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## Endocrine Disrupters and Food Safety

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**Abstract:** The general population is constantly exposed to a mixture of endocrine disrupters (ED), mainly through the food chain. The dietary exposure pathways are diverse, since ED can: i) affect diet components most liable to environmental pollution (e.g., polychlorinated and polybrominated chemicals in lipid-rich foods); ii) be employed in food production (e.g., certain groups of agrochemicals); iii) be released from food contact materials or during food production processes (such as bisphenol A or phthalates); iv) last but not least, be naturally present in food: endocrine-active nutrients and bioactive substances, such as iodine and phytoestrogens, respectively, may elicit health risks when intakes are excessive. Main health concerns from dietary exposure to ED include the building-up of a pollutants body burden and the potential for additive, “cocktail” effects. The factors modulating exposure and susceptibility are considered, including different stages of life, the modulation of risks by dietary habits and the multiple, often inadequately understood, interactions between ED and food components.

**Keywords:** Menopausa, puberty, transplacental, tumorigenesis, xenoestrogen.

### INTRODUCTION

Diet is the main exposure route to a variety of endocrine disrupters (ED) for general population. In general, ED may be divided into four broad categories from the viewpoint of exposure patterns *via* food chains: i) ED that can bioaccumulate in organisms (e.g., polychlorinated biphenyls -PCBs-, polybrominated flame retardants, perfluorinated compounds), thereby affecting components of the food chain that are most susceptible to environmental pollution [1 - 3]; ii) ED employed in the production of food, such as pesticides [4] and substances used in animal production [5]. In this case, the potential risks for consumers are largely determined by the enactment of up-to-date regulations, as well as enforcement of appropriate farming practices; iii) ED released into food from contact materials, processing aids, *etc.* The most well-known example is the plasticizer bisphenol A, recently re-evaluated by the European Food Safety Authority (EFSA); the new EFSA assessment has put into evidence such points for concern as the aggregate exposure to low concentrations present in multiple, food and non-food, sources and the presence of specific effects in developing tissues, e.g. on the proliferation of the mammary epithelium in rodents, at dose levels below those inducing overt toxicity [6]. A much less renowned example, semicarbazide, raised concern in Europe because of its release upon heating from foodstuffs sealed in glass jars, primarily baby foods [7]; it is also a main metabolite of nitrofurans, a group of antimicrobial agents [8]. Semicarbazide exerts endocrine effects on juvenile rodents, possibly mediated by N-methyl-D-aspartate receptors [7]; iv) the fourth group of ED - or, more accurately, endocrine-active substances - includes a variety of bioactive compounds naturally present in food. In such cases, the effects may be beneficial or detrimental, depending on the dose, chemical form and endocrine status of the organism (e.g., age, gender). For instance, the ability of certain phytochemicals (e.g., quercetin, largely present in fruits) to interfere with androgen-related pathways has been recently shown to depend also from their specific intracellular distribution [9]. In the case of certain essential nutrients, “endocrine disruption” may be caused by a deficiency, as well as by an excess. A paramount example is iodine: iodine-deficient hypothyroidism is a major endocrine disorder worldwide, but iodine excess may also alter thyroid function,

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such as that resulting from high-dose supplementation of feeds and the consequent carry-over in milk and eggs [10].

The following sections will discuss some critical issues: the “cocktail” effect, the relationship of ED-related risks with age and gender, and the importance of dietary habits to influence both exposure and susceptibility.

