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ENDOCRINE DISRUPTORS IN FOOD CONTACT MATERIALS; IS THERE A HEALTH THREAT?

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ABSTRACT

Food Contact Materials (FCMs) are a major source of endocrine disrupting chemical substances (EDCs), thus forming an important part of human exposure to these compounds, to which this article is addressed. The potential impact of such exposures on endocrine function, and thereby health outcomes, requires scientifically valid evidence so that appropriate risk management decisions can be taken to diminish human exposure, particularly in vulnerable population groups like infants and small children. Relevant aspects of exposure assessment are discussed based on testing migration of EDCs from FCMs, together with the different approaches so used. The specific migration testing determines whether limits for defined substances are met. However not all EDCs present in the leachate may be found by these means. In fact, the chances of detecting EDCs in the food simulant (leachate) are improved when it is subjected the relevant biological testing, thus helping to provide improved protection against these chemical substances. Nevertheless, official controls and risk management decisions do not necessarily take such testing into account, as the relevant legislation is based on specific migration limits that may be easily quantified and addressed in the risk management process. Elucidating the link between observed endocrine activity and any toxic effects so arising, is complicated by the complexity of endocrine interrelationships coupled with relatively limited sensitivity of toxicological tests. Any risk assessment implies a rather high uncertainty and should include also any cumulative effects. This review discusses the effects of the EDCs like bisphenol A, phthalates and benzophenone found in FCMs. In addition, the approaches from the USA and EU for systematically evaluating man-made EDCs in the environment are also considered, including appropriate prioritisation criteria.

Key words*: endocrine disruptors, food contact materials, food packaging, exposure assessment, risk assessment, benzophenone, bisphenol A, phthalates, substances migrating/leaching from food packaging*

STRESZCZENIE

Materiały do kontaktu z żywnością (ang. food contact materials, FCMs) stanowią istotne źródło substancji zaburzających funkcjonowanie układu hormonalnego określanych jako endocrine disrupting chemicals (EDCs). FCMs mają ważny udział w całkowitym narażeniu człowieka na te substancje. Potencjalny wpływ EDCs na funkcjonowanie układu hormonalnego i skutki zdrowotne wynikające z narażenia na te substancje, dostarczają potwierdzonych dowodów do podejmowania decyzji w ramach zarządzania ryzykiem, zmierzających do zminimalizowania narażenia na te związki, co ma istotne znaczenie, zwłaszcza w przypadku grup populacji szczególnie wrażliwych, takich jak niemowlęta i małe dzieci. Omówiono niektóre aspekty oceny narażenia na podstawie badania migracji EDCs z materiałów do kontaktu z żywnością, w zależności od zastosowania różnych metod badania migracji. Badanie migracji specyficznej umożliwia sprawdzenie czy spełniane są limity migracji ustanowione dla poszczególnych substancji. To podejście stwarza ryzyko, że nie wszystkie migrujące EDCs zostaną wykryte. Zastosowanie odpowiednich testów biologicznych do analizy płynu pomigracyjnego stwarza większe prawdopodobieństwo wykrycia obecności EDCs zapewniając lepszą ochronę konsumenta przed tą grupą związków. Jednakże wyniki takich badań nie zawsze umożliwiają podejmowanie decyzji przez urzędową kontrolę w ramach zarządzania ryzykiem, ponieważ większość przepisów opiera się o limity migracji specyficznej, które łatwo mogą być skwantyfikowane w procesie zarządzania ryzykiem. Wyjaśnienie zależności między zaobserwowanym wpływem na układ hormonalny a wystąpieniem szkodliwego skutku działania napotyka na trudności wynikające z ogromnej złożoności wzajemnych zależności w układzie hormonalnym i ograniczonej czułości testów toksykologicznych. To z kolei implikuje stosunkowo dużą niepewność oceny ryzyka, która powinna także uwzględniać możliwość wystąpienia efektów skumulowanych. Przedyskutowano aspekty związane z bisfenolem A, ftalanami i benzofenonem, jako EDCs występującymi w materiałach do kontaktu z żywnością.

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Przedstawiono również podejścia USA i UE do systematycznej oceny antropogennych EDCs w środowisku, z uwzględnieniem kryteriów umożliwiających ustalanie priorytetów.

