coatings

MDPI

Review

Migration and Safety Aspects of Plastic Food Packaging Materials: Need for Reconsideration?

Andreas Panou [1] and Ioannis Konstantinos Karabagias [2,*]

[1] Independent Researcher, George Papandreou 23, 16451 Athens, Greece; andr_panou@yahoo.gr
[2] Department of Food Science & Technology, School of Agricultural Sciences, University of Patras, G. Seferi 2, 30100 Agrinio, Greece
* Correspondence: ikaraba@upatras.gr; Tel.: +30-697-828-6866

Abstract: The aim and the novelty of the present review article was to provide the literature with a collective study focusing on the migration and safety issues in plastic food packaging materials that have been raised in recent years and proposing the use of safer and biodegradable ones. The conventional packaging materials used for the preservation of foods may exhibit many disadvantages that are related to the migration of micromolecular chemical substances incorporated in the packaging material net to the packaged food. There are many chemical substances in the matrix of plastic packaging materials and epoxy-resins that are used in food packaging materials, varnishes, and can coatings. Many migrants have high toxicity, such as acetaldehyde, antimony, antimony (III) oxide, 2,4-di-tert-butylphenol, tris (2,4-di-tert-butylphenol) phosphate, tris(2,4-di-tert-butylphenyl) phosphite, *bisphenol* A, and the plasticizers di(2-ethylhexyl) phthalate), di-n-butyl phthalate, benzyl-butylphthalate, di-isononylphthalate, and di-isododecylphthalate. It is therefore necessary to take a detailed look at the migrants in conventional packaging materials (plastics) used for foods, point out the migration of certain compounds into foods and the need to reconsider their use, and establish updated protocols for the safety of consumers and the industrial production of biodegradable packaging materials (films or coatings) based on natural sources.

Keywords: plastics; migration; foods; consumers; safety; natural films and coatings

Citation: Panou, A.; Karabagias, I.K. Migration and Safety Aspects of Plastic Food Packaging Materials: Need for Reconsideration? *Coatings* **2024**, *14*, 168. https://doi.org/10.3390/coatings14020168

Academic Editors: Amit K. Jaiswal and Swarna Jaiswal

Received: 8 December 2023
Revised: 12 January 2024
Accepted: 23 January 2024
Published: 28 January 2024

1. Introduction

A matrix of plastic packaging material, except for macromolecular substances, consists of micromolecular substances such as metals as catalysts, very low amounts of solvent and monomers, and various reaction products that are produced during the manufacturing of plastic materials. Thermal decomposition products and various additives are added for the improvement of plastic materials' disadvantages, such as plasticizers, stabilizers, antioxidants, extinguishers, etc. When a plastic packaging material is in contact with food, the transfer of micromolecular substances from the matrix of the plastic material to the food occurs. This phenomenon is called migration, and the migrating substances are named migrants [1]. Regarding migration, when the migration of a specific substance occurs, it is named specific migration, while when migration concerns all the migrating substances, it is named overall migration. There are migration cases that lead to desirable results, such as the incorporation of antistatic media into packaging materials and the controlled diffusion of medicines from the net of plastics [1]. However, in most cases, migration is undesirable because of the diffusion of harmful chemical substances such as plasticizers from plasticized PVC (in toys and shower curtains), flame retardants (in plastic casings of televisions and computers), and various harmful chemical substances into foods and medicines, which can deteriorate the taste of food and the active compound of the medicine.

The process of migration can be divided into four stages:

(1) Diffusion of the migrants through the polymeric molecules of the plastic packaging material;

(2) The desorption of substances from the surface of the packaging material;
(3) The absorption of substances from the interface between the food and packaging material;
(4) The absorption of substances onto the food [2].

The main factors that are responsible for the migration of these micromolecules are as follows: (a) the presence of attractive forces between the micromolecules and the food constituents, (b) the low dimensions and molecular weight of the micromolecules, and (c) the volatility of the micromolecules. For example, low-size molecules (monomers and debris solvents) have low boiling points and exhibit high migration levels. Some monomers, such as formaldehyde, vinyl chloride, ethylene, and butadiene, present high migration levels even at ambient temperature [3]. Regarding molecular weight, a substance of high molecular weight presents low migration levels on account of its large dimensions. The migration levels are also influenced by the concentration of substances inside the plastic packaging material, the thickness of the packaging material, and the crystallinity and surface structure of the packaging material [3]. Migrants are divided into two categories: (i) IAS and (ii) NIAS [1]. The first type includes substances such as additives, monomers, metals, and various starters, and the second type includes substances such as polymer decomposition products and products from various reactions. The produced degradation products depend on the type of polymer, the degradation mechanisms, and environmental factors, such as temperature and oxygen. During the thermal degradation of plastic materials containing nitrogen (nylons, polyacrylonitrile, and *polyurethane*), HCN is produced, plastic materials containing chloride (PVC, PVdC) produce HCl and dioxins during thermal degradation, and plastic materials containing fluorine (*polytetrafluoroethylene*, *polyvinyl fluoride*) produce HF and perfluoroisobutene. Polymers such as polystyrene, polyesters, polycarbonates, polyamides, and polyurethanes can be depolymerized via chain scission of their initial monomers [4–6].