### THE “COCKTAIL” EFFECT ISSUE

This long-debated issue concerns the potential additive effects of different ED present in the same foods at low levels, but interacting with the same targets, *e.g.*, nuclear receptors [11 - 13]. Furthermore, it is not simply the daily dose alone that is of concern, since many ED bioaccumulate in lipid compartments of tissues, giving rise to a mixed “body burden” of contaminants of different origins, including dioxins, polychlorinated biphenyls, chlorinated pesticides and their metabolites, as well as brominated flame retardants [14]. Seafood is highly vulnerable to the combined presence of different contaminants due to the persistent contact of edible organisms with water and sediments, as well as the biomagnification through food chains (including the use of protein- and lipid-rich feedingstuffs in aquaculture); besides lipophilic substances [1, 2], other ED may also contribute to the overall ED burden in seafood, *e.g.*, perfluorinated chemicals [3] and organotins [15]. Some of these compounds represent relatively “simple” cases. Organotins are considered together, as having essentially the same toxicity and bioconcentration potential [15]. Polychlorinated dioxin-like chemicals (dioxins, dibenzo-furans, coplanar PCB) are customarily assessed together, by assigning to each chemical a Toxicity Equivalency Factor (TEF): the TEF is based on the molecular mechanism of dioxin-like chemicals, the strength of binding with the aryl hydrocarbon receptor (AhR), and represents the “weight” to be attributed to a certain amount of a given dioxin-like substance within a mixture [16]. Brominated dioxin-like chemicals should also be included in the AhR-based TEF approach [16]. *In vitro* studies indicate that also the non-dioxin-like PCB may be grouped according to their molecular mechanisms in clusters, such as the “estrogenic” and the “highly persistent-cytochrome P-450 inducers” [17, 18]: considering that in most cases non-dioxin-like PCB make the bulk of human dietary exposure and related toxicological hazards [18], these findings may have quite a significance for risk assessment.

However, the issue of mixture effects of ED likely extends much beyond the groups of chemicals sharing the same chemical structures and molecular mechanisms. Of special interest for risk managers is the presence of multiple pesticide residues in the 15-20% of fruits and vegetables [19]. The EFSA has engaged in developing methodologies for assessing cocktail effects of pesticides in order to respond to concerns posed by multiple pesticide residues. This work has put into evidence that the available toxicological framework is insufficient for interpreting the data about co-occurrence of ED in food, mainly because of a lack of clarity about which mixture risk assessment methods should be chosen. On the other hand, EFSA has made an important step forward, concluding that, based on the available knowledge, the most robust and conservative approach is the assumption of effect additivity: compounds that have the same effect in the same target organ (*e.g.*, causing hypothyroidism) are assumed to act in an additive way, even though their chemical structures and molecular mechanisms are different [20, 21]. Pesticides assumed to act in an additive way on the same target are included in “cumulative assessment groups” [20]; the ensuing phase will be the identification of “risk drivers”, *i.e.*, those chemicals that make up most of the risk associated to a given cumulative assessment group because of their potency and/or exposure. Thus, the developing risk assessment framework for multiple pesticide residues might be relevant also for contaminants, food contact materials, natural compounds and other chemicals present in foods and feeds.

### DIFFERENT STAGES OF LIFE

The health risks related to dietary exposure to ED are also associated to stages of life.

*Newborns and small infants* are exposed to ED in quite a different manner than adults, since an early body burden may be derived from *in utero* exposure and small infants consume a very limited variety of food, only breast milk in many cases, so that contamination of a single item may determine the safety of their entire diet. Furthermore, internal defences of neonates against contaminants are limited by the immaturity of both hepatic detoxification and the blood-brain barrier [22]. Breastfeeding may transfer a mixture of lipophilic compounds (PCBs, brominated flame retardants, dioxins) from the maternal body burden to the newborn. Exposure *via* this route can be considerable: in the 90's it has been estimated that approximately 10% of the body burden of dioxin-like substances at 25 years of age may be attributable to breastfeeding during the first six months of life [23], while breast-fed infants are among the population groups with high intake of PBDE [2]. However, the presence of contaminants in human milk must be balanced against the indisputed benefits of breastfeeding for the child health, including neurocognitive and behavioural development.

Breast milk makes also an important contribution to neonatal intake of iodine, which is essential to optimal thyroid function and thus to the functional development of the nervous system [24]. Because of these enormous benefits, it is not recommendable to reduce exposure to ED by restricting breastfeeding, except in circumstances associated with exceptionally high levels of contamination, *e.g.*, contamination by dioxins from e-waste pollution in developing countries [25].

