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The impact of the endocrine disruptors on child health

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ABSTRACT

During recent years, Endocrine Disruptor chemicals (EDCs) have been the subject of particular attention because they are ubiquitous and able to cause adverse effect in humans, and particularly in children. Substances capable of interfering with the normal activity of the endocrine system can be of both man-made and natural origin. They often come into contact with the body through diet, water, air or skin. However, although the body is continuously exposed to their action, it is difficult to fully quantify the negative effects of these substances. Available data show that individuals most exposed to endocrine disruptors more frequently have cancers, reproductive, (ie: infertility, endometriosis, miscarriage.), metabolic (ie: diabetes) and/or immune disorders. Behavioral and developmental disorders are also observed in children exposed to Endocrine Disruptors. The presence of EDCs has been demonstrated during pregnancy in maternal blood, urine, and hair. At the placental level, EDCs can affect normal development and endocrine function and promote inflammatory reactions. The aim of this brief narrative review is to raise the attention of general pediatricians on the most prevalent multiple or interconnecting risks caused by EDCs to children's health by summarizing the existing knowledge on these toxic chemicals. Authors also report the effort made by the European Union to develop an effective Hazard Control Decision Support System which aim is to improve risk-based procedures able of detecting, monitoring and managing toxic substances in food chain.

1. Introduction

During the 20th century, the chemical industry has synthesized more than 140,000 molecules[1] and about 60,000 chemical products of industrial origin are currently marketed in the world.[2] Many of these contain substances for which an actual or potential ability to interfere with the endocrine system has been demonstrated. During recent years, such substances, referred to as Endocrine Disruptor chemicals (EDCs) have been the subject of particular media attention because they are ubiquitous in people's daily lives.[3] They are found in food, clothing and furniture, but also in the air and water children normally breath and drink, and often come into contact with skin. However, although the body is continuously exposed to their action, it is difficult to fully quantify the negative effects of these substances.[4] Available data show that individuals most exposed to endocrine disruptors more frequently have cancers, reproductive conditions, (ie: infertility, endometriosis, miscarriage.), and develop metabolic (ie: diabetes) and/or immune disorders.[5] Most importantly several studies have emphasized that EDCs may have severe effects at a neurological and cardiovascular level.[6,7,8,9]

Behavioral and developmental disorders are observed in children, as hormones are essential for cognitive and sexual development.[5] Indeed, children represent a very sensitive population, particularly in the early years of life. That is for several reasons, including the amounts of air, water, and food, which introduced into their bodies, per unit of body

Abbreviations: Edcs, Endocrine disruptor chemicals; who, Worlds health organization; eu, European union; eas, Endocrine active substances; fcms, Food contact materials; fda, Food and drug administration; sccs, Scientific committee on consumer safety; pops, Persistent organic pollutants; bpa, Bisphenol a; dehp, Diethylhexylphthalate; pvc, Polyvinyl chloride; bbzp, Butylbenzyl phthalate; pfas, Perfluorooctane sulfonate; pfoa, Pperfluorooctanoic acid ammonium salt; pcbs, Polychlorinated biphenyls; PBDEs, Polybrominated diphenyl ethers; PAHs, Polycyclic aromatic hydrocarbons; DDT, Dichloro-diphenyl-trichloroethane; CPF, Chlorpyrifos; DES, Diethylstilbestrol.

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weight, are greater than those of adults are. In addition, the blood-brain barrier is not yet fully mature, which makes them more susceptible to neurological damage. Skin is also a most common object of contamination in children.[5] Contaminants are frequently introduced in the body of children, in particular in infants, because their skin is more permeable than in adults. Children spend most of their time in homes, daycare centers and schools and are more susceptible to contact with airborne EDCs. Especially toddlers are often in contact with soil and floors and are in the habit of sucking on toys or objects that may contain EDCs. Finally, during developmental age, biological systems and organs are at different stages of maturation and function, which makes the detoxification system less effective.[3,4]