Moreover, regulation of the "limits of specific migration" has been established by the European Safety Food Authority (ESFA) based on data on the toxicity of each substance. For the total quality assurance of plastic packaging materials, the European Commission 2002a [7] established the directive 2002/72/EC, which regulates the application of monomers, additives, and their residual amounts in packaging, as well as their migration limits for the manufacturing of plastics that are intended to come in contact with foods (food-contact materials). As far as coatings are concerned, the resolution AP(96)5 (Council of Europe 1996) was edited [8], adopting a list of approved materials (starting materials) and additives of the directive 90/128/EEC (European Commission 1990, preceding directive of 2002/72/EC).

The use of food simulants to imitate real food samples was introduced for migration tests of all food-contact materials, in particular, plastic food -ontact materials in the European Council Directive 85/572/ECC in 1985 [9]. This directive was then replaced in 2011 by the regulation EC 10/2011 issued by the European Commission [10], which specifies further migration test conditions, again focusing on migration from plastic food-contact materials. To ensure the suitability of the presented food simulants, the associations between real food, food simulants, and migration conditions were thoroughly established [11], even though, in 2016, this directive was amended and corrected [12].

The limit of overall migration should not exceed 60 mg/Kg in food or 10 mg/dm^2 in food-contact material. This regulation also sets out the use of representative simulants for each food category [9]. The reasons for the substitution of real foods with food simulants in migration studies are the complexity of foods, the presence of difficulties during analysis, and the increase in the reproductivity of the results. Indeed, the selection of simulants depends on the food matrix to be imitated. More specifically, a mixture of ethanol/water (50:50, *v*:*v*) should be applied to imitate food with lipophilic properties, alcoholic food (alcohol content > 20%), and oil-in-water emulsions. Furthermore, a mixture of ethanol/water (10:90, *v*:*v*) is recommended by the European Union for the simulation of food with hydrophilic properties [10]. Real food samples typically consist of a complex composition of

multiple components in equilibrium that interact and define the properties of each food. Therefore, the selection of suitable food simulants is of great interest and might require a general hypothesis [11]. According to the FDA [13], the food simulant contents that are recommended are as follows: for aqueous and acidic foods, 10% ethanol is recommended; for low- and high-alcoholic foods, 10% or 50% ethanol is proposed; and for fatty foods, food oils such as corn oil, synthetic glycerides (HB307), and miglyol 812 derived from coconut oil have been proposed.

Based on the above, the aim of the present review was to provide the literature with a collective study on the migration of the most known chemical substances to foods from packaging materials, while at the same time discussing the toxic effects of these compounds on consumers, and the need for replacing conventional polymers from the market with new biodegradable and more safe packaging materials for foods, including alcoholic beverages. The general hypothesis driving this study represents the novelty of the present review article.

2. Food Simulants

The basic food simulants that are proposed by the Commission Regulation (EU) 2016/416 [12] represent five different food categories and are listed in Table 1.

Table 1. Simulants according to Commission Regulation (EU) 2016/416 [12].

Simulant	Food Category	Shortcut
10% ethanol (*v*/*v*)	Hydrophilic foods	A
3% acetic acid (*w*/*v*)	Acidic foods with pH below 4.5	B
20% ethanol (*v*/*v*)	Alcoholic foods with an alcohol content of up to 20%	C
50% ethanol (*v*/*v*)	Alcoholic foods with an alcohol content of above 20%	D1
Vegetable oil	Fatty foods	D2
Poly(2,6-diphenyl-p-phenylene oxide), particle size: 60–80 mesh, pore size: 200 nm, commonly named Tenax)	Dry foods	E

3. Migrating Chemical Substances

Regarding the specific migration of starting materials and the products of the reactions that happen in can coatings, the 10 derivatives of BADGE and Bisphenol F diglycidyl ether (BFDGE) are limited to 1 mg/Kg of food according to the directive 2002/16/EC (European Commission 2002b) [14]. However, most of the starting materials for the coatings are a mixture of substances or prepolymers that react with other substances in the coating. The migrating substances from the coatings are monomers that belong to a positive list. The Scientific Committee on Food (SCF, European Commission 2001) [15] emphasized the importance of the identification of migrating substances, and their quantity and toxicity. Therefore, only substances with a molecular weight below 1000 Da are cause for concern because these can be absorbed so easily by the gastro-intestinal tract.

The most common chemical substances that migrate to foods are the following: acetaldehyde, methanal, antimony, Sb_2O_3, 2,4-di-tert-butylphenol, tris (2,4-di-tert-butylphenol) phosphate, Irgafos 168, BPA, and the plasticizers DEHP, DBP, BBP, DINP, and DIDP.

