



Evidence of the Possible Harm of Endocrine-Disrupting Chemicals in Humans: Ongoing Debates and Key Issues

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Evidence has emerged that endocrine-disrupting chemicals (EDCs) can produce adverse effects, even at low doses that are assumed safe. However, systemic reviews and meta-analyses focusing on human studies, especially of EDCs with short half-lives, have demonstrated inconsistent results. Epidemiological studies have insuperable methodological limitations, including the unpredictable net effects of mixtures, non-monotonic dose-response relationships, the non-existence of unexposed groups, and the low reliability of exposure assessment. Thus, despite increases in EDC-linked diseases, traditional epidemiological studies based on individual measurements of EDCs in bio-specimens may fail to provide consistent results. The exposome has been suggested as a promising approach to address the uncertainties surrounding human studies, but it is never free from these methodological issues. Although exposure to EDCs during critical developmental periods is a major concern, continuous exposure to EDCs during non-critical periods is also harmful. Indeed, the evolutionary aspects of epigenetic programming triggered by EDCs during development should be considered because it is a key mechanism for developmental plasticity. Presently, living without EDCs is impossible due to their omnipresence. Importantly, there are lifestyles which can increase the excretion of EDCs or mitigate their harmful effects through the activation of mitohormesis or xenohormesis. Effectiveness of lifestyle interventions should be evaluated as practical ways against EDCs in the real world.

Keywords: Chemical mixtures; Endocrine-disrupting chemicals; Exposure assessment; Epidemiology; Evolution; Metabolism-disrupting chemicals; Non-monotonic dose response relationship; Predictive adaptive response hypothesis; Persistent organic pollutants; Reliability

INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are defined as exogenous compounds that interfere with any aspect of endogenous hormones, including their production, release, transport, metabolism, binding, action, or elimination [1,2]. The chemicals classified as EDCs are highly heterogeneous. They include pesticides, fungicides, plastics, plasticizers, synthetic chemicals used as industrial solvents, heavy metals, and pharmaceutical agents

[1,2]. Although most EDCs are man-made, some EDCs are naturally present in the human diet [1,2].

The list of EDCs is rapidly growing. According to the TEDX (The Endocrine Disruption Exchange) database, the number of suspected EDCs was 881 in 2011, increasing to 1,419 in 2017 [3]. As EDCs do not share any structural similarities, it is difficult to predict whether a compound will exert endocrine-disrupting actions [1]. Even nanoparticles are suspected to be EDCs [4].

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Humans are continuously exposed to a variety of EDCs via food, air, water, and consumer products. The exposure to EDCs begins *in utero* as many EDCs are easily transferred across the placenta of pregnant women to the developing fetus. During infancy, breastmilk is the main source of exposure to EDCs.

During the last decade, the number of research articles on EDCs has increased dramatically; however, our knowledge of EDCs is still limited and fragmentary. It is noteworthy that a section in the 2012 World Health Organization/United Nations Environment Programme (WHO/UNEP) summary for decision-makers was titled “The tip of the iceberg,” despite including a very long list of references [5]. Indeed, debates are continuing about the evidence of the possible harm that EDCs may cause in humans.

This review article (1) provides a brief history of research into EDCs, (2) discusses debates and issues surrounding the evidence of the potential harm of EDCs to humans, (3) describes evolutionary aspects of epigenetic programming due to the exposure to EDCs during developmental periods, and (4) suggests practical ways to mitigate the possible harm caused by EDCs.

A BRIEF HISTORY OF RESEARCH INTO EDCs

The term “endocrine disrupter” was first used at the Wingspread meeting in 1991 [6]. However, the hormone-disrupting effects of certain chemicals have been reported since the mid-20th century. Initially, research into EDCs focused on their estrogenic property and their role in decreased fertility, decreased semen quality, and increased birth anomalies [7]. Soon, concerns expanded to more hormone-disrupters, including those that affect androgens or thyroid hormones [8], and other health issues, such as hormone-related cancers [9] and problems with neurodevelopment [10].

Over recent decades, researchers have begun to recognize that environmental chemicals can disturb many other hormonal pathways, as well as sex and thyroid hormones. In particular, evidence is accumulating that environmental chemicals are linked to metabolic diseases, including obesity and diabetes, via diverse mechanisms [11]. As such, the new term “metabolism-disrupting chemicals” (MDCs) was coined [11]; a chemical can be an EDC or MDC, depending on the context. Although in this review, EDCs will be used as a general term encompassing these compounds, it is worthwhile to note that the terms EDC and MDC are not sufficient to cover the extensive disturbing features of these environmental chemicals in living organisms.