In most situations controlling food chains so to reduce the body burden of the population at fertile age is the best way to protect the infant from undesirable high levels of lipophilic ED whilst ensuring the benefits of breastfeeding, in the true spirit of “sustainable food safety” aimed at protecting transgenerational health [26].

Patterns of food consumption are also different in *children and adolescents* compared to adults; for instance, due to higher intake compared to adults, milk may be a particularly important source of exposure for children to dioxins and PCBs [27] and PBDE [2]. Moreover, children may be subject to higher exposure simply because they ingest more food in proportion to their body weight, a ratio that slowly decreases during adolescence to become more stable at approximately 20 years of age [28]. Moreover, foods popular among children and adolescents, such as fast-food, might be an important source of some ED, *e.g.*, dioxin-like compounds [29]. It is not just a matter of exposure: childhood is a period of dynamic growth and development [30]; in particular, the pre- and peripubertal period represents a window of specific susceptibility to the effects of ED on reproductive and endocrine maturation, including disturbances of puberty onset [31, 32], as well as on several other targets, such as the development of cognitive, immune and metabolic functions and also as to the susceptibility to cancer later in life [33]. Consequently, a specific attention to risk assessment for infants and children has been proposed, in terms of both exposure patterns and targeted toxicological testing [22, 32].

Whereas children are an important and ongoing development for risk assessment, undisputed scientific evidence points out the *prenatal development* as the phase most susceptible to ED effects on all body systems regulated by the endocrine networks: thus the potential ED effects include the reproductive system, but extend much beyond, being relevant to neurobehavioural development, the risk of obesity and/or type II diabetes, *etc.* [34]. Typically, ED elicit “delayed developmental effects”, where interferences with the programming of normal endocrine-signalling pathways during prenatal life (including gene expression regulated by specific nuclear receptors) lead to adverse consequences later in life [34]. Experimental toxicology studies provide an ample range of examples. Lindane, a persistent chlorinated compound widely used in the past as insecticide, does alter the female reproductive development through the interaction with ER- $\beta$  [35]; lindane also reduces spermatogenesis in male mice exposed *in utero*, an effect which might be related to an enhanced, CYP-mediated testosterone catabolism [36], suggesting a sex-related differential mechanism. The widespread neurotoxic insecticide chlorpyrifos acts as an ED in rodents only when exposure does occur *in utero*: the adult offspring of mouse dams exposed to non-neurotoxic dose levels show alterations of oxytocin and vasopressin brain levels [37] as well as of thyroid hormone balance [38], more pronounced in males. Ethylenethiourea (ETU) is the common metabolite of the widely used ethylenebisdithiocarbamate fungicides, and is identified as ED given its ability to interfere with thyroid hormone biosynthesis by inhibiting thyroid peroxidase activity; in addition, upon *in utero* exposure to dose levels devoid of apparent toxicity, ETU markedly impairs the reproductive function (*e.g.*, oestrus cyclicity) in female rat offspring [39]. Notwithstanding a global trend in reducing and limiting its use, the plasticizer di-2-ethylhexyl phthalate (DEHP) is still widespread in most foods, albeit low concentrations are present in the majority of cases [40]. DEHP may impair the early steps of steroidogenesis and it can affect the development of the male reproductive tract in rodents with semen quality being the most sensitive outcome [41]; in addition exposure to DEHP *in utero* does alter the programming of adrenal steroidogenesis [42] as well as of hepatocyte metabolism [43].

These few examples indicate the top relevance of the effects upon intrauterine exposure for the risk assessment of ED, as well as point out some problems deserving close attention. First, the exposure should be assessed taking into account the possible differences in toxicokinetics between human and rodents, including those related to the physiology and structure of the placental filter; indeed, the recent assessment of toxicological studies on BPA by the EFSA has made an effort to translate the dose levels used in rodent developmental toxicity studies into oral human equivalent doses [7]. Second, in general the delayed developmental effects are quite specific, related to the ED mechanisms, as well as subtle; therefore it might be difficult to assess a proper dose response for such effects in standard toxicity assays, or even to identify them, unless previous data (*in vitro* assays, toxicokinetics *etc.*) are used to target the most adequate endpoints [44].