3.1. Acetaldehyde

Acetaldehyde is produced by the thermal degradation which PET undergoes during the manufacturing of bottles. In a study of migration in packaged water in PET bottles, acetaldehyde was identified. The concentration of acetaldehyde was proportional to its concentration in the bottle [16]. In another study, acetaldehyde was identified in packaged

water in PET bottles, and its concentration was correlated with temperature and the presence of carbon dioxide [17]. In carbonated beverages packaged in PET bottles at 5, 20, and 40 °C for 6 months, acetaldehyde was identified, and its concentration was also correlated with temperature and time of storage [18]. Bottles stored at 40 °C exhibited a considerable change in acetaldehyde concentration. Also, in a study on carbonated beverages packaged in PET bottles, the concentration of acetaldehyde in beverages at 60 °C was higher compared to the concentration of acetaldehyde at 40 °C [19]. According to the International Agency for Research on Cancer (IARC), acetaldehyde is ranked among the most carcinogenic substances (Group 2B, IARC monograph 1999, volume 36, sup7,71) [20]. Acetaldehyde may cause and generate pathophysiological disorders, such as facial flushing, nausea, vomiting, tachycardia, hypotension, and in extreme cases, even death [21–23]. Regarding the human body's reactions, acetaldehyde is turned into acetic acid through the enzyme aldehyde dehydrogenase, but the excessive amount of acetaldehyde prevents the reaction of aldehyde dehydrogenase. In this context, there is the possibility of the gathering of acetaldehyde molecules and their transfer to other organs through the bloodstream. This consequently results in the development of chronic diseases such as hepatitis and liver cirrhosis [24].

The off flavor that is developed in mineral water packaged into PET bottles is attributed to the presence of acetaldehyde. The odor threshold of acetaldehyde in water fluctuates between 10 and 25 μg/L. 2-Aminobenzamide is an acetaldehyde scavenger which binds acetaldehyde before the final stage of PET bottle manufacturing. For the scavenging of acetaldehyde, a large quantity of 2-aminobenzamide must be added to fused PET. The scavenger can migrate to packaged mineral water, so the addition of this scavenger must be considered in order to be in compliance with the specific migration limit (SML) of this scavenger. According to the European Union and USA authorities, the SML of 2-aminobenzamide is 50 μg/L and 500 mg/Kg. It should be mentioned that the swelling of the PET matrix can lead to the overestimation of migration in typical food simulants like ethanol/water mixture, especially at 60 °C [25,26]

3.2. Antimony and Antimony(III) Oxide

Antimony originates from antimony(III) oxide, which is used as a catalyst during the condensation reaction for the manufacture of PET. Antimony was identified in water packaged in PET bottles stored at 40, 50, and 60 °C. The concentration of antimony in water was correlated with the levels of temperature and the presence of carbon dioxide [17]. Also, the product of phenolic antioxidant degradation 2,4-di-tert-butylphenol was identified at temperatures higher than 60 °C. Antimony(III) oxide was also identified in water packaged in PET bottles. An increase in the concentration of antimony(III) oxide in water was observed during the increase in temperature [27]. In another study, the authors reported a correlation between the migration of antimony(III) oxide and the pH of water [28].

3.3. Irgafos 168

Irgafos 168 and its degradation products have been detected in PP packaging material during its extrusion, storage, processing with ultraviolet radiation, and exposure to sunlight [29]. 2,4-Di-tert-butylphenol was the predominant degradation product after the exposure of PP material to ultraviolet radiation, while tris (2,4-di-*tert*-butylphenol) phosphate was the predominant degradation product, produced after extrusion, storage, and exposure to sunlight. However, these products had no significant toxicological effects on human health.

Yang et al. [30] studied the effects of ultraviolet and microwave treatment in the production of degradation products of Irgafos 168 alone and the Irgafos 168 added to PP films for food packing. Irgafos 168 was added to PP, followed by ultraviolet and microwave treatments. The corresponding degradation rates were 31.88% and 11.7%, respectively, and three degradation products were produced. Two of these degradation products were 2,4-di-tert-butylphenol and tris(2,4-di-tert-butylphenyl)phosphate, and the other was postulated

to be the result of Irgafos 168 after the removal of the di-tert-butylphenol group. The degradation rate of Irgafos 168 standard was less than 5% under ultraviolet and microwave treatment. Marcato et al. [31] studied the migration of the antioxidant additives Irganox 1010 and Irgafos 168 from polyolefin packaging into oily vehicles. The polyolefins used were the following: PP, RACO, an EP heterophasic copolymer and EP amorphous copolymer blend, and HDPE. Each polymer contained Irganox 1010 (0.15%, *w*/*w*) and Irgafos 168 (0.15%, *w*/*w*) and was processed into blown bottles. The leaching of the two antioxidants varied remarkably depending on the polyolefin crystallinity and structure. The amount of Irganox 1010 transferred into the contact medium at 25 °C was higher in EP. RACO and PP exhibited lower amounts of Irganox 1010, while the lowest amount was presented in HDPE. The same was observed in Irgafos 168, except for PP and HDPE, which presented the same quantity of this additive. The migration of Irgafos 168 was higher compared to that of Irganox 1010, and the transfer of both antioxidants increased at higher temperature (50 °C).

3.4. BPA

BPA is an organic compound which has a white color, and in ambient conditions, it is found in a solid state and it has a mild phenolic odor. The first attempts to produce this polymer began in the 1930s [32], while its synthesis was performed in 1891. BPA is used for the manufacturing of carbonated films through the reaction of BPA and phosgene, and the containers and bottles that are produced from BPA are characterized by high lightness, transparency, and durability. BPA is also used to produce coatings as epoxy-resins that are submitted to cross-linking reactions for further stabilization and/or modifications. Can coatings are produced using epoxy-resins for the protection of the taste of packaged foods, for the prevention of corrosion of the metal can, and for reducing contact between the metal and food.