In general, the entire period of growth and development is considered critical with respect to adulthood, but in recent years the focus has been particularly on fetal life.[5,10,11] In fact, 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, EDCs can affect normal development and endocrine function and are able to promote inflammatory reactions.[11,12,13,14] Their transplacental passage has also been documented, which can occur either passively or through specific modes of transport that are still not fully clarified. The differences noted between maternal and fetal concentrations suggest that no more than twenty-five percent of the substances studied are metabolized by the placenta.[11] So, it is possible that such contaminations may cause alterations in the pregnancy course and be responsible for miscarriages and maternal pathologic conditions, such as pre-eclampsia and gestational diabetes. Finally, at the fetal level EDCs can generate developmental alterations in the male genital system, decreased pre and postnatal growth and induce epigenetic alterations and damage in neuro-cerebral development.[11,12,13,14]

Surveys of population samples have confirmed a low degree of knowledge and awareness of the possible risks posed by pollution and the possible consequential contamination by EDCs in early ages.[5,10,11] It is therefore important that physicians, in particular pediatricians, receive more accurate and thorough training about the risks of chemical contaminations, so that they will be able to best perform primary prevention and correctly inform families and caretakers about important forms of hazards for children's health, including EDCs.[3,4] Thanks to the available data it is currently becoming easier to understand how to avoid contact with these substances and to take legislative action to reduce their use.[3]

The aim of this brief narrative review is to raise the attention of general pediatricians on the most prevalent multiple or interconnecting serious risks caused by EDCs to children's health by summarizing the existing knowledge on these toxic chemicals. Finally, this article reports the effort by the European Union to develop an effective Hazard Control Decision Support System to improve risk-based procedures able of detecting, monitoring and the managing biohazards.

2. Methods

This is a brief narrative review that focuses on EDCs and their toxic effects in humans, emphasizing the impact of EDCs on children's health. Article selection was performed using established methods as described elsewhere.[15,16,17] In particular, for this review authors followed the principles, rationals and methods described in the international Melbourne criteria for systematic reviews for health sciences and medicine.[17] In this article the authors summarize key information on EDCs obtained from scientific articles published during the past 20 years, including original studies, systematic review and meta-analysis. Articles search was performed using top academic search engines.[17] Used search engines included the classic academic databases Web of Science, Scopus and PubMed, the search engine of the United States National Library of Medicine. Additional search engines were also used, which included Google Scholar that covers approximately 200 million articles, Science.gov which offers access to search results from more than 15 U.S. federal agencies, covering approximately 200 million articles and reports and Core that is an academic search engine dedicated to open-access research papers that covers approximately 136 million articles. Search words used included "endocrine disrupting chemicals", child/children, pediatric/pediatrics, health, hazard and all chemicals listed in the abbreviations section. Inclusion criteria involved all peer-reviewed articles published in English language, limited to child studies and published since 2003 (20 years). There was no geographical limitation for the articles considered for the review.[17]

3. Endocrine disruptors: Definition and characteristics

Endocrine disruptors are chemical compounds, which function as mimics of authentic agonist or antagonist ligands to endocrine receptors in animals[5] and are able to inhibit the actual functions of endocrine units of animals/humans. The Worlds Health Organization (WHO) considers EDCs to be exogenous substances or mixtures thereof that can alter the function(s) of the endocrine system and consequently causing adverse effects in humans or in specific sub-populations, which in certain conditions are particularly exposed to the risk of contamination.[18] The Endocrine Society by the term of EDCs refers to exogenous, nonnatural chemicals or a mixture of them that interfere with any aspect of hormonal action in humans.[3,4,19] Similar effects have also been observed in other animal species. Disrupting chemicals are effective in extremely low concentration ranges (picograms to nanograms per liter in blood) when they enter cells.[5,10,20]

Hormones are substances produced in the endocrine system that regulate many activities in the body. Endocrine active substances (EAS) are molecules that can intervene in these production and regulatory processes. Those that have adverse health effects are called endocrine disruptors or endocrine disrupters.[11,19] They generally cause disturbances in development, reproduction, metabolism, and behavior in various animal species, including humans.[11] Substances capable of interfering with the normal activity of the endocrine system can be of both natural and man-made origin.[21,22,23] Natural endocrine disruptors include hormones produced by the body (such as estrogen and testosterone) and substances of plant origin that mimic their action, as in the case of phytoestrogens. They are sometimes used in drugs and phytochemicals, in controlled doses, to treat endocrine disorders (such as in hypothyroidism or birth control pills) .[21,2,23] Man-made endocrine disruptors may be byproducts of human activities or be synthesized on purpose. Those originating incidentally can result from industrial and combustion processes (e.g., from the incineration of substandard waste). Those purposefully produced are used in industry, for agricultural use (such as pesticides), or for consumer materials (e.g., plasticizers), so they can also be released into the environment from household discharges.[21,22,23]

