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The effects of climate change and exposure to endocrine disrupting chemicals on children's health: A challenge for pediatricians

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ABSTRACT

The natural, economic and public health crises that have periodically struck the world over the past two decades have often revealed a low degree of self-sufficiency and a high degree of unpreparedness on the part of European and non-European countries. It is generally the most vulnerable who suffer the consequences, and adverse events have shown their effects and direct negative impact mainly on the population aged 0–18 years, with major implications for families and communities. Climate change and environmental pollution are certainly prominent among the natural disasters impacting children's health. In particular, environmental pollution events have been increasingly correlated with health conditions, including allergic diseases related to increased allergen production, infectious diseases, diabetes, respiratory diseases, and cardiovascular diseases. Data from the literature have shown how chemicals can interfere with children's health, and special attention has been paid to endocrine disruptors because of their possible damage on various endocrine and nonendocrine systems. This brief overview explores the important impacts of climate change and environmental pollution on children's health, with the goal of further raising awareness among pediatricians and public health authorities on this critical issue for the future of children's health.

Introduction

The natural, economic and public health crises that have periodically struck the world over the past two decades have often revealed a low degree of self-sufficiency and a high degree of unpreparedness on the part of European and non-European countries [1–3]. It is generally the most vulnerable who suffer the consequences, and adverse events have shown their effects and direct negative impact mainly on the population aged 0–18 years, with major implications for families and communities. A rational approach to adequately address future public health emergencies is to learn from past adverse experiences in order to explore, identify, and clarify what priorities govern the management of major health emergencies at all levels in this population group. Climate change and environmental pollution are certainly prominent among the natural disasters impacting children's health [4].

In a recent commentary, the European Pediatric Association, Union of National European Pediatric Societies and Association (EPA-UNEPSA) highlighted the evidence that global climate change and environmental pollution have a high impact on children's health [5]. EPA-UNEPSA has emphasized the notion that children, particularly those of lower socioeconomic status, are at increased risk of developing diseases for which climate change may be directly or indirectly responsible [4,5]. The potential health effects of climate change and related adverse events that have affected the world's population in recent years have been widely studied [6]. These include disasters due to extreme weather events and heat waves, increased zoonoses, respiratory diseases due to air pollutants and aeroallergens, water scarcity, and low nutritional quality of food [4–6].

Abbreviations: epa-unepsa, european pediatric association, union of national european pediatric societies and association; Saffi, safe food for infants; Edcs, endocrine disruptors; ENDs, Endocrine And Nerve Disruptors; POPs, Persistent organic pollutants; PFAS, Perfluoroalkyl substances; BPA, Bisphenol A.

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In particular, environmental pollution events have been increasingly correlated with health conditions, including allergic diseases related to increased allergen production, infectious diseases, diabetes, respiratory diseases, and cardiovascular diseases [6]. Data from the literature have shown how chemicals can interfere with children's health, and special attention has been paid to endocrine disruptors because of their possible damage on various endocrine and nonendocrine systems, as experimental evidence has shown over the years [7–9]. Governments around the world have made increasingly serious efforts to protect children's health from the effects of food contaminants. Recently, under the European Horizon 2020 program, the European Union funded the multicenter Safe Food For Infants (SAFFI) project, a research program that aims to develop an integrated approach to improve the identification, assessment, detection, and mitigation of safety risks from microbial and chemical hazards along child food chains in the EU and China (https://www.saffi.eu/). This brief overview explores the important impacts of climate change and environmental pollution on children's health, with the goal of further raising awareness among pediatricians and public health authorities on this critical issue for the future of children's health.

Climate change and natural disasters

Natural and economic disasters and health emergencies are interconnected phenomena [10,11]. The effects of natural disasters and public health crises on economic instability have been the subject of decades of research that has engaged experts since the beginning of the last century. However, interest, studies and analyses of these phenomena seem to be limited to experts and practitioners in the area of public health, economics and disaster management, because natural, economic and public health emergencies seem to be regarded by governments and legislators as unpredictable events.