BPA presents a three times higher migration rate in octanol compared to its migration rate in water [33–35]. Under aerobic conditions in surface water in a range of concentrations between 0.05 and 0.5 µg/L, BPA presents a short half-life of 3–6 days [36]. Residual BPA has been found in the tissues of several aquatic organisms, which could be attributed to the transfer of BPA-derived residues from algae. The accumulation of BPA in algae may result in the accumulation of BPA in the food chain. After a considerable number of tests in rats and mice, it was shown that there was a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg body weight/day and a Lowest Observed Adverse Effect Level (LOAEL) of 50 mg/kg body weight/day. These results of trials were established by the EFSA and FDA.

The migration of BPA into a fatty food simulant increased following an increase in temperature [37]. The same authors, in a previous study, reported a non-significant increase in the migration of BPA into an acidic food simulant after an increase in temperature [38]. In canned tomatoes, an increase in the migration of BPA was observed after an increase in storage temperature [39]. Fang et al. [29] found, in water packaged into PC bottles, a percentage of BPA equal to 60% of the quantity of water after 1 year of storage. It is believed that BPA may originate from non-polymerized amounts of BPA or during the degradation of polycarbonate resins after its reuse. Also, the migration levels of BPA were significantly higher in damaged cans in comparison to non-damaged cans in contrast with Goodson et al. [40], who reported a non-significant increase in the migration levels of BPA in damaged cans. The authors also claimed that about 80%–100% of the BPA of the coating migrated during can processing and this percentage was independent of storage time.

BPA has a strong negative effect on estrogen. The low-dose estrogenic effects of BPA have been used for the determination of the risk and exposure levels. Dodds and Lawson demonstrated that BPA and its derivatives present estrogenic activity in rats [41,42]. Krishman et al. [43] also reported that BPA is a great inhibitor of the endocrine gland. Given these findings, the European Union prohibited the use of polycarbonate resin in the manufacturing of bottles for new-born children. Vom Saal and Hughes in 2005 emphasized

the requirement for new risk assessments related to the low-dose estrogenic effect of BPA [44]. This requirement was also supported by Myers et al. 2009 [45].

BPA mimics the action of estrogen, but can also cause disorders in non-estrogenic pathways, even at low-dose concentrations, in multiple manners [46,47]. The effect of BPA differs depending on the life stage and the kind of tissue. Life stages such as prenatal, neonatal, and (pre)pubertal have high sensitivity to the BPA effect. BPA, even at a low dose, can negatively affect the regulation of the metabolic homeostasis of the progeny, sex steroids, and thyroid hormone levels during pregnancy [48]. In zebrafish larvae (Danio rerio) from exposed parents, epigenetic effects and developmental neurotoxicity were observed [49]. Generally, it has been reported that several fish and amphibian species are very sensitive to low doses of BPA. However, more studies are required on the endocrine and systemic effects of BPA [35]. In addition to BPA, its product BADGE (bisphenol A diglycidyl ether) and hydrolyzed and chlorinated derivatives of BADGE (BADGE·H_2O and BADGE·2HCl) can also move through the human placenta and reach the fetus.

Regarding the use of BPA in varnishes and coatings, Regulation (EU) No. 2018/213 [50], an amendment of Regulation (EU) No. 10/2011 [51], established the SML of BPA to be 0.05 mg/kg. Every varnish and coating must fill these substance-specific measures and Framework Regulation (EC) No. 1935/2004 [10].

3.5. Derivatives of BPA and Other Bisphenols

Derivatives of BPA that are produced after the condensation reaction of BPA with epichlorohydrin also presented high migration levels. BADGE and BFDGE exhibited high migration levels in canned seafood with a high lipid content [52]. Sterilization conditions and storage time may also affect their migration levels. BFDGE was also found in canned fish at concentrations of up to 4.2 mg/kg [53]. BPA, BADGE, and BADGE derivatives presented an increase in their concentration in a simulant (50% ethanol) until equilibrium time (90–305 days). However, no residues of these migrants were reported [54]. In addition to BPA and its derivatives, several other bisphenols, such as BPB, BPF, BPZ, and BPS, have been found in canned foods as well as in soft and energy drinks, beers, and the filling liquids of canned vegetables [55–60]. In the covering oil of canned anchovies, BADGE was determined at a concentration of 62 mg/kg [61]. In tomato sauce, a mixture of BADGE, BADGE·2H_2O, BADGE·HCl, and BADGE·2HCl was identified at concentration of 12.6 mg/kg [62]. It is worth noting the presence of cyclo-di-BADGE at concentration of 25–2600 µg/kg in canned fish and meat products [63].