## THE INFLUENCE OF DIETARY HABITS AND OF NATURAL FOOD CONSTITUENTS

Dietary habits are influenced by socioeconomic status, cultural and religious factors and individual choices (*e.g.* vegetarianism/veganism), which may thus exert considerable impact on the intake of nutrients, bioactive substances, residues and contaminants. For instance, the extensive consumption of fatty foods of animal origin is associated with greater exposure to persistent ED [1 - 3, 27]; the contributions of individual food commodities depend on dietary habits, but also on the environmental quality of the areas of food production, as well as on patterns of food preparation, storage and processing. For instance, management of cereals and nuts before, during and after harvest is critical to the level of contamination by zearalenone, a potent estrogenic mycotoxin [45]; more in general, the many toxicological risks related to the preparation and vending of street foods (otherwise, an important food security component for developing countries) have been recently discussed [46].

Main foods, and their production chains, are vulnerable to the contamination by specific ED *Cereals*, a major food staple worldwide, are vulnerable to contamination by the potent estrogenic ED zearalenone, in particular corn [45]; moreover, cereals may accumulate from soil and water the toxic heavy metal cadmium which may have estrogen-like effects and specifically impair the production of the erythropoietin hormone within the renal proximal tubular cells, a rather peculiar ED effect [47].

The production of *fruits and vegetables* needs to be closely watched as these commodities are widely recognized as a source of nutrients, fibre and antioxidants, but are also the major source of pesticide residues [19]. Recent investigations indicate the presence of herbicides, insecticides or their metabolites in the urine of subjects with no known occupational exposure in different European countries [48 - 50], pointing out the importance of aggregate (dietary plus residential) exposure.

In general *foods of vegetable origin* are not an important source of bioaccumulating ED. In Italy vegetables and fruits make only a very small contribution (3%) to the total dietary intake of dioxin-like and non-dioxin-like PCBs, however, vegetable oils account for 11-16% of the total dietary intake of PCB, a finding potentially relevant to the protection of the Mediterranean diet [27].

On the other hand, *foods of vegetable origin* should be considered as a source of natural endocrine-active substances. Dietary patterns in Eastern Asia are characterized by considerable levels of soybeans, with a high content of phytoestrogens, mainly genistein and daidzein. In Europe soybean intake varies widely, being greater in northern European countries, which probably reflects the wider spread of vegetarianism [51]. Phytoestrogens may afford some protection against certain diseases, *e.g.*, osteoporosis, but the effects of early and/or prolonged exposure (*e.g.*, from “healthy” diets or taking supplements) on prenatal development or the risk of breast cancer are still controversial and the available evidence does not rule that a risk may exist [52, 53]. In addition, when iodine intake is suboptimal, an excessive consumption of soybeans and related products may have an adverse effect on thyroid function, by inhibiting thyroid peroxidase, especially in children [54]. Furthermore, many phytoestrogens may interfere with iodination of thyroid hormones: some (*e.g.*, naringenin, and quercetin, which contain a resorcinol moiety) by direct and potent inhibition of thyroid peroxidase and others by inhibition (myricetin, naringin) or competitive inhibition (biochanin A) of tyrosine iodination [55].