Trauma is a global problem [11]. Disasters and painful natural events occur periodically around the world and must be addressed with relief and recovery interventions that include appropriate health approaches [11]. The nature and effects of these disasters are progressively more complex because they are influenced by several factors, including climate change, population shifts, economic interdependence and the general phenomenon of globalization [12]. Over the past 30 years, geophysical and climate-related disasters have killed about 1.3 million people, including 320,000 children, and left another 4.4 billion people injured, homeless, displaced or in need of emergency assistance [12]. Most casualties were caused by geophysical events; more than 90 percent of all disasters were caused by floods, storms, droughts, heat waves and other extreme weather events. Floods affected the largest number of people, more than two billion, and droughts affected another 1.5 billion individuals [12]. In the same period, earthquakes killed nearly 750,000 people and storms, including tropical cyclones and hurricanes, killed 233,000 people. Single events can be devastating, as in the case of the 2008 earthquake in China, which killed nearly 70,000 people and injured nearly 375,000, with about 18,000 missing [13]. The number of children affected by natural disasters attributed to climate change is estimated to be more than 170 million per year, and the number of children seriously injured or dying each year as a result of such disasters is high but as yet undetermined [14]. Direct economic losses due to the sum of natural disasters are estimated at over $2900 billion. Climate-related disasters, which caused an estimated $23 trillion last year, or 77% of total economic losses, are responsible for economic hardship and poverty around the world, and at least 85 percent of the population that develops diseases due to climate change are children [12,15].

Finally, the pandemic outbreak caused by COVID-19, as in the two previous coronavirus disease outbreaks (SARS in 2002 and 2003, and Middle East respiratory syndrome in 2012 and 2020), has posed critical challenges for public health, research, and medical communities [3,7]. During epidemic events, children may be disproportionately affected compared to older age groups, as in the case of pandemic influenza 1-H1N1 [16].

Health and risks of exposure to environmental pollutants

In recent years, an increasing number of studies have been directed toward better understanding the possible correlations between environmental pollution and health status in the general population and especially in children. Indeed, children constitute a very sensitive population, especially in the early years of life, for several reasons: the amounts of air, water and food introduced into their bodies, per unit of body weight, are greater than those of adults; the blood-brain barrier is not yet fully mature, making them more susceptible to neurological damage. Their skin is more permeable; they spend most of their time at home, daycares, and schools and are more susceptible to contact with endocrine disruptors (EDCs) in the air; especially young children are often in contact with soil and floors and have a habit of sucking on toys or objects that may contain EDCs. In addition, during the developmental age, biological systems and organs are at different stages of maturation and functioning, which makes the detoxification system less effective.

It is therefore important that physicians, particularly pediatricians, receive more thorough and in-depth training in this area so that they can better do the job of properly informing families who come to them for guidance [17]. This action is also particularly important because surveys of population samples have confirmed a low degree of knowledge and awareness of the possible risks posed by pollution [17].

The effects of endocrine disruptors (EDCs) on children's health

Among environmental pollutants, a particular development has been research on EDCs, of which there are various definitions: the World Health Organization considers them to be exogenous substances or mixtures capable of altering the functions of the endocrine system and, consequently, of causing adverse effects in intact organisms or their offspring or in specific subpopulations. By this term, the world-leading Endocrine Society refers to exogenous (non-natural) chemicals or a mixture thereof that interfere with any aspect of hormonal action.

According to some estimates, 140,000 chemicals have been produced since the end of World War II, with an annual average of 1000–2000, of which about 800 are known or suspected to interfere with the endocrine system. However, only a fraction of them have been studied extensively and systematically.

