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Review

Endocrine disrupting chemicals and other substances of concern in food contact materials: An updated review of exposure, effect and risk assessment☆

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ABSTRACT

Food contact materials (FCM) are an underestimated source of chemical food contaminants and a potentially relevant route of human exposure to endocrine disrupting chemicals (EDCs). Quantifying the exposure of the general population to substances from FCM relies on estimates of food consumption and leaching into food. Recent studies using polycarbonate plastics show that food simulants do not always predict worst-case leaching of bisphenol A, a common FCM substance. Also, exposure of children to FCM substances is not always realistically predicted using the common conventions and thus possibly misjudged. Further, the exposure of the whole population to substances leaching into dry foods is underestimated. Consumers are exposed to low levels of substances from FCM across their entire lives. Effects of these compounds currently are assessed with a focus on mutagenicity and genotoxicity. This approach however neglects integrating recent new toxicological findings, like endocrine disruption, mixture toxicity, and developmental toxicity. According to these new toxicology paradigms women of childbearing age and during pregnancy are a new sensitive population group requiring more attention. Furthermore, in overweight and obese persons a change in the metabolism of xenobiotics is observed, possibly implying that this group of consumers is insufficiently protected by current risk assessment practice. Innovations in FCM risk assessment should therefore include routine testing for EDCs and an assessment of the whole migrate toxicity of a food packaging, taking into account all sensitive population groups. In this article I focus on recent issues of interest concerning either exposure to or effects of FCM-related substances. Further, I review the use of benzophenones and organotins, two groups of known or suspected EDCs, in FCM authorized in the US and EU.

Contents

Abbreviations: BMI, body mass index; BPA, bisphenol A; CMR, carcinogenic, mutagenic, reproductively toxic; EDCs, endocrine disrupting chemicals; EFSA, European Food Safety Authority; ER, estrogen receptor; EU, European Union; FCM, food contact material; FDA, Food and Drug Administration; FRF, fat consumption reduction factor; HSD, hydroxysteroid dehydrogenase; LDPE, low-density polyethylene; PC, polycarbonate; MCF7, Michigan Cancer Foundation cell line 7; MOSH, mineral oil saturated hydrocarbons; MOAH, mineral oil aromatic hydrocarbons; PET, polyethylene terephthalate; PPAR, peroxisome proliferator-activated receptor; ppb, parts per billion; PVC, polyvinylchloride; RXR, retinoid X receptor; TDI, tolerable daily intake; US, United States of America.

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1. Introduction

By far most food packaging materials and processing equipments are made of plastics, or they contain a polymeric layer in direct contact with food like a laminate or coating. Plastics, polymeric laminates and coatings are complex chemical mixtures. Understanding the leaching of chemicals from plastic-type food contact materials (FCM) into food is an important task of food packaging risk assessment. The common chemical risk assessment paradigm, RISK = EXPOSURE · EFFECT, also applies to FCM. However, in the case of plastic-type FCM there are several unknowns:

1.1. Exposure

Which chemicals are present in the FCM? Due to the complex chemistry of polymers several unknown substances can be incorporated in the final plastics material and potentially migrate into the food [1]. These substances are the so-called NIAS ("*non-intentionally added substances*"): side products of the polymerization process and impurities from the starting material batches and other sources. Identification of NIAS is challenging and not all compounds can always be identified, even if the starting substances and additives are known [2].

How high are the levels of leaching, and thus the actual exposure of consumers to substances from FCM? Assessment of migration levels is usually performed using food simulants—solvents that resemble chemical properties of foods [3]. Analyzing migrants directly in foods is difficult due to the complexity of food matrices. However, consumers are exposed to chemicals in actual foods, and the approximation using food simulants can over- or under-estimate actual exposure levels [4]. Another possibility is to calculate migration using partitioning models; this is commonly done however only for additives [5].

1.2. Effect

What is the toxicity of a given substance? Commonly effects are assessed for monomers and additives, but not for the whole leacheate that can contaminate foods. Furthermore, the final packaging with printing inks, adhesives and labels might leach additional compounds into the foods [6]. Currently there is no systematic assessment of the whole packaging leacheate's toxicity.