Słowa kluczowe: *endocrine disruptors, materiały do kontaktu z żywnością, opakowania żywności, ocena narażenia, ocean ryzyka, bisfenol A, ftalany, beznozfenon, substancje migrujące z opakowań żywności*

INTRODUCTION

Materials and articles intended to contact with food (Food Contact Materials; FCMs), including food packaging, are not generally perceived to be a chemical health threat when compared to pesticides, veterinary drugs, heavy metals or mycotoxins that are well recognised food contaminants arising from agricultural practices, the environment or improper food storage. However within the last decade, it has become accepted that FCMs are important contributors to human xenobiotics' exposure [27] due to the worldwide debate on such substances like bisphenol A and their impact on the endocrine system. This underpins risk management decisions for placing limits of human exposure to this compound, particularly when directed towards vulnerable groups like infants and small children.

The high migration of phthalates observed from FCMs into foodstuffs required the European Food Safety Authority (EFSA) to undertake a new risk assessment and to establish legally binding FCM limits [45]. In recent times, the Rapid Alert System for Food and Feed (RASFF) notifications on FCMs have increased concerning unacceptable migration levels from FCMs of permitted substances as well as those not allowed [9, 46].

The term 'endocrine disruptors' has recently been substituted by 'endocrine disrupting chemicals' (EDCs) [53] and will henceforth be referred to in this article since it concerns only chemicals and not any other endocrine risk factors. These EDCs, i.e. chemical substances that interfere with endocrine system homeostasis are often defined as xenobiotics, which after being ingested by humans or animals cause unusual endocrine activity resulting from an interaction with relevant receptors. Some definitions further describe the toxic effects on exposed organisms, its progeny or human populations [57]. Extending this definition seems relevant for distinguishing between noxious effects that suggest a toxic response as opposed to rather mild, modulatory activity which may or may not result in a toxic response from the organism.

EDCs mechanisms of action are exceptionally diverse and exposure responses may involve many tissue, organs or system functions. Disorders endocrine system function may due to over-stimulation or depression, resulting in an excessive or insufficient secretion of hormones.

Numerous chemical substances may affect the endocrine system such as phytoestrogens, however the majority of environmental EDCs are both produced and introduced into the environment by human activity. EDC effects on man may be thus considered as a complex response due to interactions of numerous natural and synthetic chemical substances with target receptors in different tissues and organs [29].

Many studies have investigated and reviewed the effect of EDCs on the environment and man [8, 13, 53]. When the relevance of these exposures are evaluated, serious difficulties arise because of the many different factors or variables involved, which include assessing the whole spectrum of possible endocrine responses.

In all the biological response to EDCs are complex due to the many relationships and feedbacks between organs and glands that serve to preserve the organism's homeostasis.

EXPOSURE ASSESSMENT

Dietary exposure to chemical substances from food packaging and other food contact materials may occur as a result of migration from the packaging materials into the food products.

Migration tests of chemical substances from FCMs into foodstuffs or food stimulants, which mimic the eluting properties of food, are used for evaluating consumer exposure to these substances. Since the exposure may be defined as a function of the amount of the substance that migrates into the food and the amount of this food consumed, it may be evaluated indirectly by quantifying a given migrating substance into the food or food simulants specially developed for this purpose. The migration level of substance depends on the kind of packaging material itself, the chemical nature of the foodstuffs having the contact, the concentration of the substance in the packaging material, time and temperature and also on the ratio to the surface area of the packaging material to the amount/volume of the food product.

Migration data for plastic food contact materials may be obtained from monitoring of chemical substances in food or from migration testing into food simulants. Because of the analytical difficulties resulting from complexity of food matrixes migration data are obtained from migration experiments using the food

simulants [47]. The diffusion model for the estimation of the migration of substances from the plastic materials has been also legally allowed for the compliance checking with the specific migration limit (SML).

For assessing the exposure to chemical substances present in packaging it is necessary to know what type of food is packed in what kind of material. Methods proposed to be used in the UE for testing of substances migrating from plastic FCMs have been described and reviewed in detail by *Cwiek-Ludwicka* et al. [11]. One of the major disadvantages of methods for specific migration is that they are designed for quantifying a particular chemical amongst the many others which are usually present in the food simulant used. This is especially important, since the leachates normally found in these studies depend on the materials tested which may contain many potentially toxic chemical substances. It is thus obvious that specific migration testing only focuses on specific substances and does not provide information on any other substances present that may be toxic.