EDCs are industrially produced substances found in everyday objects, clothing, drugs, some medical devices, disinfectants, foods and their containers, furniture and building materials, cosmetics and personal care products, toys, and with which both humans and animals often come into contact. EDCs can enter the body via the oral, respiratory and dermal routes. In general, the oral route is considered the most important because of the possible presence of EDCs in contaminated water and food, either through direct contamination or migration from so-called "Food Contact Materials" (FCMs), materials that come into contact with food during production, packaging, transportation, storage, processing in the kitchen, and the manner in which it is served [18]. Knowledge about the role of FCMs is still too scarce and needs to be deepened. However, it is important to say that about 175 chemicals that could migrate have been identified, and more than half of the additives allowed to be used in the United States do not have adequate toxicological studie [18].

We also need to increase our knowledge about transdermal access of EDCs. A recent review of known data on the use of parabens, contained in many cosmetics, concluded that a significant percentage of the population uses these cosmetic products in excessive amounts [19]. The authors suggested that it cannot be ruled out that excessive use of these cosmetics may lead to health damage, particularly in children, adolescents and infants, whose skin is more sensitive and in whom the use of these substances is estimated to be greater than in adults [19].

The mechanisms by which EDCs alter hormonal or homeostatic balance in general have been partly known for many years and partly the result of much more recent studies. Initially, research focused on the direct action that EDCs can play on hormone receptors in the cell nucleus, mimicking or antagonizing the effects of steroid hormones (estrogen and androgen). Much of the original work was thus focused on possible hyper-estrogenization on the one hand or hypo-androgenization on the other. A classic example is the so-called testicular dysgenesis syndrome, according to which reduced androgenic activity during fetal life is responsible for both anatomical abnormalities of the male external genitalia (hypospadias, cryptorchidism) and reduced fertility and an increased risk of testicular carcinoma in situ.

To this type of action, which always remains of primary importance, others have been added as studies have progressed. It has been shown that EDCs can also act on steroid receptors not present in the nucleus, on nonsteroid receptors, on so-called orphan receptors, and finally modify their concentration. In addition, they interfere with hormone synthesis and the binding of the endogenous hormone to the specific transport protein in the blood, contributing to its metabolization.

Interference on the enzymatic steps that characterize steroidogenesis and neurotransmitter synthesis has also been demonstrated. Regarding influence on neuro-cerebral development, which is a major current concern for fetal health, EDCs were initially thought to adversely affect the action of thyroid hormones, whose importance for normal brain development is well known. However, it is now believed that more than 80 percent of the action occurs through other pathways, and the term "endocrine and nerve disruptors" (ENDs) has been proposed to replace the previous definition of EDCs [20].

The definition of “metabolic disruptors” was also proposed because many ENDs have been associated with metabolic diseases such as metabolic syndrome, insulin resistance, and type 2 diabetes and are "obesogens." They may in fact act through various mechanisms on adipogenesis, pancreatic beta function, and hypothalamic neuropeptides that regulate both the hunger/satiety mechanism and energy metabolism. In particular, BPA is able to activate an important transcription factor (proliferator-activated receptor gamma, PPARγ) that is expressed in adipocytes, but also in macrophages, hepatocytes, and enterocytes, and regulates key endocrine-metabolic processes involving lipid and glucose metabolism and insulin sensitivity. In addition, an interaction with the gut microbiota has also been hypothesized that could act on immune mechanisms and create situations of dysbiosis that promote metabolic alterations.

Finally, a growing body of evidence indicates that EDCs are capable of altering the extensive epigenetic reprogramming action that takes place during early embryogenesis and cell specialization, contributing to increased susceptibility to typical adult "noncommunicable diseases" and, through an action on germ cells, paving the way for intergenerational transmission.

A common way in which contaminants enter the human body is through food. Food contaminants include environmental contaminants, food processing contaminants, unapproved adulterants, food additives, and migrants from packaging materials [20]. Generally, chemicals used for pest control or for cleaning and sanitizing food contact surfaces and food preparation equipment can contaminate food. Persistent organic pollutants (POPs) are a common and hazardous group of chemical contaminants that persist in the environment, bioaccumulate through the food web, and have the risk of causing adverse effects to human health and the environment (Table 1).