According to some estimates, since the end of World War II an annual average of 1000–2000 chemicals have been produced, of which about 800 are known or suspected to be endocrine disruptors.[4] However, only a fraction of them has been extensively studied. They are mainly industrially produced substances to which often are also added natural substances such as phytoestrogens that also have adverse effects on the endocrine system when used in high dosages. Industrially produced EDCs can be found in everyday objects, clothing, drugs, some medical devices, disinfectants, foods and their containers, furniture and building materials, personal care products and toys with which both humans and animals often come into contact. The wide use of EDCs in various sectors may explain their environmental spread in the atmosphere, water, including seas and oceans, and soil.[21,22,23]

4. Endocrine disruptors in the environment

EDCs are normally classified into persistent and non-persistent EDCs.[20] Characteristics of non-persistent EDCs, which are not the focus of this brief review, are their short half-lives and rapid metabolism.

They include phenols parabens, phthalates, and organophosphate pesticide. This types of non-persistent EDCs are present in several products commercially available to consumer, including sunscreen lotions (phenols) given their property to filter UV light, and frequently used as plasticisers (phthalates).[20] Children are often exposed to the hazard of non-persistent EDCs because they have frequent contact with potentially contaminated soil and dust and the frequent and direct hand-to-mouth or object-to-mouth route of contact.[20]

Persistent EDCs present a particular risk for children as they are exposed to low doses of these chemicals and their mixtures for long periods (days, month and years), with different effects which depend upon various factors including the dose and the presence of other chemicals. Exposure to EDCs during pregnancy, infancy and childhood may significantly distress the health and development of a child for the rest of his/her life. The impact of persistent EDCs on the environment can be considerable if one takes into account their ubiquitous presence and their persistence, as well as their potential effects on living things. The main sources of environmental risk from EDCs include behaviors non-compliance with current legislation, processing and disposal processes industry and the improper disposal of products containing plastics, such as glues, paints, and other. EDCs characterized by high environmental persistence have greater ability to accumulate in organisms. EDCs may contaminate the food chain at different stages and may transfer from one organism to another, resulting in increased concentrations along the food chain, potentially causing severe effects on children's health, which are reported in a later section of this review discussing the single main EDCs.[24] Controls on the use of EDCs are stringent in several countries. In the European Union, the 7th Environment Action Programme, adopted in 2013 by the European Parliament and the Council, provides for the harmonization of hazard-based criteria for the identification of endocrine disruptors and for the issuing of regulations for single chemical substances that have been identified as endocrine disruptors.

5. Mechanism of action and entry routes

Endocrine disruptors can modify signals normally sent by hormones. Typically, the endocrine disruptor is a hormone-like molecule. Because receptors function like locks and respond only to certain forms of hormones it is possible for the receptor of a hormone to bind with the endocrine disruptor. In this way, the hormone cannot gain access to the receptor. Instead, the endocrine disruptor is able to access the "natural" hormone, resulting in greater or lesser activation of its normal mechanism.[20,21,22,23] However, they can also act at other points in the process of regulating hormone activity. In general, endocrine disruptors can act in different ways:

(a) mimicking the action of the hormone naturally produced by the body, inducing an excessive or mistimed response (agonist effect);
(b) blocking the receptor, that is, by preventing the hormone from binding to it so that it cannot act (antagonistic effect);
(c) altering the regulation of hormone production and acting "upstream" of hormone production;
(d) altering the transport of hormones in the bloodstream.