Most EDCs identified to date interact with the nuclear receptors of several hormones as agonists or antagonists. However, research has shown that their mechanisms of action are much broader than originally recognized. As well as through nuclear receptors, EDCs act via non-nuclear steroid hormone receptors, non-steroid receptors, orphan receptors, and enzymatic pathways involved in steroid biosynthesis and/or metabolism [12].

Recently, organizations such as the Endocrine Society [1,2] and the WHO/UNEP [5] have issued official reports describing the possible health threats posed by EDCs. They focused on exposure during critical periods of development and concluded that exposure to EDCs is related to a multitude of diseases, including impaired reproduction, neurodevelopment, thyroid function, and metabolism, as well as increases in hormone-sensitive cancers. In particular, EDCs show their effects at low doses within the range of human environmental exposure that are assumed to be safe under the current regulations on chemicals. Thus, these reports called for urgent action to regulate EDCs.

DEBATES ABOUT THE EVIDENCE OF HARM TO HUMANS

After the release of the WHO/UNEP report in 2012, however, debates have continued between researchers who support the conclusions of the report [13-17] and those who oppose it [18-21]. Although the opponents are often accused of being associated with or funded by chemical industries [15,16], some of their arguments deserve sober discussion from the scientific community. One criticism is the lack of evidence of the harm of EDCs to humans, despite the persuasive evidence from *in vitro* and *in vivo* studies.

In fact, in contrast to the conclusion of official reports on EDCs [1,2,5], many recent systemic reviews or meta-analyses focusing on epidemiological studies, especially of short-lived EDCs, seem to support the opponents' position. For example, reviews of the effects of bisphenol A (BPA) in humans reported conflicting results with respect to pubertal development [22] and diabetes [23]. Similar conclusions have been reached on phthalate and obesity [24], triclosan and diverse health effects [25], and developmental exposure to many EDCs and male reproductive disorders [26].

The economic costs from EDC exposure-related disease burden in the EU and USA have recently been estimated to be huge [27,28]. However, the articles describing cost estimations were criticized as pseudoscience by opponents [29,30] because these estimations were reasonable only with the assumption of cau-

sality in humans.

WHY IS EVIDENCE OF HARM IN HUMANS STILL AN UNSOLVABLE PUZZLE?

Although consistent findings from epidemiological studies is regarded as one of the critical elements needed to support the establishment of a causal link between an exposure and disease, studies of EDCs in humans may be the exception. In fact, inconsistency may be inevitable due to insuperable methodological issues. Herein, three key issues will be briefly discussed. This topic was thoughtfully discussed in another article in which other issues, such as complicated interactions with established risk factors such as diet and obesity and the difficulty of exposure assessment during critical periods of the lifespan, were also addressed [31].

Issue 1: can we predict the net effect of EDC mixtures in the real world?

Mixtures of EDCs are the most complicated of these three issues. Until now, laboratory studies of EDC mixtures were mainly performed using several similarly-acting compounds, such as mixtures of estrogenic compounds, antiandrogens, and thyroid-disrupting chemicals, and mostly reported additive or synergic interactions [32]. However, studies of mixtures of several EDCs with different endocrine-disrupting properties demonstrated modulating or antagonistic interactions that could not be predicted in terms of additivity or synergistic concepts [33-36]. In fact, all EDC mixtures used in laboratory studies are very simple, unrealistic mixtures compared to real-world EDC mixtures. As such, the net effect of the mixture of several hundreds of EDCs, all with diverse activities, is unpredictable at the individual level in humans.

Issue 2: can non-monotonic dose-response relationships be validly evaluated in human studies?

The biological responses to EDCs are often non-monotonic dose responses (NMDRs) [37]. NMDRs can arise from numerous mechanisms, such as opposing effects induced by multiple receptors differing in their affinity, receptor desensitization, negative feedback with increasing doses, or dose-dependent metabolism modulation [38]. Hormesis, the overcompensation of various adaptive responses through cellular stresses, is also a mechanism of NMDRs [39].

NMDRs have been also observed in human studies of many environmental chemicals; the risk of diseases does not increase

with an increasing dose, but often tends to plateau or even decrease with an increasing dose [40-45]. Importantly, the identification of NMDRs in a particular human dataset is difficult when non-exposure groups do not exist (as is the case for many common EDCs) and the exposure range is limited [31]. Depending on the exposure range of the population, positive, null, and even inverse associations are possible [31].