How relevant are low levels of chemicals leaching from FCM? Effect assessment for new substance authorizations is currently based on exposure levels. For a low exposure to an intentionally added substance (based on migration studies) a reduced toxicity testing is required (reviewed in [7]), focusing on genotoxicity and mutagenicity. Studies assessing reproductive toxicity are only required, if the leaching substance will be present in food simulants at 1 ppm (1 mg/kg food) or higher in the US, or 5 ppm or higher in the EU. Assuming a 60 kg adult consumes 3 kg of foods and liquids per day, exposures to individual substances not tested for reproductive toxicity can be up to 50 μg/kg bw/d in the US and 5-fold higher in the EU. Of special interest in this context are endocrine disrupting chemicals (EDCs): compounds altering hormonal and homeostatic systems [8]. EDCs act via receptor binding, but also via "enzymatic pathways involved in steroid biosynthesis and/or metabolism, and numerous other mechanisms that converge upon endocrine and reproductive systems" [8]. Originally of concern for reproductive and developmental toxicity, these chemicals have in addition been linked to diverse effects like cardiovascular disease, obesity, diabetes, cancers, and neurological effects and are "a significant concern to public health" [8]. The group of EDCs is highly diverse in terms of structure and origin (natural or anthropogenic) [8]. One well-known representative is the synthetic chemical bisphenol A. For chronic exposures to bisphenol A effects are seen in animal studies at low doses [9] and especially if exposures occur during the perinatal period [10,11]. The ongoing scientific debate about low dose effects of bisphenol A is controversial; however, if low dose effects of bisphenol A are generally accepted to be of concern for human health in-depth toxicological testing of FCM substances will need to be carried out at lower levels than 1 (US) respectively 5 ppm (EU).

Is a food content of 10 ppb for any given substance leaching from food packaging not of concern? Currently 10 ppb is the threshold level below which NIAS are thought to be negligible in the EU, with the exception of CMR substances (carcinogenic, mutagenic, reproductively toxic) [7]. In the US no effect assessments are required for any substances present in the diet at or below 0.5 ppb [12]; again, this approach only applies to single substances, not to the overall mixture of the packaging leacheate. However, chemicals that target the same biological endpoint can act additively [13] or even synergistically [14] if they are present in the mixture at or below their individual effect levels. Therefore a toxicologically more relevant approach for assessing FCM chemicals would be to test for the total migrate's toxicity, as has been done for paper and board packaging [15,16].

European FCM legislation demands safety for all substances that can migrate from food packaging at relevant concentrations (Art. 3, EC 1935/2004), but in practice the migrates partially remain unidentified. Unknown compounds cannot be quantified, implying an uncertainty whether the 10 ppb limit is adhered to. In addition, it is not possible to assess the toxicity of an unknown compound from a complex mixture, adding further to the uncertainty. Testing whole migrate therefore offers an opportunity for reducing uncertainty.

In conclusion, exposure assessment for chemicals leaching from food packaging currently is estimated with apparent uncertainties. Effect assessment for industrial chemicals that are endocrine disrupters has recently been shown to be a controversial issue with differing scientific views depending on scientists' backgrounds and competing interests [17]. Improving consumer protection from harmful FCM chemicals is in the interest of public health. Achieving this goal will imply resolving the issues at hand on a scientific level—starting with an urgently needed definition of endocrine disruption cut-off criteria that are accepted by all stakeholders.

2. Exposure assessment

Quantifying the exposure of the general population to substances from FCM relies on estimates of food consumption and leaching into food. Recent studies show that (1) food simulants do not always predict worst-case leaching, (2) exposure of children to FCM substances is not always realistically predicted using con-

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ventions, and (3) exposure to substances leaching into dry foods is underestimated.

2.1. Migration vs. release: systematic underestimation of exposure to bisphenol A from plastic baby bottles

Chemicals that leach from food packaging into food are usually intentionally added compounds, like additives, processing aids and un-reacted monomers. Furthermore, NIAS (side products like oligomers and impurities) can contribute to overall leaching. Leaching of these substances is generally defined as migration and systematically assessed prior to market authorizations. On the other hand, polymers can degrade under the influence of acidic or alkaline foodstuffs, UV light, and heat. As a result monomers can leach—this process is known as "release". The release from plastic FCM is only assessed for repeated use articles, like baby bottles.

In the past, leaching of bisphenol A (BPA) from polycarbonate (PC) plastic baby bottles has been thought to be low, around or below 1 ppb [18,19], with higher levels detected at increased temperature and in repeatedly used bottles [20–22]. When a German consumer magazine reported leaching of bisphenol A from microwave-heated PC baby bottles into tap water the levels were far higher, with up to 157 ppb found [23]. At first, microwaves were suspected to degrade the PC polymer, but a subsequent study found this not to be the case [24]. Recently another study delivered an explanation for diverging measurements of BPA: the type of food or food simulant used in the studies plays a key role [25]. The official food simulant is purified, distilled water. This medium was generally used to assess BPA migration. On the other hand, the German consumer magazine used the actual foodstuff, in this case tap water. If the tap water is "hard", i.e. sourced from groundwater with a high content of dissolved CO_2 and Ca^{2+}/Mg^{2+}, then CO_2 will gas out over time with heating at normal pressure. This leads to a change in the buffer system, ultimately resulting in an increased pH of around 9 [26]. Water that is alkaline can degrade the PC plastic and lead to a release of BPA [27], a phenomenon not observed when baby bottles are tested for migration using salt-free pure H_2O. The most relevant parameters for degradation of PC thus are temperature, the food's chemical properties like pH, and polymer age [27].