EDCs reach our bodies mainly by oral, respiratory and dermal routes. In general, the oral route is perceived as the most important, due to the possible presence of EDCs in contaminated water and food either through direct contamination or migration from so-called "Food Contact Materials (FCMs)," that come in contact with food during production, packaging, transportation, storage, food processing in the kitchen and the manner in which food is served.[3,25,26,27] However, knowledge is still insufficient about the role of FCMs in the endocrine disruption activity of toxic chemicals and there is a need to investigate this further. Over 175 chemicals that could migrate and cause adverse effects in humans have been currently identified. However, approximately more than half of the additives allowed to be used in the U.S. and Europe, currently lack appropriate toxicological studies.[3,22,23,28]

In the atmosphere, chemical contaminants come from waste combustion, automobile emissions, the volatilization of pesticides and herbicides, the use of cosmetic sprays, and the adherence of EDCs to dust and particulate matter. They have been most frequently detected in both outdoor and indoor air in homes and educational institutions. Indeed, recent preliminary research in France has shown non-negligible rates of some EDCs, including phthalates, in schools.[22,23,28]

In water, EDCs can be present both in wastewater from homes, hospitals, commercial, agricultural, and industrial facilities (partly because filtration systems are not always able to remove them) and in clear surface and deep water. In the seas and oceans, the presence of flame retardants has been identified not only in seawater but also in sediments along coastlines and in all ocean sediments from the Pacific to the Arctic Sea.[29]

Transdermal passage is also a common route of entry.[30,31] However, the knowledge regarding the interactions between the skin and the EDCs seems to be still incomplete and further studies are needed, such as in the typical case of parabens.[32] They are a class of preservatives used mainly in cosmetics but also in drugs and some foods. They belong to the category of parahydroxybenzoates or esters of parahydroxybenzoic acid and have antibacterial and antifungal properties. That is why they have been widely used for more than 70 years to ensure that shampoos, creams, toothpastes and some foods do not become breeding grounds for bacteria and fungi, by remaining open and in use for a long time.[32,33] Experiments with laboratory animals have shown that parabens have mild estrogenic activity, acting like female hormones naturally produced by the body. A recent review of known data on the use of parabens, which are contained in many cosmetics, shows that a significant percentage of the population uses these cosmetic products in excessive amounts.[32,33] Therefore, it cannot be ruled out that this leads to health damage. That is a problem particularly for children, adolescents and infants whose skin is especially sensitive and because the use of these substances is estimated to be greater than in adults.[4] However, the degree of their toxicity remains unclear, and the Food and Drug Administration (FDA) and the European Union's Scientific Committee on Consumer Safety (SCCS) although recording data from the literature that show their adverse effects ion humans, report that there is no solid evidence so far that parabens are unsafe.[33]

Finally, in soils they are present because they are deposited through displacements in the atmosphere, or by dispersion of improperly collected and recycled wastes or, in croplands, from pesticide residues.

6. Main EDCs affecting children's health

Substances that can act as endocrine disruptors are still being studied. At present we know of about 800 of them. The most common, as well as the most controlled, endocrine disruptors are mainly found in plastics, building materials, combustion products and pesticides, but they are also produced naturally by some organisms. Most of these substances are included in the generic definition of Persistent Organic Pollutants (POPs), which describes a group of organic compounds that have toxic properties, persist in the environment, accumulate in food chains and pose a risk to children's health and the environment.[34] A summary of main persistent organic pollutants (POPs), the food they contaminate, and the major health hazards caused by POPs are reported in Table. The main endocrine disruptors are listed below with a brief description of their toxic profile.

6.1. Bisphenol a (BPA)

Bisphenol A is an aromatic compound that is a precursor to some plastics and chemical additives.[35] It is used in the production of polycarbonate plastics that are popular for their transparency, heat and

Table
List of food contaminated by most common organic pollutants (pops) and their potential hazards to health.