Issue 3: can exposure to EDCs with short half-lives be reliably assessed in humans?

The quality of exposure assessment is a key determinant of the overall quality of environmental epidemiological studies [46]. Serial measurements of many ubiquitous EDCs with short half-lives in spot urines have demonstrated large within-subject variability [47-49]. Even 24-hour urine samples did not help in the estimation of typical exposure levels due to large day-to-day variability [47-49]. Thus, the collection of repeated biospecimens is recommended to estimate typical exposure levels for these EDCs. However, this recommendation is often unrealistic. For example, in a simulation study, the pooling of 35 repeated urine samples from a single individual was estimated as being necessary to reduce the attenuation bias of BPA to 10% [50].

CAN THE EXPOSOME BE A SOLUTION?

The exposome has emerged as a methodology to evaluate the health effects of EDCs in humans [51,52]. Although the concept of the exposome sounds fascinating (for example, the totality of lifetime environmental exposure or the development of omics-based chemical fingerprints), the study of the exposome is inevitably affected by the fundamental methodological limitations discussed above.

Besides genomics, all omics are dynamic. Epigenomics, proteomics, and metabolomics are continuously affected by every aspect of the continuously changing external and internal environment [53]. Although epigenetic programming during the developmental period is stable, its evolutionary aspects need to be considered, as discussed below. Additionally, although sophisticated statistical methods have been suggested for analyzing huge datasets derived from the exposome [54,55], they ironically presume unrealistic simple conditions, such as linearity.

WHAT CAN BE EVIDENCE OF THE HARM OF EDCs IN HUMANS?

Although we can observe an increasing trend of EDC-linked

diseases at the population level, traditional epidemiological studies based on individual measurements of EDCs, especially many short-lived EDCs currently in wide use, may fail to provide consistent results due to methodological limitations. Additionally, pinpointing specific EDCs as the culprit for certain conditions is neither possible nor useful because diseases in the endocrine system may be the result of a mixture of a tremendous number of EDCs, including those we know as well as those we do not currently know.

Meanwhile, chronic exposure to a low dose of persistent organic pollutants (POPs), a mixture of strongly lipophilic chemicals, has been recently associated with obesity-related diseases such as type 2 diabetes in human studies [56,57]. Even though the study of POPs also suffers from some inconsistencies, these findings have at least been more consistent than those of studies of common EDCs with short half-lives [57]. Importantly, human studies on POPs, especially chlorinated POPs, are less affected by methodological issues due to their long half-lives, the presence of a reference group that is closer to a non-exposure group, and the role of several POPs as surrogate markers of lipophilic chemical mixtures, including measured and unmeasured ones. Even though POPs are well-known EDCs, the findings on POPs in humans cannot be attributed to the hormone-disturbing properties of POPs because POPs are a mixture of diverse EDCs. Other mechanisms, such as mitochondrial dysfunction or chronic glutathione depletion, have been suggested as possible mechanisms linking chlorinated POPs to health outcomes [56,58].

PRACTICAL RECOMMENDATIONS FOR CLINICIANS AND THE PUBLIC: WHAT CAN WE DO ABOUT EDCs RIGHT NOW?

If environmental chemicals are really harmful to humans, what is the next step?

Exposure during critical periods and irreversible epigenetic programming

Early-life exposure to EDCs, especially during the fetal and infant stages, is the primary concern in the field of EDCs because exposure during these periods has permanent effects on the exposed individuals and their descendants through epigenetic programming, even in the absence of further exposure. Unfortunately, however, it is almost impossible to provide sensible advice to pregnant women on how to effectively avoid EDCs in order to protect their children [59].

Although the prenatal and early life periods are the most susceptible to toxicity of environmental chemicals, importantly, epigenetic programming during critical periods triggered by various environmental stressors is a key mechanism for developmental plasticity to buffer individuals from environmental changes [60]. After birth, if offspring have to live in conditions similar to the *in utero* conditions, their overall survival may be enhanced by virtue of the epigenetic programming.

