time and around the globe. Notably, epidemiological studies have linked recent impairment of child and adolescent mental health with increasing educational and economic stressors [255, 256]. Stress regulation is programmed during foetal life, and recent studies have shown that any disruption during this period leads to long-lasting dysregulation of stress and predisposition to later diseases including neuropsychiatric disorders, cardiovascular diseases, adiposity, and impaired reproductive health [257, 258]. Such observations are consistent with the developmental origins of health and disease paradigm that links the risk of adult disease with the environmental conditions of early life [259]. Therefore, the continued ability to respond appropriately to stress is a necessary component of disease prevention [258].

Future Research Priorities

Major challenges include the definition and evaluation of stress, as well as the identification of system-specific endpoints. Future studies should focus on these aspects.

- Strong data now support a sex difference in the regulation and response to stress, including early-life exposure to stress [260]. Such sex differences should systematically be taken into account when exploring mechanisms of action and consequences of stress as they may depend on hormonal or genetic regulation.
- Rodent models have illustrated the role of the placenta in mediating the effects of gestational stress on neurodevelopment or metabolic health [261]. Studies are needed to elucidate the link between the placenta and later health in humans and identify relevant placental markers of stress. This might open new avenues for preventing metabolic or neuropsychological diseases in future generations.
- Parental stress occurring before conception leads to alteration of the adrenal response to stress as well as impaired psychological health in the descendants. Preclinical models suggest that epigenetic modifications of germ cells might explain such transmission [262]. As epigenetic changes in sperm are associated with early-life adverse events in men, further studies are required to identify whether such changes lead to specific outcomes in the descendants.

Conclusions

The aetiology and/or manifestation of several non-communicable diseases that are on the rise often contain an element of hormonal dysregulation. The endocrine system plays a crucial role in regulation of homoeostasis within the human body through hormone signalling. In response to external factors, the endocrine system sustains homoeostasis by changing internal conditions as

required to survive the external challenges. Thus, evolutionary endocrine systems have developed to cope with natural environmental changes (e.g., changes in temperature or differences in resources due to seasonal or climatic variation).

However, since the beginning of industrialization, anthropogenic changes to our environment have accelerated at an unprecedented rate, and to the extent that the resilience of endocrine systems is challenged. Understanding the interaction between environmental factors, human exposures, and disease calls for interdisciplinary collaborations. In this collaboration, clinical and basic endocrinologists can play an important role in contributing expert knowledge about the endocrine system, including crosstalk between different hormone pathways and the important considerations of sex and different life stages.

Conflict of Interest Statement

The authors have no conflicts of interests to declare.

Funding Sources

No funding was received.

Author Contributions

Anna-Maria Andersson (investigation [equal], methodology [equal], project administration [equal], writing – original draft [equal], and writing – review and editing [equal]); Stefano Cianfarani (investigation [equal], methodology [equal], project administration [equal], writing – original draft [equal], and writing – review and editing [equal]); Josef Köhrle (investigation [equal], methodology [equal], project administration [equal], writing – original draft [equal], and writing – review and editing [equal]); Katharina Main (investigation [equal] and writing – original draft [equal]); Anne-Simone Parent (investigation [equal] and writing – original draft [equal]); Robin Peeters (writing – review and editing [equal]); Martin Reincke (writing – review and editing [equal]); Kristina Saravinovska (investigation [equal], visualization [equal], and writing – original draft [equal]); and Maria E. Street (investigation [equal], writing – original draft [equal], and writing – review and editing [equal]).

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