Pops	Potential hazards to health	contaminated food
Perfluorinated compounds (PFCs/PFOS and PFOA)	Breast cancer	Eggs, Fish, Water
Organochlorine pesticide (OCPs)	Neurological 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	Eggs, Dairy products, Meat and meat products, Rice, Fruit and vegetables, Honey, Oil, Fish, Mussel, Water
Polyaromatic hydrocarbons (PAHs)	Mutagenicity/ carcinogenicity, DNA damage, oxidative stress, impaired male fertility, respiratory diseases, cognitive dysfunction among children and cancer (breast cancer)	Dairy products, Grain, flour and bran, Rice, Fruit and vegetables, Oyster, Water
Hexabromocyclododecanes (HBCDs)	Endocrine disruption, reproductive problems and behavioral disorders	Eggs, Oil, Fish,
Dioxins/furans	Language delay, disturbances in mental and motor development, cancer, diabetes, endocrine disruption, high blood pressure, glucose intolerance and cardiovascular problems	Eggs, Dairy products, Meat and meat products, Oil, Fish,
Polychlorinated biphenyls (PCBs)	Endocrine disruption, neurological disorders, liver injury, diabetes, cancer (breast, prostate, testicular, kidney, ovarian and uterine), cardiovascular problems and obesity	Eggs, Dairy products, Meat and meat products, Rice, Fruit and vegetables, Oil, Fish, Mussel, Water
Organochlorine pesticide (OCPs)	Neurological 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	Eggs, Dairy products, Meat and meat products, Rice, Fruit and vegetables, Honey, Oil, Fish, Mussel, Water
Polychlorinated naphthalenes (PCNs)	Cancers	Meat and meat products

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

mechanical resistance properties and utilized in food containers and in epoxy resins that provide internal protective coating in most food and beverage cans, including infant feeding bottles. Bisphenol A is also used in thermal receipt paper, in aluminum can linings to reduce corrosion, and dental devices. It can alter thyroid, reproductive, nervous and immune system activity. BPA has the molecular characteristics of an obesogenic substance. It enlarges fat cells, disrupts the adiponectin, and function as a synthetic estrogen. Infants and fetuses are particularly vulnerable, which is why the use of BPA is banned in baby bottles and other baby products.[35] Its use is regulated by the European Commission Regulation (EU) 321/2011 of April 1, 2011 amending Regulation (EU) 10/2011 regarding restrictions on the use of Bisphenol A in plastic baby bottles, which clearly states "Bisphenol A: not to be used in the manufacture of polycarbonate infant feeding bottles."[27]

6.2. *Dioxins*

Dioxins are environmental pollutants. More than 90% of human exposure to dioxins is through the food supply. Fatty foods such as meat, poultry, seafood, milk, egg and their products are the major dietary sources of dioxins. Accidental exposure to large amount of dioxins could lead to the development of chloracne, a skin condition, excessive body hair and other skin lesions such as skin rashes and skin discolouration. They result from herbicide production, paper bleaching, forest fires and waste incineration. State-of-the-art technologies make it possible to minimize the release of dioxins into the environment and prevention or reduction of human exposure is best done via source-directed measures, such as a strict control of industrial processes to reduce formation of dioxins. Regarding regulations on the presence of dioxin in food, maximum levels and action thresholds related to dioxins and polychlorinated biphenyls are set out in Commission Regulation (EU) 2017/644 of April 5, 2017. This regulation lays down methods of sampling and analysis for monitoring levels of dioxins, dioxin-like PCBs, and non-dioxin-like PCBs in certain children's foodstuffs and repealing Regulation (EU) No 589/2014.[27]

6.3. *Phthalates*

Among phthalates, Diethylhexylphthalate (DEHP) is an important example of ubiquitous environmental pollutant.[36] They are widely used as plasticizers because their presence in the plastic material (especially polyvinyl chloride, PVC) makes it more flexible and expandable, improving the use of the objects from which it is made. They are found in films of various kinds, in building materials such as paints, floor coverings, pipes and cables. It can be also found in containers such as disposable bottles, films, trays, blister packs, crown caps, and transport packaging They have a variety of uses as lubricants, antifoaming agents, solvents, and in hygiene and personal care products such as nail polishes, hair sprays, cosmetics, perfumes. Finally, they may be present in pesticides and even in the gastro-resistant coating of drugs.[37] This endocrine disruptor mainly affects the reproductive system, decreasing fertility, and the metabolic system, possibly predisposing to diabetes and obesity. Recent studies performed in Asia, Europe, and the US suggest that childhood exposure to DEHP and butylbenzyl phthalate (BBzP) may increase the risk of allergic diseases including asthma and eczema. Other studies from four different prospective cohorts report that gestational BBzP, DEHP, di-butyl phthalate (DBP), and di-ethyl phthalate (DEP) exposures are associated with alterations in infant/toddler physical development as well as parent-reported externalizing, internalizing, and autistic-like child behavior.[33] In Europe, its use is increasingly reduced and regulated. For example, it is now strictly banned in toys. In fact, its use is regulated by Commission Regulation (EU) 10/2011 of January 14, 2011, and (EU) 143/2011 of February 17, 2011 on plastic materials and articles intended to come into contact with food. Phthalates DEHP are included in the list of substances requiring authorization. Regarding food contact materials, Regulation (EC) No. 1935/2004 sets out the general requirements they must meet.[27]