For the protection of consumers' health, the European Food Safety Authority (EFSA) in 2015 established a tolerable daily intake (TDI) of 4 µg/kg bw per day. The EFSA also claimed that the possibilities of the presentation of any harm coming from BPA exposure were eliminated [64]. The same was also claimed for BADGE by the EFSA [65]. Marqueno et al. [66] reported that BADGE and BADGE·2HCl exhibited higher cytotoxicity compared to BADGE·H_2O. BADGE and BADGE·2HCl caused alterations in placenta cell lipids and endocrine disruption. On account of the high toxicity of these migrants, the authors suggested the requirement for more studies on the determination of their TDIs. Regarding the derivative of bisphenol F, Zhang et al. [67] claimed that tetramethyl bisphenol F and its reaction products with epichlorohydrin have very low toxicity levels. For this reason, tetramethyl bisphenol F was suggested by the authors as a substitute for BADGE in the production of epoxy-resins. Other bisphenols, such as BPB, BPE, and BPF, exhibited estrogenic activity without any mutagenicity. Chen et al. [68] concluded that the estrogenic activity of a bisphenol was increased by a reduction in its polarity. According to other studies BPA, BPS, and BPF are considered responsible for causing acute oxidative stress [69,70]. A study has demonstrated that BPF and BPS are responsible for obesity in children, like previous observations with BPA [71]. Also, according to Horan et al. [72], BPS and BPF presented negative effects on male spermatogenesis.

Considering the high toxicity of BFDGE, BADGE, and BADGE's hydrolyzed and hydrochloric derivatives, the Regulation (EC) No. 1895/2005 has established a 9 mg/kg

maximum specific migration limit (SML) for BADGE and its hydrolyzed derivatives and also a 1 mg/kg SML for its hydrochloric derivatives. Also, the use of BFDGE in the production of FCM has been prohibited [73].

3.6. Melamine

Melamine is a heterocyclic aromatic compound with a white color, and when it is powdered, it has a crystal structure [74]. Melamine is excreted with urine in mammals, and its half-life is equal to 5 h in rats [75], 4 h in pigs [76], and approximately 6 h in humans [77]. Although lactic acid bacteria may change melamine levels through the conversion of melamine into cyanuric acid, resulting in an increase in nephrotoxicity, i.e., kidney stones [78], melamine cannot be decomposed in activated sludge treatment systems [79]. Melamine resin is used for the production of surface coatings for paper, cardboard, and beverage cans and jar lids. Melamine is primarily employed in films and coatings as a crosslinking agent (in the form of melamine formaldehyde) by improving hardness, chemical resistance, and durability, or as a co-resin to enhance films' and coatings' properties and performance by improving their adhesion, hardness, gloss, and resistance to staining and abrasion. In addition, melamine is used to enhance the thermal stability of films and coatings, making them more resistant to heat-induced degradation [80].

Also, melamine resins can be used for the manufacturing of commercial products, such as unbreakable dinner/kitchenware and electrical equipment, after their blending with cellulose fibers, fillers, pigments, and other additives. Nowadays, melamine resin is frequently used in tableware [74] and can effectively substitute plastic materials because it has an "eco-friendly" character. Melamine has been used for the manufacturing of reusable plates, bowls, and coffee cups.

Given the increasing concern, at a worldwide level, about the toxic effect of BPA or its derivatives, there is a need to replace BPA with alternative plastic materials. One of the major alternatives suggested is melamine-based plasticwares. However, melamine is also a toxic chemical [78].

Melamine can migrate into food and food simulants from melamine formaldehyde tableware. Factors such as temperature, acidity, contact time, and the simulant used, as well as the decomposition of the coating, can affect the quantity of migrating melamine. Melamine can be found in foods because of its migration from materials into food, its intentional addition to food with the main purpose of the achievement of higher protein content, and the degradation of the pesticide cyromazine and disinfectants such as trichloromelamine [78].

According to the WHO in 2009, many countries have introduced limits for melamine in infant formula and other foods. Limits for melamine in powdered infant formula (1 mg/kg) and in other foods (2.5 mg/kg) would provide a sufficient margin of safety for dietary exposure relative to the tolerable daily intake (TDI), that is, 0.2 mg/kg body weight [81].

The migration of melamine can be increased by an increase in temperature [82] and is less affected by the time of heating or acidity of food [83,84]. Wu et al. [77] reported that after the consumption of hot soup in melamine bowls, the melamine content in urine was higher in comparison to that after the consumption of hot soup in ceramic bowls, indicating that the migration of melamine to the hot soup was independent of contact time. Also, microwave heating, as well as the repetition of microwave heating, causes an increase in the migration of melamine. It is important for manufacturers and suppliers of products containing melamine to point out in the instructions for consumers that the product should not be heated in a microwave oven [85].

3.7. PFAS

PFAS are fluorinated aliphatic compounds. The main difference between perfluoro and polyfluoro compounds is the total and the partial substitution of hydrogens with fluorine, respectively. PFAS are highly stable substances in high temperatures and several other chemical media and are dissoluble in both water and oil. PFAS are used in various

materials, including the production of pizza boxes, microwave popcorn bags, butter and dairy packaging, and cookware. Since the 1960s, non-polymeric PFAS have been used in paper and board products. From 1974 to 2002, SAmPaP was used in food-contact paper and packaging. After 2002, it was substituted with short- and medium-chain substances such as PFBS and its derivatives. In 2013, PFAS with different structures were used in FCM finishes [86].

The migration of PFAS, i.e., PFOA and FTOH, was reported from popcorn bags, fast food wrappers, pizza boxes, and similar oil-repellent and heat-resistant packaging. The polymer PTFE has high inertness when found in a solid state. For this reason, PTFE is used in the manufacturing of non-stick cookware. The fusion of PTFE starts at 327 °C, and its degradation occurs at over 350 °C when a toxic polymer fume is produced. PTFE-based pans can reach over 350 °C during their use on induction stoves [87], and during the heating of non-stick pans or their repeated use, an increase in the risk of polymer fumes and the migration of PFOA can be observed [88]. Residues of PFOA that remain after the complementation of the polymerization of PTFE can be released under normal cooking conditions [88].