Since phytoestrogens and xenobiotics with ED features may be concomitantly present in the diet, some studies investigated whether and how the plant endocrine-active substances and xenobiotics may interact; although the picture is far from complete, nevertheless the available data indicate that further research is worthwhile [56]. Flavonoids (daidzein, genistein, quercetin and luteolin) can partially antagonize the stimulation of proliferation of estrogen-dependent MCF-7 human breast cancer cells caused by synthetic estrogenic ED, including 4-nonylphenol (environmental by-product of polyethoxylate anionic detergents), BPA, and the PCB 4-dihydroxybiphenyl [57]. Thus, it might be hypothesized that phytoestrogens exert some protective action against estrogenic xenobiotics by competing for common biological targets. No such interaction was observed in models not specifically aimed at estrogen-regulated processes; for example, genistein did not modulate the effects of two persistent ED, the polybrominated flame retardant PBDE-99 and the PCB mixture Aroclor 1254, on human astroglial cells [58]. In rats exposed *in utero*, genistein and the estrogenic chlorinated insecticide methoxychlor exerted an additive effect on immunological development, indicating that the developing thymus is a sensitive target [59]. In estrogen reporter (ERE-tK-Luciferase) male mice, genistein modulated the actions of both estradiol and persistent ED in a tissue-specific manner: the antiestrogenic actions of beta-hexachlorocyclohexane on the testis and of o,p'-DDT on the liver were antagonized, whereas the effect of genistein on the liver was additive with that of the ER agonist p,p'-DDT on this same organ [60]. When two defined mixtures of

phytoestrogens and “xeno”ED (designed on the basis of human exposure data) were tested in the uterotrophic assay on prepubertal rats, the phytoestrogen mixture alone elicited an uterotrophic response, whereas the synthetic mixture exerted an effect only in combination with the phytoestrogens, possibly because the levels of exposure were too low [61]. The indices of hypospadias in mice exposed *in utero* to genistein, the antiandrogenic fungicide vinclozolin or both substances were 25%, 42% and 41%, respectively; based on this parameter, the combined exposure to the phytoestrogen and the environmental antiandrogen had an effect that was less than additive [62]. On the other hand, genistein, as well as the methyl donor folic acid, both antagonized the hypomethylation effect of DNA caused by BPA in mouse embryos [63]. Thus, available data indicate that interactions between phytoestrogens and ED may be important, but complex, showing additivity or antagonism, depending on the specific compounds involved, end-points determined and age of the organism.

In addition to phytoestrogens, many other natural endocrine-active compounds may be present in vegetables; as already mentioned, the endocrine effects of phytochemicals depend from their potency as well as from specific intracellular distribution patterns [9]. Several cyanogenic compounds are recognized goitrogens, such as thiocyanates and isothiocyanates derived from glucosinolates ingested in, among other items, Brassicaceae (*Brassica spp*). The presence of cyanogenic compounds in animal feed is a potential problems for farm animals, which calls for iodine supplementation of feedingstuffs; however, the adverse impact of glucosinolates on human health is probably very limited in the European scenarios [64].

Many flavonoids present in fruits and vegetables are powerful inhibitors of sulfotransferase enzymes involved in the removal and detoxification of xenobiotics and essential to the metabolism of steroid and thyroid hormones [65]. In particular, furocoumarines, present in grapefruit and other citrus fruits, are capable of mediating dioxin-like effects by interaction with AhR, are of growing concern. However, the risk to healthy consumers appears at present to be low (probably due to the action of intestinal bacterial flora and other detoxifying pathways), although there is a realistic possibility that the effects of certain drugs might be altered by inhibitors of sulfotransferases [66].

Finally, it is worth noting that fruits and vegetables provide dietary fibre, which is important in modulating the activity of intestinal microflora, as well as the bioavailability and intestinal metabolism of estrogens [67].

As already pointed out, *foods of animal origin* are the main source for ED able to concentrate in food chains. Obviously, each main food commodity presents specific points for concern and attention. Milk and dairy products are vulnerable to the prolonged contamination of pastures by persistent ED, related with the illegal handling of industrial wastes and leading to chronic contamination hotspots [68, 69]. The lipid content of ingested milk and dairy products also matters; for instance, the abtual consumption of partially skimmed milk in infancy may reduce exposure to dioxin-like compounds and the resulting body burden by 10-20% [70]. In general, the characteristics of the food-producing living organism are important determinants of the contamination of foods. For instance, higher levels of dioxins and dioxin-like PCBs are found in liver from sheep compared to cattle exposed to similar environmental levels. Dioxins from airborne emissions are deposited on soil: in sheep the involuntary intake of soil when feeding on pasture is high since they can nip herbage close to ground surface, while cattle normally feed on vegetation above 5-10 cm from the ground surface. Moreover, compared to cattle sheep may have a lower CYP1A1 activity, which is the key enzyme to metabolize dioxin-like compounds to hydroxy-derivatives, therefore differences in feeding behaviour as well as metabolism may both contribute to make up the marked differences in the liver storage of dioxins and related compounds between the two species [71].