Table 1
Summary of most common persistent organic pollutants: associated contaminated food and health hazards.

Persistent organic pollutants (POPs)	Contaminated food	Possible hazards
Polyaromatic hydrocarbons	Dairy products, grain, flour and bran, rice, fruit and vegetables, oyster, water	Mutagenicity/ carcinogenicity, DNA damage, oxidative stress, impaired male fertility, respiratory diseases, cognitive dysfunction among children and cancer (breast cancer)
Organochlorine pesticide	Eggs, dairy products, meat and meat products, rice, fruit and vegetables, honey, oil, fish, mussel, water	Neurologic symptoms, endocrine disruption, infertility and fetal malformation, diabetes, cancer (breast cancer, testicular, prostate and kidney cancer), reproductive problems, cardiovascular problems, high blood pressure, glucose intolerance and obesity
Polychlorinated biphenyls	Eggs, dairy products, meat and meat products, rice, fruit and vegetables, oil, fish, mussel, water	Endocrine disruption, neurologic disorders, liver injury, diabetes, cancer (breast, prostate, testicular, kidney, ovarian and uterine), cardiovascular problems and obesity
Polybrominated diphenyl ethers	Fish, mussels	Reproductive problems, cancer (testicular), diabetes, obesity and cardiovascular problems
Perfluorinated compounds	Eggs, fish, water	Breast cancer
Hexabromocyclododecanes	Eggs, oil, fish	Endocrine disruption, reproductive problems and behavioral disorders
Polychlorinated naphthalenes	Meat and meat products	Cancers
Dioxins/furans	Eggs, dairy products, meat and meat products, oil, fish,	Language delay, disturbances in mental and motor development, cancer, diabetes, endocrine disruption, high blood pressure, glucose intolerance, and cardiovascular problems

(Modified from Pettoello-Mantovani M. et al., JPEDs, 2021; 229 (2): P315–316. E2).

POPs and endocrine disruption

Persistent organic pollutants are defined by the "Stockholm Convention" (2004) as a group of chemicals that share common characteristics such as resistance to biological degradation, environmental persistence, bioaccumulation in the food chain due to strong lipophilicity, and storage in adipose tissue. A major source of exposure to POPs is food, particularly fatty animal products such as meat, fish, milk and dairy products. In addition, internal (endogenous) exposure is also possible, as POPs are stored primarily in adipose tissue and released slowly into the circulation to be excreted over several years [21]. The negative effects of chronic exposure to low levels of POPs are related to their ability to act as endocrine disruptors (i.e., substances that can affect, for example, sexual development and reproduction through estrogenic and/or anti-androgenic properties) [22]. Another negative effect of these chemicals could be their ability to promote obesity [23].

Adipose tissue should be considered an important protective organ against POPs, as it is a relatively safe organ for their accumulation, and storage of these chemicals in adipose tissue may reduce their hazard on other organs [24]. POPs accumulated in adipose tissue are released slowly and then eliminated from the bloodstream. However, if the amount of POPs released into the circulation increases, the body may not metabolize these chemicals efficiently, and they may have a greater chance of reaching critical organs. In fact, it has been suggested that weight reduction may result in increased levels of POPs in the bloodstream [25]. These chemicals are obesogenic endocrine disruptors,

therefore they could increase the risk of weight regain and weight cycling and, in turn, promote the development of cardiometabolic complications [26]. Because of the obesogenic action of these chemicals and the risk of reverse causality in studying the association between POPs and obesity, it is important to conduct longitudinal studies.