For risk assessments the actual levels of chemicals in foods are relevant and food simulants are not always good predictors as has been shown for perfluorinated compounds [28]. BPA leaching from PC under realistic conditions of use is higher than estimated using the standard food simulants; these have been shown to be less predictive of actual levels in foods because the release by polymer degradation is not assessed [25]. Thus actual exposure of infants to BPA leaching from PC baby bottles most likely also is higher than previously estimated when migration values for distilled water are used [29].

For other repeated-use articles similar issues might become relevant, especially if the monomers have shown to exert adverse effects. Examples are plastics made of melamine–formaldehyde resin [30,31] and styrene–acrylonitrile resin [32]. Furthermore, single-use articles, like polyethylene terephthalate (PET) water or soda bottles that are customarily refilled with tap water by consumers are not assessed for this type of reuse even though it is common practice.

2.2. Exposure of children to FCM substances

One of the major differences in the EU's and the US' practice to regulate FCM is the consumer's exposure assessment. In the EU, exposures are estimated based on the assumption that a person weighs 60 kg and daily consumes 1 kg of packaged food in contact with 6 dm^2 of FCM. Legal limits are given for the presence of specific substances in food [7]. In the US, consumers are thought to weight 60 kg on average and consume in total 3 kg per day of food and drinks, where 1 kg is in contact with 6.45 dm^2 of FCM. Contrary to the EU, the US FDA estimates how much of a type of food is in contact with what specific FCM type, and then calculates the approximate migration levels [12]. Estimations are based on averages of confidential market data and are the basis for the FDA's packaging consumption factors. A recent field study carried out in Portugal compared actual packaging consumption factors to the values used by FDA for exposure assessment and found a 30% lower estimate for plastics consumption in the US compared to Portugal; the difference was especially relevant for polyethylene terephthalate (PET) [33].

Exposure of British children aged 0–6 years to FCM has recently been assessed in a field study [34]. The authors found that these children on average consumed 1.6 times (ages 0–1), 2 times (ages 4–6), and 3 times (ages 1–4) as much plastic food packaging as estimated by the current EU approach. These data indicate that children have a proportionally higher exposure to substances leaching from plastic FCM than adults. The Norwegian Scientific Committee for Food Safety recommends a reduction of specific migration limits (SML) for infant food products by a factor of 10; for young children aged 1–3 years the SML is suggested to be adjusted by a factor 4–5. Further, the Committee recommends a case-by-case assessment of substances transferring from FCM into foods that are frequently consumed by infants and children [35]. Introducing such safety factors would ensure that children are not exposed to contaminant levels above the TDI: infants and children consume up to 10 times more food per kg bodyweight; in addition infants receive a limited variety of dietary products. Furthermore, small packaging sizes are especially marketed to children, with a larger surface-to-volume ratio and therefore higher migration per kg food [36].

2.3. Transfer of FCM substances into dry foods

Food contact materials can also be a relevant source of chemical contaminants in dry foods. Volatile components from packaging are transferred into foodstuff through the gas phase in the same way partitioning in environmental media (air/water/sediment) has been described using fugacity modeling [37]. Examples include migration of phthalates and mineral oil components from recycled paperboard packaging into infant food [38,39]; in this case only an aluminum-laminated inner bag offered complete protection from contamination. Dibutylphthalate, diisobutylphthalate and benzophenone were found to transfer from recycled carton food packaging into rice and breadcrumbs used for battering [40]. Highest migration levels of 3–5 ppm were observed mainly in finely ground foods like icing sugar or flour [40]. In 2009, a derivative of benzophenone, 4-methylbenzophenone was found in various European breakfast cereal samples packaged in paperboard at levels of up to 3.7 ppm in the food [41]. Benzophenone was found in the range of 232.7–580.9 mg/m^2 in freshly produced carton food packaging, while after one year levels were reduced by 50% [42]. In this study, suitable inner bag material was found to be multilayer plastic foils, while single layer polypropylene did not prevent migration of benzophenone into the foodstuff [42]. Migration has also been shown to be relevant for dry foods packaged in low-density polyethylene (LDPE) packaging, where triclosan was shown to leach into wheat flour and rice at low levels [43]. The use of triclosan as additive in FCM is not authorized for the US; in the EU, an authorization application for triclosan used as additive in plastics FCM has been withdrawn. Triclosan has been proposed as effective ingredient in active packaging where it is intentionally released into the food as a way of extending shelf life [44].

Highest food contamination has been observed for mineral oil fractions from recycled and/or printed paperboard packaging, with 19 ppm found to migrate into dry rice [45] and up to 33 ppm in

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dry baby foods [39]. Mineral oil consists of saturated hydrocarbons (MOSH) like paraffins and highly alkylated aromatic hydrocarbons (MOAH); it is estimated that MOAH constitute around 15–20% of all mineral oil found in paperboard packaging [45]. In a recent study, around 70% (19 ppm) of the volatile mineral oil fraction (up to n-C_{24}) transferred from a rice packaging into the rice after a storage time of 8 months [45]. Other retail samples had even higher levels of mineral oil content in the packaging, ranging from 265 to 1065 ppm [45] thus potentially resulting in higher food contamination levels after the same storage time.