Such a limitation should be taken into account for FCMs safety evaluations since specific migration tests for a given substance are used in the control and monitoring to check that food packaging are in line with legislative provisions rather than to assess actual consumers' exposure. This weakness was documented by *Wagner and Oehlmann* [56] who showed that the leachate from polyethyleneteraphtalate (PET) bottles in a migration study contained unidentified substances with oestrogenic potential, thus providing convincing evidence that specific migration tests should not be the only base for giving an opinion on product safety.

From the toxicological point of view, migration testing in conjunction with biological tests is more appropriate, since it provides better information on whether the substances migrating from the FCMs into foodstuffs may pose a health risk. Moreover, it also facilitates hazard characterisation. Nonetheless, such approach may create legal problems, since, as aforementioned, the legislation that has been designed to facilitate risk management in FCMs are based on the migration limits into foodstuffs or food simulants for defined substances [47]. It may therefore be expected that any risk assessment based on exposure to particular substances migrating from FCMs will bear some uncertainty. One of the possible solutions to such instances might be in setting the cut-off criteria for FCMs whenever the post-migration liquid exhibits hormone disrupting potential.

Exposure to EDCs may be extremely serious during the perinatal period as the foetal endocrine system and that in the later of the new-born is extremely susceptible to chemical stress. Such changes during early stages of development may induce irreversible effects that only emerge in later life [8, 18, 39, 51].

Bisphenol A provides a good example of complex receptor interactions as demonstrated by *in vitro* studies showing it to be both an oestrogenic receptor agonist and an androgenic receptor antagonist [6]. *In vivo* studies also noted many different responses suggesting a potential endocrine effect that was however expressed above its threshold value, i.e. 5 mg/kg body weight (bw) per day [23, 31, 36].

The quantitative exposure assessment of the general population to chemical substances migrating from the FCMs is based on the data concerning consumption of food into which the substance migrates and the magnitude of this migration. The uncertainty resulting from the exposure assessment results in this case from the fact that the food simulants do not always reflect the actual migration that occurs into the real food and not always reflects the worst case scenarios and, moreover that the conventional method for exposure assessment are not adequate for children. In addition, the exposure resulting from the migration into the dry food is generally underestimated [38]. Using food simulants for migration testing, nonetheless allows various hypothetical exposure scenarios to be developed from which a deterministic risk assessment can be performed, so that appropriate preventive measures can be implemented.

There are several approaches to assess exposure to the xenobiotics migrating from the FCMs into the food, and the choice of the right one may depend on the purpose of the assessment. If the purpose is to approximate the actual exposure to a particular substance, the evaluation should be based on the biomonitoring results of this substance or the relevant exposure indicators in the human specimens. Due consideration should be given that this method covers the exposure from all sources leading to a possible overestimation of the exposure from the foodstuff if the substance is also present in other parts of the environment. Another weakness of this method may occur if the substance is rapidly eliminated from the organism and so large fluctuations in short time intervals may occur. This may be partially limited by increasing number of samples tested.

In evaluating product safety, exposure assessment is more relevant for testing FCMs migration into food stimulants as this provides expected real life conditions, enabling different modelling methods to be used and tailored according to the conditions of contact. The more detailed aspects of these two approaches were discussed elsewhere [32].

RISK ASSESSMENT

As mentioned previously, the action of chemical substances affecting the endocrine system is by their ability to hinder or to facilitate functioning of one or

more elements that constitute the endocrine system. It does not necessarily mean that in such cases any adverse effects can arise. The distinguishing the endocrine modulatory activity which does not necessarily cause toxic changes from the activity that triggers the toxicity resulting from the damaging one or more elements of endocrine system is important in the evaluation of potential risk for human health. It is generally accepted that there are threshold levels of exposure below which a given organism is not expected to produce any toxic response [14]. However, due to the rather limited sensitivity of toxicological tests, establishing such thresholds leads to considerable uncertainty. Thus, an important part of any evaluation should determine the relationship between endocrine activity and toxic effect. In the case of an endocrine impact, the mechanisms maintaining homeostasis, protecting the cell against harmful xenobiotics effects should also be taken into account. However, in itself, mobilising such mechanisms may indicate that the xenobiotic has already reached the target cell and induced a protective response. In certain developmental stages of an organism, the ability to induce homeostatic maintenance may be limited resulting in elevated susceptibility of the organism [19] which in the case of perinatal exposure, may be of special concern. In such instances, the precautionary principle approach for risk management seems to be justified, all the more so if currently proposed tests for the endocrine activity in mammals [43, 44] do not include the effects of perinatal exposure, which hitherto emerge in later life stages. The possibility of such delayed effects was indicated by *Betancourt et al*. [4], who found a positive relationship between intrauterine exposure to BPA and elevated susceptibility for mammary carcinogenesis induced by 7,12-dimethyl(a)anthracene in the rats. A similar, but greatly worrying relationship was observed by *Markey* et al. [33] who showed that even small exposures of pregnant mice to BPA altered the development and tissue organisation in the mammary glands of the progeny.