In addition to PFOA, several other PFCAs of different molecular weight can be released under normal or overheating conditions [89]. One of the factors that can increase the migration of PFAS from paper is the addition of an emulsifier to the oil [90]. Also, the main disadvantage of PFAS is its ability to join to proteins, so analytical methods for the determination of PFAS must be improved. Still et al. [91] reported the presence of PFCAs and FTOH in dairy products from coated packaging during their processing and storage. Also, authors reported that the quantity of FTOH was 1000 times higher in comparison to that of PFCA. Studies have reported the presence of PFOS and PFOA in human blood samples [92–94] because of the high bioaccumulation, chemical and thermal stability, and double nature (hydrophobic and lipophobic) of PFAS. Other studies have reported a decrease in PFOS and PFOA levels and an increase in PFBS and PFHxS levels [95–97]. On account of the high persistence of PFAS in the environment, these can be found in every human and can potentially accumulate in the fetus during pregnancy [98] as a result of the transfer of PFAS to infants that can happen during breastfeeding [99].

Many negative effects of PFOA and PFOS in human health have been reported [93,100–102], such as liver dysfunction [103], testicular and liver cancers [104,105], high levels of cholesterol [106], ulcerative colitis [107], and a low response of the immune system to vaccines [108]. PFOA causes a reduction in fecundity and fetal growth [90] and takes part in the function of splenocyte and thymocyte precursor cells, and as a result, leads to changes in inflammatory responses [86,109]. For the other PFAS, there are not many reports about their effects on human health. The Madrid Statement that was signed in 2015 by over 120 researchers had as a main goal the limitation of further negative environmental and human effects of the production and use of PFAS [110]. Three years later, the Zurich Statement was published, in which a series of actions were proposed for the most effective assessment and management of PFAS. Also, the Zurich Statement highlighted the effect of the insufficient ability to regulate PFAS on the protection of human health [111]. According to the literature concerning PFAS, limited data for PFAS should not justify the delay in efforts toward the substitution of PFAS [105]. The Nordic Council of Ministers announced that the total annual health-related costs were at least EUR 2.8 to EUR 4.6 billion in the Nordic countries and EUR 52 to EUR 84 billion in the European Economic Area (EEA) countries [112]. There are no general regulations for PFAS that are intended to come in contact with foods. Materials such as PFOA and PFOS have restriction limits in some member states. In 2009, the Stockholm Convention restricted the use of PFOS. Also, in 2020, the Stockholm Convention restricted the use of PFOA. Other PFAS that are included on the Candidate List for authorization are PFUnDA, PFDoDA, PFTrDA, PFTeDA (2012), PFNA and its sodium and ammonium salts (2015), PFDA and its sodium and ammonium salts (2016), PFHxS and its salts (2017), HFPO-DA (also known as GenX) and its salts and acyl halides (2019), and PFBS and its salts (under authorization since 2020).

The manufacturing and delivery to market of the substances PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, and PFTeDA and their salts and precursors were restricted by Sweden and Germany in 2017. This restriction had as its main purpose the prevention of the use of these substances as substitutes for PFOA. The RAC (Risk Assessment Committee) and the SEAC (Committee for Socio-Economic Analysis) agreed to the restriction proposal. In 2018, new guidelines for PFOS and PFOA were established by European Food Safety Authority (EFSA) as concerned the tolerable daily intake (TDI) of PFOS and PFOA [113]. The TDI of PFOS and PFOA decreased from 150 to 2 ng/kg body weight/day and from 1500 to 1 ng/kg body weight/day, respectively.

In June 2019, the European Council of Ministers proposed the elimination of all non-essential uses of PFAS because of its high environmental persistence [114]. Six months later, the Netherlands declared to the delegations that they wanted to take over this restriction proposal in cooperation with the competent authorities in Denmark, Germany, Sweden, and Norway, and the European Chemical Agency (ECHA). PFAS have also been found in drinking water. For the presence of PFAS in drinking water, limits of 0.1 μg/L for 16 individual PFAS, and 0.5 μg/L for all PFAS as a group, have been proposed by the EU Drinking Water Directive. A reconsideration that was discussed in Sweden's regulation concerned a better understanding of what kinds of chemical products contain PFAS. The regulation included all chemical products, i.e., impregnation or lubrication oils, but not articles.

3.8. Phthalates

Phthalates are organic substances that are used in plastic packaging materials as plasticizers. Chemically, phthalates are esters that are produced by the esterification reaction of o-phthalic acid (1,2-benzenedicarboxylic acid) and several alcohols, such as methanol, ethanol, tridecanol, and others. The hydrocarbon chains of the ester groups define the name of the phthalate and define its properties [115]. Phthalates are divided into two groups proportionally to the hydrocarbon chain of alcohol. The first group is named short-chain phthalates and includes compounds with 3–6 carbon atoms in the carbon chain, such as DBP, DiBP, BBzP, and DEHP. The second group is named long-chain phthalates and includes compounds with 7–13 carbon atoms in the carbon chain, such as DiDP, DiNP, DPHP, DiUP, and DTDP [116,117].