While the toxicological relevance of these findings remains to be established there are two important implications:

(1) Dry foods can also be significantly contaminated with packaging-related xenobiotic chemicals from printing inks and/or recycled paperboard, especially after long storage periods of several months. Use of an inner bag is recommended, however not all materials are effective barriers; some plastic bags can be contaminant sources as well [46].
(2) Material recycling is a societal interest, however a more stringent source control seems necessary. In the short term this applies to material sources used for recycling into food contact applications. In the long term source control needs to be discussed for use of printing inks for non-food contact paper products that might be recycled into FCM (like newspapers).

3. Effect assessment

Consumers are usually exposed to low levels of substances from FCM across their entire lives. In general, effects of these compounds are assessed with a focus on mutagenicity and genotoxicity, if the expected exposure levels are low. This approach however neglects integrating recent new toxicological findings, like endocrine disruption, mixture toxicity, and developmental toxicity. Women of childbearing age and during pregnancy thus are a sensitive population group. Furthermore, in overweight and obese persons a change in the metabolism of xenobiotics is observed, possibly implying that this group of consumers is insufficiently protected by current risk assessment practice.

In 2009, the Endocrine Society published a scientific statement about EDCs and expressed concern about the widespread exposure of humans to these compounds [8]. Endocrine disrupting chemicals are known to have diverse modes of action and can affect multiple endpoints within living organisms. A closer look at food packaging revealed that there are at least 50 compounds authorized for use in FCM that have known or suspected endocrine disrupting properties [7]. However, when FCM substances are assessed for their health risk they are not routinely tested for their endocrine disrupting potential.

3.1. New toxicological paradigms of relevance for FCM effect assessment

Chemicals that can mimic or interfere with endocrine signaling, the EDCs, have been shown to exert adverse effects already at low doses and during sensitive windows of development (i.e. during pregnancy and childhood) [8]. In the past mainly estrogenic effects of FCM substances or food packaging [47] have been investigated. More recently studies are finding FCM substances to be (anti) androgenic, to interact with the thyroid hormone receptor, the peroxisome proliferator-activated receptor (PPAR), retinoic acid receptor and vitamin D receptor [48–50]. FCM substances that activate or antagonize several different hormone signaling pathways are especially of concern as this multiplicity might enhance the effect in the intact organism [50]. Furthermore, it has been established that mixtures of chemicals with common biological endpoints can act additively [51].

On the other hand, assessment of food packaging toxicity is performed using a single substance approach. Only recently whole packaging migrates from different FCMs have been studied for their overall toxicity [15,16,47,52–54]. It is noteworthy that in all studies effects of the whole leacheate were observed that could not be explained only by the known toxicity of identified or putative mixture components. These findings suggest the need for a systematic effect assessment of whole packaging migrate that include endocrine disruption.

Moreover, effects of chemical exposure on the epigenome may persist transgenerationally, leading to disease predisposition [55]. Implications of this recent finding need to be evaluated for FCM.

3.2. A changing population poses new challenges for chemical effect assessment

Current regulatory risk assessment relies on safety factors to extrapolate from animal experiments to humans: for toxicokinetic differences between mammalian species a factor 4 is applied, for toxicodynamic variation a factor 2.5 is used, resulting in a factor of 10 for interspecies extrapolation [56]. Furthermore, risk assessment takes into account that there is variability within the human population, such as polymorphisms or other intraspecies differences reflected in individual toxicodynamics (factor 3.16) and toxicokinetics (factor 3.16), resulting again in a factor of 10 [56]. This means that in general a safety factor of at least 100 is applied for deriving the safe human exposure level from a rodent study, but factors can vary [57].

However, rethinking the safety factor for intraspecies toxicokinetics might become necessary in light of a changing population. In the US currently 68% of inhabitants are overweight with BMI $\geq$ 25 and 33.8% of the US population is obese with BMI $\geq$ 30 [58]. It is important to note that the issue of an increasingly obese population is not limited to the US, but has become a global pandemic [59]. Of particular concern are the higher frequencies of obesity and overweight in children and adolescents [60]. An increased BMI has been linked to nonalcoholic fatty liver disease [61]. For some xenobiotics obesity showed higher toxicity in rodents [62,63] while for other compounds more rapid clearance is observed [64,65]. A constantly growing body of scientific studies indicate that the toxicity of substances can change with obesity [66]; this matter is receiving increased attention by medical practitioners and in pharmacology [65]. It is obvious that far more research is necessary to understand this background of disease and also its relevance for chemical risk assessment.