When undertaking risk assessment, the possibility of cumulative effects arising should also be taken into account when the organism may be exposed to more than one substance of a common mode of action or when the toxic effect is the same but results from different modes of action [49]. This situation is very alike to when numerous environmentally persistent organochlorine anthropogenic compounds may contribute to cumulative effects [50].

Risk assessment for EDCs exposure is additionally challenging due to the complexity of interrelationships within the endocrine system that result in chemical substances acting at different endocrine system sites or expressing an affinity to different receptors that may cause the same final effect. This phenomenon was discussed by *Datson* [12] who drew special attention to the uncertainty inherent in evaluating potential exposure effects to mixtures of EDCs. For this reason the opinion that in case of exposure to multiple ECDs, their potential to produce similar effects should rather be taken into account than the modes of their action seems to be justified [29].

ENDOCRINE DISRUPTING CHEMICAL SUBSTANCES IN FOOD CONTACT MATERIALS

During last decade many chemical substances hitherto recognised as safe have now been found to adversely affect hormonal balance in organisms. They include bisphenol A, phthalates, benzophenone and its derivatives [3] along with organic compounds of tin [41] that migrate from FCMs into foodstuffs. The migration of potential EDCs into foodstuffs has stimulated efforts for developing a uniform approach, specially tailored for their identification and evaluation. *Muncke* [37] has listed 50 chemical substances authorised in food contact materials which are known or potential endocrine disruptors.

The endocrine system regulates most of an organism's biological function and there are a vast number of receptor sites, within a complex milieu complex of interrelationships where, following a chemical stimuli, the system may become disrupted. For this reason the indication of the tests that would allow classifying substances as EDCs is very difficult [26]. In case of pesticide residues in foodstuffs that are of special concern, a strategy and temporary criteria for undertaking procedures preceding risk management have been proposed by *Max-Stoeltig* et al. [35]. This takes into account consumers' safety, and proposed two approaches for classifying chemical substances as EDCs. The first approach utilises exposure assessment through determining the amount of substance which enters the organism *via* food, whilst the second approach evaluates and reports the endocrine disrupting potential of the given substance. However, *Rudén* [48] stress that the proposed approaches should be treated as temporary, until the science based criteria enabling the risk assessment to be performed are developed according to EU regulations. It may be anticipated that such criteria would also be relevant for the chemical substances that migrate from FCMs into foodstuffs.

The diversity of materials intended to contact with foodstuffs results from the numerous functions they are designed for. By implication, this also leads to a diversity of problems for evaluating whether, and under which circumstances, a given material may safely be used for making contact with foodstuffs and when the risk becomes unacceptable. One of the major purposes

of food packaging (excluding any marketing role) is to ensure appropriate protection against external factors such as chemical and biological contaminants, preventing oxidation by atmospheric oxygen, light, loss of gas from beverages, loss or absorption of humidity and aroma, etc. In some instances, basic packaging material may also adversely affect the health quality of the packed product, for example metal cans that require internal lacquer coatings to prevent any direct contact of food with the metal surface thus constitute a risk of lacquer components migrating into the food.

Currently used food packaging is made from different plastic materials and numerous laminates. Moreover, the packed foodstuff may come into contact with the internal walls of cans, gaskets and coatings used in lids, which may be a source of harmful or inadequately tested substances [10, 45, 46]. This particularly concerns EDCs which have been exhaustively detailed by *Muncke* [37] who demonstrate that food packaging may indeed contain numerous substances suspected of acting as EDCs. Since foodstuffs may interact with the internal surface of packaging, a migration of its constituents may be expected. Migrating substances may be expected to include monomers, polymerisation initiators, catalysers and numerous other chemical ingredients as well as polymer degradation products like nonylphenol, and also other substances that are intentionally added during production and food processing [7, 25]. Ter *Veld* et al. [54] showed oestrogenic potency of 21 food-packaging-associated compounds, including bisphenol A, nonylphenol and antoxidants such as butylated hydroxyanisole (BHA) and propyl gallate. Examples of endocrine disrupting chemical substances, their role in food contact materials and modes of action are presented in Table 1.