Seafood, with its variety of species, classes and even *phyla*, is the paradigm to show the role of the characteristics of the edible organisms. In general, large fatty fishes are more liable to contamination by lipophilic pollutants like PCBs or PBDE [1, 3]; the persistent, but not lipophilic, PFOS is more prevalent in large predatory fishes (like tuna) and in molluscs and crustaceans, which might suggest, respectively, biomagnification in food webs and uptake from sediments [2]; the contamination patterns of seafood by organotins are similar to PFOS [15]. Benthic seafood organisms are particularly liable to contamination by nonylphenols [72] and cadmium [73]. Remarkably, farmed fish present background levels of persistent pollutants comparable to caught fish; this is due to the use of highly concentrated feeds in aquaculture that are made with proteins and fats derived from marine organisms, thus reproducing the marine food web in the aquaculture farm [74, 75]. Accordingly, the use of feed ingredients less vulnerable to pollution would facilitate the exploitation of fish as an important source of nutrients such as iodine and polyunsaturated fatty acids [74, 75].

An interesting aspect of seafood is that it contains contaminants and nutrients that act on the same pathways, e.g.,

ED targeting thyroid and iodine. Infants exposed to high levels of PCBs and hexachlorobenzene (another bioaccumulating ED that may alter the metabolism of thyroid hormones) through fish in their diet demonstrated only modest changes in thyroid parameters, possibly due to a protective effect of the iodine also present in fish [76]. In rats treated orally with an important fish pollutant, pentaBDE-71, the critical effects were reduced levels of hepatic apolar retinoids and serum thyroid hormones [77], suggesting that real-life exposures of several ED might act as antinutritional factors, interacting with deficiencies or imbalances of specific nutrients [56].

## CONCLUSION

Although the diet is recognized as a major route of exposure to ED, risk assessment in this context currently involves a number of areas where increased scientific knowledge is required: examples are the mechanisms underlying combined effects, the assessment of long-term effects on programming of target organs and systems upon pre- and/or post-natal exposures, the role of the metabolism and ecology of edible organisms as determinants of food contamination, the impact of dietary styles on the exposure of population subgroups, the interactions between contaminants and natural food components to support the scientific bases of risk-benefit analyses.

Science based risk management of food safety should integrate timely monitoring of the environment and the food production chain, starting from primary production, and effective exchange of information with food producers [78]; under this respect the origin and quality of feedstuffs should not be overlooked as it significantly influences the levels of contamination in such vulnerable foods of animal origin as farmed fish, milk and dairy products [5, 75]. Current systems for control of food hygiene, which focus mainly on microbiological risks (HACCP-Hazard Analysis Critical Control Point), could be extended to the prevention of long-term toxicological risks [46, 78]. The establishment of maximal acceptable residues (*e.g.*, of pesticides and feed additives) or tolerable levels (of contaminants) and their enforcement though good quality controls are necessary, but cannot be sufficient, even though official monitoring programmes are updated to include additional emerging contaminants. For instance, the control system cannot, at present, afford protection against prolonged exposure to low levels of multiple, potentially additive ED. Prevention should focus on primary production. Cost-effective strategies for reducing exposure to ED should be directed towards the sources of contamination of food and animal feed and be designed to achieve safer production, as well as an integrated management of risks. A timely and effective transfer of science to risk analysis is needed in the whole field of food safety, but especially in an evolving and complex field such as ED risk assessment.

## CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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