6.4. *Perfluorooctane sulfonate (PFAS) and perfluorooctanoic acid ammonium salt (PFOA)*

These are two persistent chemical compounds that are increasingly prevalent in the environment.[38] According to EFSA's Panel on Contaminants in the Food Chain, some foods (particularly seafood) appear to be an important source of exposure to these contaminants. However,

other "non-food" sources of PFOAs also contribute to total exposure, such as indoor pollution through dust and air contaminated by products treated with perfluorinated compounds (PFCs). These chemicals can accumulate and it takes years before they are eliminated, thus representing a serious hazard to people's health.[38,39] Therefore, high or prolonged exposure to PFOS and PFOA can have harmful health consequences, especially to the liver, thyroid and even fertility. Animal and human studies suggest that PFCs may alter sexual maturation.[38,39] PFOA has in the past been used in the production of nonstick coatings (ie: food cooking equipment). Currently, European cookware companies no longer use coatings produced with PFOA. Therefore, consumers should turn their attention to products from countries outside Europe, especially if they lack the CE mark.[38,39] PFOS and its derivatives are included, by Regulation (EU) 757/2010, in the list of persistent organic pollutants (POPs) .[27] The production, placing on the market and use of PFOS either in its pure state or within preparations or articles is prohibited. There are exemptions for very limited uses, subject to periodic reviews, and specific rules for the management of PFOS-containing wastes. PFOA is included in the European Commission Recommendation of March 17, 2010 on the control of perfluoroalkyl substances in food. Decisions 2009/544/EC and 2009/543/EC, dated August 13, 2008, establish the ecological criteria for the Community eco-label standards for indoor and outdoor paints and varnishes. Regulation (EC) No. 1935/2004 establishes the general requirements that food contact materials must meet. In particular, the standard stipulates that these materials must be produced in accordance with good manufacturing practices and, under normal conditions of use and must not transfer components to food in quantities that pose a danger to human health.[27]

6.5. Polychlorinated biphenyls (PCBs)

PCBs are used as thermal and electrical insulators, particularly in building materials, lubricants and plasticizers.[40] They are banned in most of the world, but are sometimes still detectable in some foods and breast milk because they are persistent, that is, difficult to dispose of. These environmental pollutants are among the most toxic of anthropogenic pollutants. The origin in the environment of dioxin-like compounds can be very different. PCBs were produced and used massively in industry approximately until the 1980s. The characteristic of their environmental persistence has allowed them to accumulate in the environment to levels that are harmful to humans and other living things. The main exposure occurs through food, and in particular, fish, dairy products and meats represent the most contaminated foods.[40,41] These compounds accumulate in fatty tissues and are released at certain physiological times including lactation. Exposure in utero and postnatal exposure through breast milk can lead to alterations in the reproductive, immune and nervous systems, with consequences that may persist into adult life.[41] In addition, as also highlighted by recent studies on the sexually immature female rat and a mother-newborn cohort in Taiwan attention should also be given to the effects of dioxins on thyroid function.[41] Their presence in the environment is regulated by Council Directive 85/467/EEC of October 1985 amending for the sixth time (PCBs/PCTs) Directive 76/769/EEC addressing the unclarity of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations.[27]