Phthalates exhibit a tendency toward migration in packaged foods. This tendency depends on the nature of the food, the initial quantity per area unit of the plasticizer in the plastic material, the temperature and storage exposure, and the extension of the surface which is in contact with the food [118]. A higher migration level of phthalates in high-lipid-content foods and food simulants has been reported in comparison with other foods and food simulants categories, because of the low polarity of phthalates [119,120]. Regarding the toxic effects of phthalates, studies have shown that phthalates can cause disruptions in the production of endocrine gland hormones, as well as other negative health effects, such as various cancer forms and immune and metabolic diseases [121]. In the prenatal stage, in utero exposure to various phthalates leads to numerous abnormalities in new-born babies, such as preterm birth, abnormal birth length and weight, abnormal head circumference, and altered reproductive hormone levels that further lead to a delay in uterus development. According to Katsikantami et al. [116], phthalates are sex-specific and affect male and female new-born babies in substantially different ways. In the stage of childhood, phthalates are responsible for a great number of disorders, such as asthma and allergic symptoms, obesity, anti-androgen effects, delays in growth and puberty, changes in systolic blood pressure, etc. Table 2 lists the migrant substances and their toxic effects on human health.

Table 2. List of migrant substances and their toxic effects on human health.

Migrant Name	Toxic Effects and Health Issues	References
Acetaldehyde	Facial flushing, nausea, vomiting, tachycardia, hypotension, hepatitis, liver cirrhosis, and in extreme cases, even death.	[21–24]
Antimony and Antimony(III) oxide	Carcinogenic potential for humans.	[28,29]
Irgafos 168	Not any significant toxicological effects.	-
BPA	Negative effect on estrogen, great inhibitor of endocrine gland, Negative effect on the metabolic homeostasis of the progeny, sex steroids, and thyroid hormones levels during pregnancy. Epigenetic effects and developmental neurotoxicity.	[40–43,48,49]
Derivatives of BPA and other bisphenols	Negative effect on the regulation of metabolic homeostasis of the progeny, sex steroids, and thyroid hormone levels during pregnancy. Epigenetic effects and developmental neurotoxicity in zebrafish.	-
Melamine	Increase in urea content, increase in nephrotoxicity, i.e., kidney stones. Cannot be decomposed in activated sludge treatment systems.	[78,79]
PFOA PFOS	Liver dysfunction, testicular and liver cancers, high levels of cholesterol, ulcerative colitis, and low response of immune system to vaccines.	[91,93,100–109]
Phthalates	Endocrine disruption, various cancer forms, immune and metabolic diseases, abnormalities. In new-born babies, preterm birth, abnormal birth length and weight and head circumference, and altered reproductive hormone levels. During childhood, asthma and allergic symptoms, obesity, anti-androgen effects, delay in growth and puberty, and changes in systolic blood pressure.	[121]

4. Biodegradable Packaging Materials (Films or Coatings)

In our previous work [122], we exhaustively studied the most common biodegradable packaging materials used for foods preservation, focusing on their sources, advantages, limitations, and future perspectives. For this purpose, a considerable number of studies were examined (170 publications), and the results showed that there is a need for reconsideration of the conventional plastics used for food preservation. Moreover, there is the challenge of adopting new innovative and biodegradable packaging materials (films or coatings) based on natural sources such as polysaccharides, proteins, lipids, etc., to avoid the migration and safety issues documented in the present review article, and at the same time, decrease the environmental pollution of plastic disposal.

5. Conclusions and Future Perspectives

The present review article highlighted in a conclusive way that many migrants, such as acetaldehyde, antimony, Sb_2O_3, 2,4-di-tert-butylphenol, BPA, and the plasticizers DEHP, DBP, BBP, DINP, and DIDP, have potential toxicity, and therefore, the use of these materials in food packaging holds many health risks for humans. It is therefore necessary to replace

or minimize these materials in the packaging industry with films and coatings for food applications, based on the production of bio-degradable, eco-friendly, and natural materials, coupled with innovative regulations that support the solid safety of consumers, and at the same time, retain the quality and wholesomeness of the packaged products. These decisions by the Food Authorities and, of course, the food industry, will also have a direct positive outcome for human health, with a decrease in the health disorders presented herein caused by the use of these compounds in food packaging materials. The specific hypothesis driving this study and the workflow used have not been reported previously, thus constituting the originality of this review article.

Author Contributions: Conceptualization, I.K.K.; methodology, A.P. and I.K.K.; software, A.P. and I.K.K.; validation, I.K.K.; formal analysis, A.P.; investigation, A.P. and I.K.K.; resources, A.P. and I.K.K.; data curation, A.P. and I.K.K.; writing—original draft preparation, A.P.; writing—review and editing, I.K.K.; visualization, I.K.K.; supervision, I.K.K.; project administration, I.K.K.; funding acquisition, A.P. and I.K.K. All authors have read and agreed to the published version of the manuscript.