4. Specific compounds present in FCM

Benzophenones and organotins are compound groups of special interest due to the well-studied endocrine disrupting properties of single exponents like benzophenone-3 and tributyl tin. These compounds are widely used in various products, also in FCM. In this section an overview of the use of benzophenones and organotins in FCM is given, accompanied by a brief review of the exposure and endocrine disrupting effects that are known for these compound groups.

4.1. Benzophenones

Benzophenone is a non-substituted diphenylketone that is widely used in FCM and also as food additive in the US. It is a photoinitiator in UV-cured printing inks, with a final content in the printing ink of 5–10% [67]. Because benzophenone is a fairly small molecule that is not chemically bound to the printing ink it can

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Table 1
Benzophenone and its derivates used in FCM in the US and EU.

CAS #	Name (synonyms)	FDA	EU
119-61-9	Benzophenone (diphenylketone)	21CFR172.515: synthetic flavoring substances and adjuvants 21CFR177.2600: rubber articles intended for repeated use 172.515: synthetic flavoring substances and adjuvants	Additive list SML = 0.6 mg/kg FRF applies
131-56-6	Benzophenone-1 (2,4 dihydroxybenzophenone)	Not authorized	Additive list SML(T) = 6 mg/kg
131-57-7	Benzophenone-3 (oxybenzone; 2 hydroxy 4 methoxybenzophenone)	21CFR177.1010: acrylic and modified acrylic plastics, semirigid and rigid	Additive list SML(T) = 6 mg/kg FRF applies
131-53-3	Benzophenone-8 (dioxybenzone; 2,2′dihydroxy 4 methoxybenzophenone)	Not authorized	Additive list SML(T) = 6 mg/kg FRF applies
1843-05-6	Benzophenone-12 (octabenzone; methanone; 2 hydroxy 4n-octyloxybenzophenone)	21CFR178.2010: antioxidants and/or stabilizers for polymers (restrictions apply) 21CFR178.3710: petroleum wax	Additive list SML(T) = 6 mg/kg FRF applies
345-92-6	Difluorobenzophenone (4,4′fluorobenzophenone)	Not authorized	Monomer list SML = 0.05 mg/kg
611-99-4	4,4′Dihydroxybenzophenone	Not authorized	Monomer list Additive list SML(T) = 6 mg/kg
3293-97-8	2 Hydroxy 4n-hexyloxybenzophenone	Not authorized	Additive list SML(T) = 6 mg/kg FRF applies
1322-77-6	2-Hydroxy-4-methoxy-2-carboxybenzophenone	21CFR177.1010: acrylic and modified acrylic plastics, semirigid and rigid	Not authorized
14984-21-5	4,4′Diphenoxybenzophenone (Bis(4-phenoxyphenyl)methanone)	21CFR177.1556: polyaryletherketones	Not authorized

transfer from the outer, printed carton into foods. Furthermore, benzophenone was found in recycled carton board even if it had not been printed, presumably due to previous material contamination [40]. Several benzophenone derivates with similar functions currently are authorized for use as additive or monomer in plastic FCM in the EU, and as direct or indirect food additives in the US (Table 1). One of the benzophenone derivates, benzophenone-3, is widely used in cosmetic applications (like sunscreens) with this exposure source thought to be most relevant; benzophenone-3 was detected in 96.8% of the US population during a recent representative sampling [68]. Recently 4-methoxybenzophenone was found in dry foods due to migration from the printed packaging carton [41].

The chronic toxicity of benzophenone has been studied in the Sprague-Dawley CD rat in a 90 day feeding study using 20, 100 or 500 mg/kg bw/d. Neither after 28 days, nor after 90 days were statistically significant differences observed between control animals and the 20 mg/kg bw/d group [69]. In a chronic 2 year feeding study some evidence of carcinogenic activity for benzophenone was found in rats and mice using 312, 625 and 1250 mg/kg bw daily doses [70]. An increase in kidney cancers in male animals, liver tumors in male mice, and histiocytic sarcomas in female mice was observed.

There are conflicting findings on the estrogenicity of benzophenone in the literature: estrogenicity was found neither *in vivo* nor *in vitro* using the uterotrophic assay and a human estrogen receptor α (ERα) reporter gene assay [71]; estrogenicity was observed in a MCF7 cell proliferation assay for benzophenone and various derivates, including benzophenone-1 and benzophenone-3 [72]. For benzophenone-1 binding to ERα in a transgenic reporter assay has been shown [13].

The main metabolites of benzophenone in rats were shown to be benzhydrol (CAS# 91-01-0) and 4-hydroxybenzophenone (CAS# 1137-42-4) [73]. The latter, 4-hydroxybenzophenone has been found to be estrogenic in MCF7 cells [72,74]. Benzophenone-1 almost completely blocks 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) activity *in vitro* [75]. The 17β-HSD3 enzyme is required for testosterone synthesis in Leydig cells and plays an important role during male sexual development.