So far there are no internationally recognised classification or evaluation criteria for EDCs for foodstuffs, which could be used as a base for risk assessment. In pesticides for example, the European Commission anticipating new criteria for allowing EDC identification, proposed, (in the Regulation (EC) 1272/2008), that those substances classified as carcinogenic (Category 2) and/or toxic for reproduction (Category 2) should also be treated as endocrine disruptors [21].

In the following are described some examples of substances formerly used in FCMs together with their toxicological evaluations which resulted in their use becoming limited/restricted due to the legal decisions arising from risk management. When describing these substances their functional role in the technological process was ignored.

Bisphenol A (BPA)

This was found in FCMs made of polycarbonate and internal lacquer coatings in metal cans. Toxicological studies on this compound [27, 28, 52] allowed the No Observed Adverse Effect Level (NOAEL) to be established as 5 mg/kg bw/day, and consequently a Tolerably Daily Intake (TDI) level found to be 0.05 mg/kg bw/day.

From the toxicological evaluation report on BPA, EFSA concluded that exposure to relatively high doses, well above 5 mg/kg bw/day, may be related to some estrogenic effects [16]. This value was confirmed in the later scientific opinion where it was shown that even worse, but still realistic exposure scenarios, the safety

Table 1. Endocrine-disrupting substances in food contact materials (FCMs)

Compound name	Role in FCMs	Mode of action toxicological endpoint
Benzophenone	Additive - photo initiator UV to printing inks used for printing cardboard food packaging	Weak estrogen, binds to estrogen receptor
Bis(2-ethylhexyl) phthalate (DEHP)	Additive - plasticiser in plastic foils, resins, PVC hoses, tubing, foams and plastic kitchenware	Affects reproduction and fertility in 2-generation studies
Dibutyl phthalate (DBP)	Additive – plasticiser	Estrogen
Bisphenol A (4,4'-dihydroxy-2,2--diphenylpropane)	Monomer, starting compound in epoxy resins, lacquer coatings of internal surfaces of cans, polycarbonate plastic materials, thermal papers	Estrogen, binds to estrogen receptor
Butylated hydroxyanisole (BHA)	Additive - antioxidant	Estrogen in α and β cell lines of human osteoblasts
Cadmium	FCM contaminant	Activates estrogen receptor
Dimethyltin bis(isooctyl mercapto-acetate)	Plasticiser	Affects 17β-estradiol biosynthesis
Lead	FCM contaminant	Affects reproductive system
Perfluorooctanoic acid (PFOA)	Surface coatings, food containers surfaces	Alteration of thyroid hormone levels
Propyl gallate	Additive- antioxidant	Estrogen in α and β cell lines of human osteoblasts
Semicarbazide	Twist-off type closure internal coatings	Endocrine disrupting potential not confirmed
Thiram	Rubber vulcanisation accelerator, wood preservative	Thyroid hormone disruption

margin for the proposed TDI was 100 [17]. However, further evaluation by EFSA became necessary due to new, but not yet evaluated results suggesting that BPA affects neuro-development after *in utero* exposure of experimental animals followed by the exposure during infancy through the milk of mothers exposed to this compound [51]. Moreover, new toxicokinetics studies, including transplacental transport, have demonstrated the need for renewing risk assessment regarding perinatal exposure.

From numerous *in vitro* and *in vivo* studies of the effects on receptors, hormones, the immune system, cell proliferation, apoptosis, intercellular communication, changes in proteomics, genomics (including epigenetic changes), EFSA evaluated their impact on the endocrine system and confirmed that currently used safety margins are still adequate [18].