6.6. Polybrominated diphenyl ethers (PBDEs)

PBDEs show a bioaccumulation capacity not unlike PCBs.[42] They are mainly from flame retardants and can be found in draperies, furniture, carpets and polyurethane fillings (such as mattress and seat foams), also contaminating dust in homes. PBDEs are included in the list of persistent organic pollutants, and some are particularly persistent and difficult to be disposed. So that they can accumulate in the bodies of animals, and therefore in food. PBDEs accumulate in the fatty tissues of organisms and can interfere with the endocrine system. They alter in particular the thyroid function and impact the neurological and neurobehavioral development. In addition, their chemical stability results in bioaccumulation in the food chain, which can lead to high concentrations of these substances in some foods.[42] Their use is regulated by Directive 2003/11/EC of the European Parliament and of the Council of February 6, 2003, amending for the 24th time Council Directive 76/769/EEC related to the restrictions on the marketing and use of certain dangerous substances and preparations.[27]

6.7. Polycyclic aromatic hydrocarbons (PAHs)

Normally, PAHs are a product of combustion, resulting from the reaction to oxygen that produces a high degree of energy, usually in the form of a flame.[43,44] Typically, they are produced in industrial settings. Therefore, significantly contributing to air pollution. However, PAHs come not only from industrial air pollution, but also from other sources such as cigarette smoke, cooking smoke, incense burning, and candle smoke. To avoid exposure, lifestyle and diet are of great importance. In fact, PAHs are formed during high-temperature cooking as food is charred. They are contained in foods that are barbecued or fried, roasted or smoked, but also baked. There are many PAHs, of which about 15 are considered toxic. Exposure to PAHs produces genotoxic and carcinogenic effects by increasing the risk of cancers associated with hormone imbalances, such as postmenopausal breast cancer and prostate cancer, and the occurrence of lung cancer among nonsmokers. Prenatal exposure to PAHs is associated with an increased risk of low birth weight.[45] Their use is regulated by European Commission Act (EU) 835/2011 of August 19, 2011, which amends Regulation (EC) 1881/2006 with regard to the maximum levels of polycyclic aromatic hydrocarbons in foodstuffs. In addition, European Commission Regulation (EU) 231/2012 of March 9, 2012, establishes specifications for food additives listed in Annexes II and III of Regulation (EC) 1333/2008, which includes PAH.

6.8. Other common endocrine disruptors

6.8.1. Pesticides

They are also referred to as agrochemicals and generally divided into classes according to the purpose of their use. The most important are those of herbicides, insecticides, fungicides, and rodenticides. The former are mainly used in agriculture while the latter have a wider use including domestic, commercial and industrial environments and means of transportation. They include, a) dichloro-diphenyl-trichloroethane (DDT) which particularly impact food chain. Although its use has been banned for a long time, it is still used in some countries and traces of it can still be found given its long environmental permanence; b) Chlorpyrifos (CPF), a widely used pesticide, although its use has also been strictly regulated. It interferes with the nervous system and the thyroid gland.[42] This pesticide has been the subject of a multi-year legal battle that recently led to its suspension for agricultural use in the U.S. and the marketing ban in France and Austria. It is an example of the difficulty in finding a balance between production, scientific research and legislative authorities, although public health is in stake.[22,23,24]

6.8.2. Perchlorates

They are waste products from the aerospace, weapons and pharmaceutical industries as well as fireworks. They can be found in water and the animals that live in it and therefore contaminate those animals that enter in the food chain.[22,23,24]

6.8.3. Phytoestrogens

These substances are produced by plants, and have a structure similar to estrogens Therefore, once in humans bodies they can have effects similar to these. Foods containing phytoestrogens (isoflavones,

coumestans and lignans) include legumes, fruits and vegetables. In particular, soybeans are rich in them and contain more than 100 different types. Studies show that phytoestrogens have several positive effects: they reduce menopausal symptoms and have a protective effect for some types of cancer. However, it has been reported that excessive amounts of phytoestrogens interfere with estrogen activity, amplifying or reducing it, with potential negative effects on the body. For example, an excess of phytoestrogens could result in early sexual development in girls. This phenomenon is still being studied.[22,23,24]

6.8.4. Triclosan

This substance has antimicrobial activity, so it has long been used in personal hygiene products and dish soaps, as well as in kitchen utensils, toys, and textiles. However, it has two main downsides. Like all antimicrobial products, it can fuel the phenomenon of antibiotic resistance, or the ability of bacteria to survive the action of antibiotics. In addition, triclosan is difficult to be disposed and it accumulates in water and agricultural soils. In several species, including ours, it turns out to cause irritation and contact dermatitis and reproductive and immune system problems.[22,23,24]