A related compound, benzophenone-2 (CAS# 131-55-5), also blocks 17β-HSD3, albeit with less affinity [75]. Furthermore, benzophenone-2 caused hypospadias in male mice exposed during *in utero* development via an estrogen receptor dependent mechanism [76]. It has also been shown to reduce thyroid hormone levels in rats, possibly via inhibition of thyroid peroxidase, an enzyme required for thyroid hormone synthesis and the target for treating hypothyroidism [77]. Benzophenone-2 is currently not authorized for use in FCM in the US and as plastics FCM additive in the EU. There is no information available on the actual presence of this substance in FCM or foods.

Benzophenone-3 is widely used in sunscreens and is absorbed via skin [78]. It was found to possess estrogenicity in rats at high dose and lead to proliferation of MCF7 cells [79]; in another study benzophenone-3 activated estrogen-receptor controlled gene transcription in an *in vitro* reporter assay [80], but not *in vivo* in zebrafish that were stably transfected with an estrogen-responsive reporter gene [81]. The main metabolites of benzophenone-3 in rats have been identified as benzophenone-1, benzophenone-8 and 2,3,4-trihydroxybenzophenone. Benzophenone-8 has been tested *in vitro* and *in vivo* for its genotoxic and mutagenic potential with no effects observed [82], however it was found to be estrogenic *in vitro* in a yeast reporter gene assay [80]. Benzophenone-12 was originally isolated from the brown algae *Desmarestia menziesii* [83]. There are no studies available in the literature investigating the estrogenicity or genotoxicity of this compound. The monomer 4,4′ dihydroxybenzophenone was estrogenic *in vitro* in a yeast reporter gene assay, as well as its S9 metabolite mix [84]. This benzophenone has also been shown to be a metabolite of bisphenol F (CAS# 620-92-8) and its estrogenicity has been investigated *in vitro* with a reporter gene assay, showing agonism for both human ERα and ERβ [85]. For the other benzophenones used in FCM there is no publicly available information on their endocrine disrupting properties.

In the EU currently the tolerable daily intake (TDI) for benzophenone is 0.01 mg/kg bw/d. The currently applicable migration limit for benzophenone from packaging into foods is 0.6 mg/kg food and this value assumes that all human exposure to benzophenone will result from FCM (basis: 1 person is 60 kg and consumes 1 kg of packaged foodstuff per day). Benzophenone was found in all tested bev-

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erage samples from Italian retail [86]; the packaging for all samples was multilayer laminated carton bricks. Migration of benzophenone derivates used in paperboard printing inks to food has been tested for different foodstuffs, with highest levels detected to leach into cakes, followed by bread, breakfast cereals and rice. In pasta the observed contamination with benzophenones was lowest [87].

4.2. Organotins

Organotins have been used for many years in plastics food packaging as heat and light stabilizing additives or as starting substances in polymerization [88]. They prevent polyvinylchloride (PVC) degradation by binding chloride in a substitution reaction, resulting in chlorinated organotin species [89]. Around 70% of worldwide organotin production is used as additives in PVC plastics [90].

In the EU, 27 different organotin compounds or mixtures are authorized for use in plastic-only food contact materials (Table 2). Specific migration limits vary strongly because they are based on tin content (by weight), not actual molecular weight. In effect, this means that permitted levels in food for most organotins are in the 10–100 ppb range. One exception is the oligomeric organotin additive dibutylthiostannic acid polymer (CAS# 26427-07-6) used in plastics and coatings with no specific migration limit.

For some of the organotin additives the fat consumption reduction factor (FRF) applies. The FRF is a special measure of EU FCM regulation to take into account that products high in fat content will be consumed in less quantity. For such foods use of the FRF allows higher specific migration. Thus, for highly fatty foods the FRF mirrors the US' approach to FCM regulation that is based on consumer exposure [36].

In the US the FDA has authorized the use of 15 different organotins as indirect food additives for various applications (Table 2). Many of the organotins permitted in the EU are also legally used in the US, but there are a few compounds only authorized in either economic region.

Based on *in vitro* studies using Caco-2 cells the uptake of organotins through the gut is estimated to be highest for dibutyltin and tributyltin and lowest for monobutyltin [91,92]. The toxicity of organotins also varies with alkylation, with tri- and di-substituted tins being more toxic than monoalkylated tins [93,94].

Several organotins have been tested *in vitro* for their effect on 17β-estradiol biosynthesis. Dibutyltin and monobutyltin were found to upregulate 17β-hydroxysteroid dehydrogenase type I, an enzyme that is highly activated in human placenta cells and catalyses the conversion of estrone to 17β-estradiol [95].

Tributyltin and triphenyltin are well-established EDCs. They are known to cause imposex in marine mollusks by increasing testosterone levels [96], via inhibition of androgen-converting aromatase [97]. These compounds bind with high affinity to the peroxisome proliferator-activated receptor γ (PPARγ) and the retinoid X receptors (RXR), receptors that play critical roles in adipocite differentiation, energy storage and nuclear receptor signaling. These organotins have thus been linked to the obesity pandemic [98]. Both tributyltin and triphenyltin are not authorized for use in FCM in the US and EU.