For example, the findings from a cohort of babies from the Dutch famine during World War II, in which malnutrition during pregnancy led to the increased risk of many chronic diseases, are now referred to the exemplary case supporting the developmental origin of health and disease (DOHaD) [61]. However, studies of the famine in Leningrad failed to replicate the findings from the Netherlands [62]. The difference between these two cohorts was the nutritional status of individuals after birth. In the Netherlands, many starved babies were promptly well-nourished postnatally, but the Leningrad cohort experienced similar poor nutritional status even after birth [62]. The degree of mismatch between the prenatal and postnatal environment, rather than prenatal exposure itself, may be a major determinant of DOHaD; this is known as the predictive adaptive response (PAR) hypothesis [63]. It is not only confined to nutrition. The PAR hypothesis warrants investigation in the field of EDCs as well.

Although the obesity-inducing effects of EDCs are a major research topic, this issue also should consider an evolutionary perspective. Although obesity is an important risk factor of many chronic diseases, the expansion of fat mass is not itself pathological, but primarily conveys a protective and adaptive role with regard to maintaining insulin sensitivity [64]. When hypertrophic adipocytes face limits of expansion, dysfunctional adipocytes and/or insulin resistance can develop [65]. Therefore, the expansion of adipose tissue by EDCs itself cannot be considered as harmful, but provide a protective role by securing a relatively safe storage organ for strongly lipophilic EDCs with long half-lives [66].

Exposure during non-critical periods and reversible effects

Exposure to EDCs in adulthood can also alter the physiology of the endocrine system [67], although this topic has not received as much attention as exposure during development. In particular, when exposure is continuous (as we now experience), the risk of EDC-related diseases increases. Importantly, although early-life exposure to EDCs produces irreversible effects, the effects of exposure during a non-critical period can be revers-

ible [1,2].

Clinicians may consider the direct measurement of established or suspected EDCs in biospecimens of patients to provide advice on which EDCs should be avoided or how to avoid

EDCs. However, there are insurmountable challenges in ascertaining which specific EDCs contribute to a particular disorder in individual patients, similar to the limitations of epidemiological studies. Instead, it may be wise to simply assume that EDC