Exposure modelling and biological monitoring data has allowed EFSA to demonstrate that foodstuffs are a major source of BPA in all population groups [20]. However, the modelling based estimates were considerably lower than those presented in EFSA's opinion issued in 2006. In the previous assessments, high exposure in toddlers was up to 300 ng/kg bw and in 3 month old infants this reached 11 000 ng/kg bw. According to current assessments, the exposure in toddlers was now 857 ng/kg bw and 495 ng/kg bw in infants 3-5 days old. For this opinion, EFSA drew attention that the fact that thermal paper used in printers and cash registers may also be regarded as second great source of BPA in populations older than three years [5]. It was further concluded, that biomonitoring of BPA in urine provides a reliable estimation of the overall exposure from all sources, opening promising perspectives for large scale monitoring programs.

Phthalates

These are mainly used as plasticizers in FCMs made of plastic to increase their flexibility, transparency and durability. Butyl benzyl phthalate (BBP) is used as a plasticizer for polyvinyl and cellulose resins and organic intermediates. Di-n-butyl phthalate (DBP) is used in paper coatings, elastomers and printing inks. Di-ethylhexylphthalate (DEHP) is used as a plasticizer for polyvinyl chloride, especially in manufacturing medical devices and a plasticizer for resins and elastomers. *Lamb* et al. [30] observed adverse effects of DEHP on fertility in experimental mice and proposed a NOAEL for reproduction to be set at a level of 20 mg/kg bw/day. However another study [1], following 60 days of feeding, proposed a NOAEL of 69 mg/kg bw/day for the effects on the gonads and endocrine system. A drastically decreased fertility index was also found in these studies. Other studies have confirmed a profound anti-androgen potential of DEHP [24, 39]. All this data unequivocally indicates that the animal results may trigger concerns when related to humans. Moreover, according to the EFSA's scientific opinion, even if the DEHP dietary intake is below the TDI, there are other sources of this compound that contribute towards the total exposure [15].

Benzophenone

This is used as an additive (photo-initiator UV) for printing inks and may be transferred from the food packaging made of cardboard into the packed foodstuff. Toxicological studies aimed at the hormone-mimetic potential of benzophenone and its derivatives are not unequivocal [37]. Nevertheless, its oestrogenic potential was confirmed in proliferation tests on MCF7 cells [34, 40]. It was also found that benzophenone-1 almost entirely blocked the activity of the 17β-hydroxysteroid dehydrogenase enzyme which is responsible for the testosterone synthesis in *Leidyg* cells. These results suggest that benzophenone may influence gonadal development in experimental animals [42].

In an evaluation of potential health threats arising from benzophenone in some food, *Muncke* [37] stressed that the presence of this compound was confirmed in the foodstuffs packed in multilayer cardboard packaging and that the current TDI, as proposed by the European Union, is 0.01 mg/kg bw. The migration limit into the FCMs was set at 0.6 mg/kg of the foodstuff, assuming that the consumption of packed food by an average adult weighting 60 kg will not exceed 1 kg per day.

The above examples however do not exhaust the issue of endocrine disrupting chemical substances in FCMs. Moreover, the FCMs consist only a small fraction of the numerous sources of human exposure to EDCs. Taking this into consideration, the US Environmental Protection Agency proposed a holistic and systematic approach announcing a two-tiered screening and testing process, where Tier 1 is to identify chemical substances that have potential to interact with the hormone system, and Tier 2 is to establish a quantitative dose-response relationship for adverse effects resulting from toxicological endocrine related outcomes [55]. The EU strategy for endocrine disruptors [21] includes compiling a candidate list of potential endocrine disruptors. The list prioritises the substances that must be evaluated further for any endocrine disrupting effects. Category 1 for potential ECDs contains 194 substances with comprehensive evidence of endocrine-disrupting effects in live animals. The substances should therefore be prioritised for further evaluation of endocrine disrupting properties.

CONCLUSIONS

Several aspects of risk assessment are important when drawing conclusions from toxicological studies

on ECDs released from FCMs into foodstuffs. Above all, consumer safety must be taken into account and that the exposure usually takes place from different routes of exposure and concerns more than just a single substance having endocrine disrupting potential. In the cases where some of them induce similar effects, the possibility of cumulative toxicity should be considered [29]. Furthermore, recommendations on acceptable intake of particular ECDs refer to the average consumer and may not adequately secure those individuals who consume food products containing abnormal amounts of these substances [38]. All these aspects justify a precautionary principle that is applied for making risk management decisions on ECDs in foodstuffs.

Reducing the uncertainty resulting through actual exposure to ECDs from numerous sources and further improvements in developing exposure estimates should be recommended in order to determine the contributing share of FCMs in overall exposures.

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