Also various other organotin compounds have been studied for their binding to PPARγ [99]. For dibutyltin only a weak affinity was observed, while for monobutyltin no binding was seen. Dibutyltin was almost equally cytotoxic in JAr cells as the trialkylated compounds, while monobutyltin had no effect even at highest concentrations [95].

In the manufacture of glass packaging monobutyltin chloride (CAS# 1118-46-3) is used as a hot end coating [100]. It is applied to the hot glass surface which leads to instant pyrolization of the organic moiety [101]. Butyltin has been found in wine and liquors [102–105], often in combination with dibutyltin. Under acidic conditions dibutyltin degrades to monobutyltin [100]. Both the monobutyltin and dibutyltin in these samples are thought to have originated from PVC plastic bulk storage containers [105]. Levels found in wine are higher than other alcoholic drinks, likely due to acidity-enhanced migration from PVC FCM [90]. Another possible source for organotins in wines are the closures [106].

Organotins have mainly been found in sea food [107,108], but also in beer [102], and margarine, mayonnaise and processed cheese [109]. Consumption of contaminated fish is thought to be the most relevant human exposure source [110].

5. Does risk assessment of food packaging need adaptation?

Risk assessment of FCM substances is a challenging task. Apart from the known, intentionally used compounds there are several side-products or unknown chemicals that can migrate from plastic-type FCM into foods. It is not always possible to identify these chemicals and evaluate their toxicity.

On the other hand it is in the interest of public health that food packaging is appreciably safe. With the growing public concern for EDCs like bisphenol A and phthalates that are present in food packaging, the safety assessment of FCM has become even more challenging. Currently genotoxicity and mutagenicity testing are required for low level leaching of FCM substances into foods—for a good reason, as cancer is a highly relevant non-communicable disease and public health burden. In this context it is important to understand that after many decades of cancer research the exact mechanism how cancer develops is not yet fully understood [111], however carcinogenic substances are regulated. Consequently mutagenic substances are not permitted for use in FCM in the EU and US.

Also for some EDCs there is increasing evidence for involvement in the development of several non-communicable diseases, including cancers [8,112]. Thus, systematic assessment of EDCs in food packaging offers an opportunity for avoiding broad public exposures to potentially harmful chemicals and possibly preventing various chronic diseases. Therefore it is opportune to introduce a first tier *in vitro* testing for endocrine disrupting properties when new food contact substances are authorized, analogous to the testing for mutagenicity and genotoxicity. Currently for nongenotoxic carcinogens that can also be EDCs no systematic testing is required at lower exposure concentrations. This practice is based on the assumption that thresholds for tumor development exist for nongenotoxic carcinogens. Yet this endorsement of low-dose non-linearity for risk assessment of nongenotoxic chemicals is scientifically disputed [113]. Hence it would be more prudent to assume low-dose linearity also for nongenotoxic carcinogens and EDCs according to the approach for mutagenic substances. Consequently, this also implies a retrospective systematic assessment of substances that are already authorized for use in FCM. Also the EU's toxicological testing requirements for FCM substances based on migration levels should be reviewed: currently the EU's threshold is 5-fold higher than in the US for an extended toxicological evaluation (250 μg/kg bw/d).

Another challenge for FCM risk assessment is mixture toxicity. Plastic-type food contact materials leach mixtures of substances at low concentrations. These mixtures consist of monomers, additives, manufacturing aids, side-products, impurities, printing inks, adhesives, and other compounds. Not all components of the whole migrate mixture are known. The toxicity of this total migrate in food is of concern because it is this mixture that consumers are exposed to rather than the single FCM substances. A methodical assessment of the whole migrate's biological effects could assist at adequately assessing this risk. For this purpose, standardized extraction and

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Table 2
Organotin compounds authorized for FCM in the EU and US.