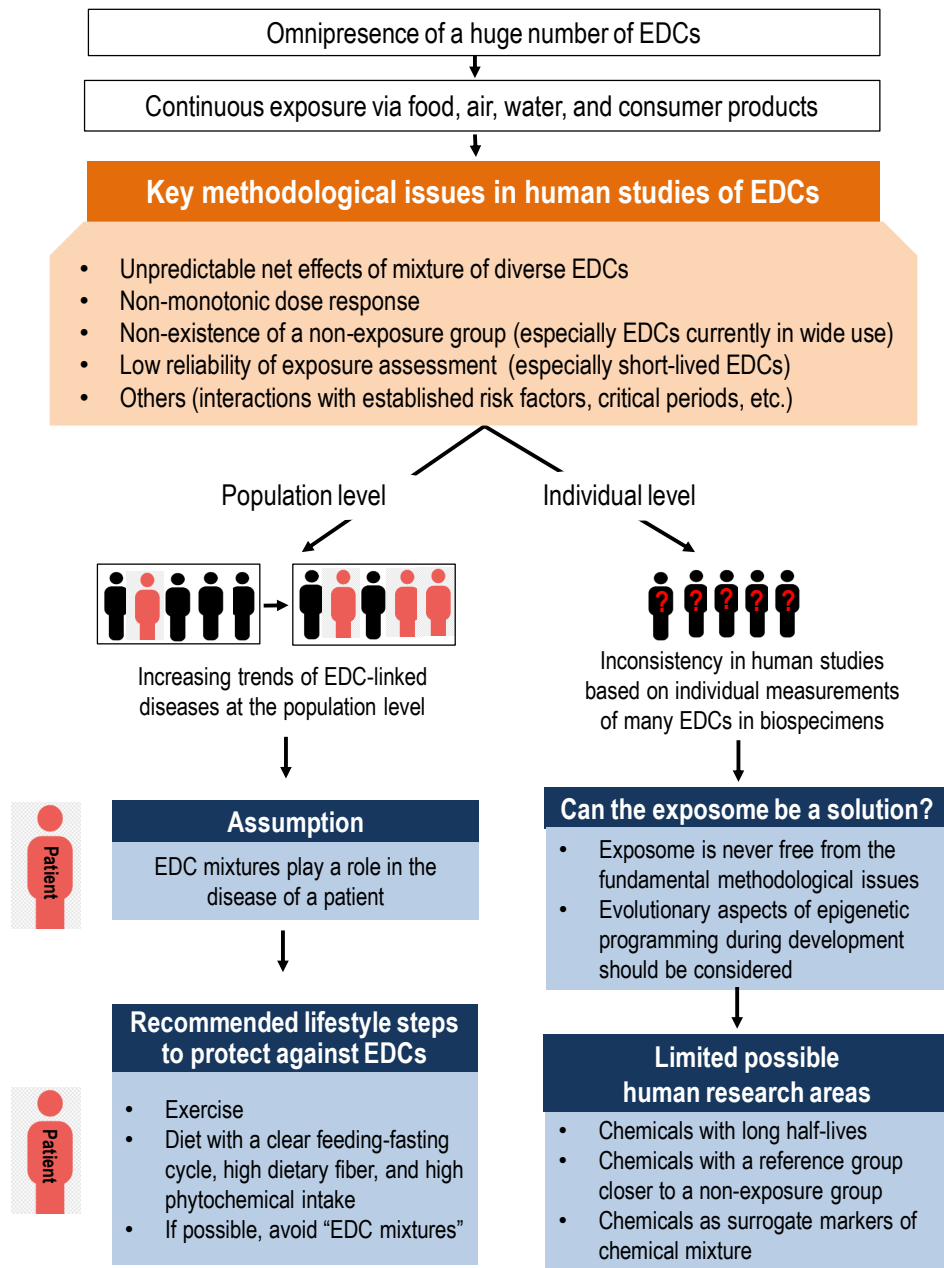


Fig. 1. Issues in human studies of endocrine-disrupting chemicals (EDCs) and practical recommendations for clinicians and the public. Despite the increasing trend of EDC-linked diseases, it is difficult to find consistent human evidence on the harms of EDCs, especially the short-lived EDCs currently in wide use, due to critical methodological issues. In the case of human studies, possible research areas are limited. Both early-life exposure during critical periods and continuous exposure during non-critical periods can be harmful to humans. However, epigenetic programming induced during critical periods is a key to developmental plasticity and evolutionary aspects should be considered. Harms due to continuous exposure during the non-critical period may be mitigated by adopting lifestyle measures that counteract the harmful effects of EDCs. Effectiveness of lifestyle interventions should be evaluated as practical ways against EDCs in the real world.

mixtures play a role in the development of disease in the patient, unless they have other obvious causes for their conditions.

The most important recommendation may be to focus on EDC mixtures, instead of several specific EDCs individually. Although largely unknown, the most important source of EDC mixtures is not outside the patient, but inside the patient. Contemporary human adipose tissue contains the most complex EDC mixtures because humans are at the top of the food chain [66]. It is particularly necessary to re-evaluate obesity-related diseases from the viewpoint of lipophilic chemical mixtures in adipose tissue because they are slowly and continuously released into circulation in an uncontrolled way in obese persons with dysfunctional adipocytes [66]. Therefore, determining how to efficiently eliminate EDC mixtures from circulation may be central to decreasing the burden of the EDC mixtures delivered to critical organs.

Interestingly, healthy behaviors can increase the excretion of chemical mixtures from the body [66] and mitigate the harmful effects of chemical mixtures at the cellular level through the activation of mitohormesis or xenohormesis [68]. Briefly, examples include exercise, a clear feeding-fasting cycle, and the inclusion of fiber and phytochemicals in the diet. Detailed mechanisms can be found elsewhere [66,68]. Additionally, similar to human adipose tissue, fat in animal food such as meat, milk, and fish is also widely contaminated with many EDCs. Thus, if people want to avoid further exposure to exogenous EDCs, avoiding animal fat would be a better choice than avoiding the various individual EDCs that are contained in consumer products.

CONCLUSIONS

Fig. 1 depicts the contents of this article. Living without exposure to EDCs is impossible. Although certain lifestyle choices, such as living without plastic, can decrease exposure to several EDCs [69], these sources account for only a tiny proportion of possible EDC exposure. Although enhanced regulation via the adoption of precautionary principles is called for, regulations also have limited value, as many EDCs have already contaminated our bodies and our environment. Therefore, alternative ways to reduce the possible harm of EDCs should be explored. Importantly, some lifestyle can guard against EDCs. Examples include exercise, a clear feeding-fasting cycle, a high intake of dietary fiber, and a high intake of phytochemicals. Although this lifestyle is regarded to be healthy even outside of the context of EDCs, adopting these behaviors is especially necessary in light of the omnipresence of EDCs and their deleterious effects.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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