Lack of studies on childhood obesity and POPs

It is very important to consider the role of POPs in obesity and related obesity research, as adipose tissue is extensively contaminated with these chemicals [24]. However, there is a lack of studies that consider their levels in relation to childhood obesity. Assessing concentrations of these endocrine-disrupting chemicals in children would be an important achievement, as it appears that exposure in the early years of life can lead to alterations that are transmitted into adulthood and cannot be reversed [23]. Endocrine disruptors could be particularly harmful in children because, in addition to increased risk of obesity, they are associated with adverse neurobehavioral outcomes and impaired pubertal development [26]. In addition, evidence suggests that exposure to these environmental chemicals early in life is associated with an increased risk of metabolic diseases during childhood [27]. The mechanism by which POPs may alter metabolism in children is still far from being fully understood, although important data are available. In cultured cells and rats, exposure to POPs alters mitochondrial function and increases oxidative stress [24]. It is also known that mitochondrial dysfunction is the central abnormality that causes insulin resistance and cardiovascular disease [25]. Therefore, to carry out future investigations in this area of POP activity, it would be important to clarify the association between POP and mitochondrial dynamics in obese children.

Focusing research on phthalates, PFAS, bisphenol A, triclosan and related chemicals

Among POPs with endocrine disrupting properties, it would be particularly important to focus on molecules that are widespread in the environment and expose the general population. Specifically, phthalates (found in food packaging, fragrance preservatives in personal care products, excipients in pharmaceuticals, and more), perfluoroalkyl substances (PFAS) (found in water-resistant coatings in nonstick cookware and food container linings), bisphenol A (BPA) (found in polycarbonate plastics, resins, food cans and more) and triclosan (found in antimicrobial soaps, personal care products and toothpastes). These chemicals are used in a wide variety of consumer products. They can interfere with the action, metabolism, or synthesis of hormones. In particular, there is evidence that some phthalates can inhibit the enzyme that can inactivate cortisol [24], reduce testosterone production at the testicular level [28] and affect levels of some thyroid hormones [26]. BPA can affect androgen and estrogen concentrations and increase thyroxine levels, PFAS can increase glucocorticoid concentrations [28], inducing changes in thyroid function and promoting changes in the metabolism of cholesterol, which is a precursor to several hormones [28]. Finally, animal studies have shown that triclosan can decrease testosterone production [28] and reduce thyroxine concentrations. However, it should be noted that most of these findings have been obtained only in animal studies, while clear evidence in humans is still lacking. Furthermore, previous epidemiological studies conducted in humans also have some limitations, as most of them evaluated the effect of single compounds, while exposure to environmental pollutants includes several chemicals; therefore, future studies should consider mixtures of different POPs [29].

Conclusions

The entire period of growth and development is considered critical with respect to adulthood, but in recent years a particular focus has been on fetal life [11]. Indeed, the presence of certain categories of EDCs has been demonstrated at various times during pregnancy in maternal blood, urine and hair. At the placental level they can affect normal development and endocrine function and promote inflammatory reactions. Their transplacental passage has also been documented, which may occur passively or through specific transport modes that have not yet been elucidated [30,31]. Differences noted between maternal and fetal concentrations suggest that no more than 20 percent of the substances studied are metabolized by the placenta [30,31]. This may result in alterations in the course of pregnancy (miscarriages), maternal pathologies (preeclampsia and gestational diabetes), and, at the fetal level, alterations in the development of the male genital apparatus, as mentioned above, decreased pre- and postnatal growth, epigenetic alterations, and damage to neurocerebral development12.

The impact of EDCs on children's health is strong, and knowledge about the mechanisms of action of these contaminants is still insufficient. Pediatricians should receive training in environmental health, as they can play a central role in the collective effort to address climate change and environmental pollution as one of the greatest global health threats of the 21st century. This would include taking preventive actions in the face of uncertainty, exploring a wide range of alternatives to possibly harmful actions, and increasing public participation in decision-making. Finally, pediatricians must take an active role in recognizing diseases associated with climate change and environmental pollution and develop early warning systems useful for improving prevention and developing important mitigation strategies [32].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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