Grouping	CAS number	Chemical name	EU migration limit	FDA ruling
Methyltins	26636-01-1	Dimethyltin bis(isooctyl mercaptoacetate)	SML(T)[a] = 0, 18 mg/kg (expressed as tin)	21CFR178.2010: antioxidants and/or stabilizers for polymers
	54849-38-6	Monomethyltin tris(isooctyl mercaptoacetate)		
	57583-35-4	Dimethyltin bis(ethylhexyl mercaptoacetate)		
	57583-34-3	Monomethyltin tris(ethylhexyl mercaptoacetate)		
	68442-12-6	Reaction products of oleic acid, 2-mercaptoethyl ester, with dichlorodimethyltin, sodium sulphide and trichloromethyltin	SML(T)[a] = 0, 18 mg/kg (expressed as tin) FRF applies	
Butyltins	23850-94-4	Monobutyltin tri(2-ethylhexoate)	Not authorized	21CFR175.300: resinous and polymeric coatings 21CFR177.2420: polyester resins, cross-linked
	818-08-6	Dibutyltin oxide	Not authorized	21CFR177.2420: polyester resins, cross-linked
	22373-43-0	Hydroxybutyltin oxide	Not authorized	
	26427-07-6	Dibutylthiostannoic acid polymer [=Thiobis(butyl-tin sulphide), polymer]	No SML available	Not authorized
Monooctyltins	26401-86-5	Mono-n-octyltin tris(isooctyl mercaptoacetate)	SML(T)[b] = 1, 2 mg/kg (18) (expressed as tin)	21CFR178.2650[d]: organotin stabilizers in vinyl chloride plastics
	27107-89-7	Mono-n-octyltin tris(2-ethylhexyl mercaptoacetate)		Not authorized
	n.a.	Mono-n-octyltin tris(alkyl(C10–C16) mercaptoacetate		
Dioctyltins	10039-33-5	Di-n-octyltin bis(2-ethylhexyl maleate)	SML(T)[c] = 0.006 mg/kg (expressed as tin)	21CFR178.2650[d]: organotin stabilizers in vinyl chloride plastics Not authorized
	26401-97-8	Di-n-octyltin bis(isooctyl mercaptoacetate)		
	15571-58-1	Di-n-octyltin bis(2-ethylhexyl mercaptoacetate)		
	33568-99-9	Di-n-octyltin bis(isooctyl maleate)		
	3648-18-8	Di-n-octyltin dilaurate		
	15571-60-5	Di-n-octyltin dimaleate		
	69226-44-4	Di-n-octyltin ethyleneglycol bis(mercaptoacetate)		
	15535-79-2	Di-n-octyltin mercaptoacetate		
	n.a.	Di-n-octyltin thiobenzoate 2-ethylhexyl mercaptoacetate		
	n.a.	Di-n-octyltin dimaleate, polymers (N = 2–4)		
	n.a.	Di-n-octyltin dimaleate, esterified		
	n.a.	Di-n-octyltin bis(ethyl maleate)		
	n.a.	Di-n-octyltin bis(n-alkyl(C10–C16) mercapto acetate)		
	n.a.	Di-n-octyltin 1,4-butanediol bis(mercaptoacetate)		
	16091-18-2	Dioctyltin maleate	Not authorized	21CFR178.2650[d]: organotin stabilizers in vinyl chloride plastics
Dodecyltins	67649-65-4	Mono-n-dodecyltin tris(isooctyl mercaptoacetate)	0.05 mg/kg food (expressed as sum of mono- and didodecyltin chloride)	21CFR178.2650: organotin stabilizers in vinyl chloride plastics
	84030-61-5	Di-n-dodecyltin bis(isooctyl mercaptoacetate)	0.05 mg/kg food (expressed as sum of mono- and didodecyltin chloride) FRF applies	
Further organotins	63397-60-4	Bis(2-carbobutoxyethyl)tin-bis(isooctyl mercaptoacetate)	SML = 18 mg/kg FRF applies	Not authorized
	63438-80-2	(2-Carbobutoxyethyl)tin-tris(isooctyl mercaptoacetate)	SML = 30 mg/kg FRF applies	Not authorized
	83447-69-2	C10–16-alkyl mercaptoacetates reaction products with dichlorodioctylstannane and trichlorooctylstannane	Not authorized	21CFR178.2650[d]: organotin stabilizers in vinyl chloride plastics

n.a., not available.
FRF applies: fat (consumption) reduction factor in the EU; an estimate that allows to assess estimated consumer exposure rather than migration levels in fatty foods.
[a] SML(T) in this specific case means that the restriction shall not be exceeded by the sum of the migration levels of the substances mentioned as Methyltins.
[b] SML(T) in this specific case means that the restriction shall not be exceeded by the sum of the migration levels of the substances mentioned as Monooctyltins.
[c] SML(T) in this specific case means that the restriction shall not be exceeded by the sum of the migration levels of the substances mentioned as Dioctyltins.
[d] Migration limit for all organotins listed under 178.2650 into food simulants 0.5 mg/kg food simulant.

migration procedures need to be developed so that mixtures can be tested in *in vitro* endocrine disruption, mutagenicity and genotoxicity assays.

Also for the exposure assessment there is potential for advancement. Recent studies indicate that exposure approximations can be improved specifically for infants and children by taking smaller, more realistic packaging sizes into account and applying additional safety factors [34,35]. Furthermore, market data underlying exposure estimates for different FCM in the US should be made publicly available. As these estimates are based on averages consumers with a strong preference for certain products or packaging materials ("high consumers") will be less protected.

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In conclusion, the challenge for regulators of FCM is to adopt recent scientific findings into systematic authorization procedures, for the benefit of public health.

Disclaimer

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