6.8.5. Thiocyanates

Highly present in cigarette smoke and in some vegetables, particularly cabbage, they can interfere with thyroid action.[22,23,24]

6.8.6. Organotin compounds

Derived from pesticides, they cause problems especially to marine organisms by interfering with their reproductive organs and thus with their life cycles.[22,23,24]

6.8.7. Diethylstilbestrol (DES)

It mimics the action of estrogens. It was used around the 1950s in the U.S. as an antiabortive. That use was discontinued because it showed serious consequences in many women, including malformations of the uterus and adverse effects on fetus. Today it is prescribed only for the treatment of certain diseases, such as prostate cancer[22,23,24]

6.8.8. Heavy metals and semimetals

Examples of these include lead, mercury, nickel, and arsenic. They are usually present in minute amounts in water and food but can also be found in clothing.[22,23,24]

7. Endocrine disruptors and food: the European Union perspective and regulations

From a health perspective, food safety relates to the integrated environmental supply chain.[1] In the legal understanding, food is defined as any processed, partially processed, or unprocessed substance or product intended to be ingested, or reasonably expected to be ingested, by human beings.[2] However, the precise definition of food safety is still not so unambiguous, and in the countries of the European Union (EU), the closest notion is that of "food at risk",[46] which is covered in Article 14 of European Regulation EC 178/20,22[3]. Interest in endocrine disruptors is growing, as they are considered substances of high public health concern and an increasing number of molecules are being investigated and are object of attention by the EU authorities. Analytical methods are complex, partly under current development and time-consuming, but regulations are very strict and released in a timely manner.[48–50]

To date, there are about 300 substances suspected of interfering with the endocrine system and currently under investigation by the European authorities. The presence of EDCs in food has been heavily regulated in Europe since 1999, which rules have been implemented in 2012 and currently progressively updated. Among the most important measures is the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Regulation, No. 1907/2006, updated in 2020, which affects manufacturers and importers of chemicals.

The European Community has drafted specific regulations regarding the use of specific substances, pesticides and biocides, water, medical devices and materials that come into contact with food, cosmetics and toys. In addition, specific regulations guarantee the protection of people in the workplace and of children in school. The strategy to reduce European citizens' exposure to endocrine disruptors includes support for research on the topic, review of substances according to the guidelines for endocrine disruptor investigation methods (defined by the OECD, Organization for Economic Cooperation and Development), and promotion of endocrine disruptor substitution with chemically inactive materials.[47,48,49]

8. Conclusions

Environmental problems affecting health protection are often addressed by prioritizing the most urgent aspects such as air pollution, brought about by emissions from industrial or residential settlements and from excessive use of vehicles especially in cities. These are aspects that are easily perceived by citizens and therefore the subject of various forms of protest that force the authorities to take measures that can be detected by everyone. Little effort, on the other hand, is given to substances that daily undermine our health in less commonly detectable, however highly harmful forms. That is the case of POPs, which although scarcely detectable, are able of causing serious and very often irreversible damage to various living organisms. The European Union is strongly engaged in supporting research programs aiming at developing systems able to effectively monitor the presence of contaminants in infants and children's food. In particular, those chemicals that cause endocrine disruption. One of the main research programs funded by the EU is the Horizon 2020 is "Safe Food For Infants" program (SAFFI), which focuses on infant food.[50] The results expected from SAFFI will contribute to the protection of this particularly vulnerable population from unforeseen contaminants, including the endocrine disruptors, through predictive toxicology. The central object of this European Union program is to provide stakeholders involved in food safety with an effective Hazard Control Decision Support System. Such system will be able to improve risk-based food safety monitoring and the management of biohazards from primary production to the consumer throughout the food chain. Finally, it is important that healthcare professionals and in particular general pediatricians be adequately informed on the risks associated with food contaminants, including, most importantly the negative effects of endocrine disruptors on children's health.[51] The ability to prevent undesirable health effects in children is critically important, therefore appropriate training should be provided to pediatricians by developing adequate academic curricula.

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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