Funding: The current study was supported by the funding program "MEDICUS" of the University of Patras.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The manuscript includes all relevant data.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

IAS	Intentionally added substances
NIAS	Non-intentionally added substances
Sb_2O_3	Antimony (III) oxide
Irgafos 168	Tris(2,4-di-tert-butylphenyl) phosphite
BPA	Bisphenol A
DEHP	Di(2-ethylhexyl) phthalate
DBP	Di-n-butyl phthalate
BBP	Benzyl-butylphthalate
DINP	Di-isononylphthalate
DIDP	Di-isododecylphthalate
BADGE	Bisphenol A diglycidyl ether
BFDGE	Bisphenol F diglycidyl ether
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
PET	Polyethylene terephthalate
PP	Polypropylene
BPB	Bisphenol B
BPE	Bisphenol E
BPF	Bisphenol F
BPS	Bisphenol S
BPZ	Bisphenol Z
PFAS	Per- and polyfluoroalkyl substances
SAmPaP	Perflourooctanesulfonamido ethanol-based phosphate
PFBS	Perfluorobutane sulfonate
PFOA	Perfluorooctanoic acid
FTOH	Fluorotelomers
PTFE	Polytetrafluoroethylene
PFCA	Perfluoroalkyl carboxylic acids

PFOS	Perfluorooctanesulfonic acid
PFBS	Perfluorobutanesulfonic acid
PFHxS	Perfluorohexanesulfonic acid
PFUnDA	Perfluoroundecanoic acid
PFDoDA	Perfluorododecanoic acid
PFTrDA	Perfluorotridecanoic acid
PFTeDA	Perfluorotetradecanoic acid
PFNA	Perfluorononanoic acid
PFDA	Perfluorodecanoic acid
PFHxS	Perfluorohexanesulfonic acid
HFPO-DA	Hexafluoropropylene oxide dimer acid
PFBS	Perfluorobutanesulfonic acid
DiBP	Diisobutyl phthalate
BBzP	Butyl benzyl phthalate
DPHP	Di 2-propylheptyl phthalate
DiUP	Di isoundecyl phthalate
DTDP	Di isotridecyl phthalate
Irganox 1010	Pentaerythrityl tetrakis (3,5-di-tert-butyl-4-hydroxyphenyl)propionate
RACO	Ethylene-co-propylene random copolymer
HDPE	High-density polyethylene
EP	Ethylene–propylene

References

1. Kato, L.S.; Conte-Junior, C.A. Safety of Plastic Food Packaging: The Challenges about Non-Intentionally Added Substances (NIAS) Discovery, Identification and Risk Assessment. *Polymers* **2021**, *13*, 2077. [CrossRef]
2. Ferrara, G.; Bertoldo, M.; Scoponi, M.; Ciardelli, F. Diffusion coefficient and activation energy of Irganox 1010 in poly(propylene-co-ethylene) copolymers. *Polym. Degrad. Stab.* **2001**, *73*, 411–416. [CrossRef]
3. Hansen, E.; Nillson, N.; Lithner, D.; Lassen, C. *Hazardous Substances in Plastic Materials*; COWI in cooperation with Danish Technological Institute: Taastrup, Denmark, 2013.
4. Ravve, A. *Principles of Polymer Chemistry*, 2nd ed.; Kluwer Academic, Plenum Publishers: New York, NY, USA, 2000.
5. La Mantia, F. *Handbook of Plastics Recycling*; iSmithersRapra Publishing: Shrewsbury, UK, 2002.
6. Lokensgard, T.L.E. *Richardson, Industrial Plastics: Theory and Applications*; Delmar Learning: New York, NY, USA, 2004.
7. European Commission. Commission Directive No. 2002/72/EC of 6 August 2002 relating to plastic materials and articles indented to come into contact with foodstuffs. *Off. J. Eur. Communities* **2002**, *220*, 18–58.
8. Council of Europe Resolution AP (96) 5 on Surface Coatings Intended to Come into Contact with Foodstuffs. Adopted by the Committee of Ministers on 2 October 1996 at the 574th Meeting of the Ministers' Deputies, 1–128. Available online: https://rm.coe.int/16804e230f (accessed on 7 December 2023).
9. Council directive 85/572/EEC of 19 December 1985: Laying down the list of simulants to be used for testing migration of constituents of plastic materials and articles intended to come into contact with foodstuffs. *Off. J. Eur. Communities* **1985**, *L372*, 14–21.
10. Commission regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. *Off. J. Eur. Union* **2011**, *L12*, 1–89.
11. Lerch, M.; Fengler, M.; Mbog, G.-R.; Nguyen, K.H.; Granby, K. Food simulants and real food–What do we know about the migration of PFAS from paper based food contact materials? *Food Pack. Shelf Life* **2023**, *35*, 10099. [CrossRef]
12. Commission Regulation (EU) 2016/1416 of 24 August 2016 amending and correcting Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. *Off. J. Eur. Union* **2016**, *L230*, 22–40.
13. U.S. Food and Drug Administration (FDA). Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations), 2007, Center for Food Safety and Nutrition. Available online: https://www.fda.gov (accessed on 9 January 2024).
14. European Commission. Commission Directive No. 2002/16/EC of 20 February 2002 on the use of certain epoxy derivatives in materials and articles indented to come into contact with foodstuffs. *Off. J. Eur. Communities* **2002**, *L51*, 27–31.
15. European Commission, Health and Consumer Protection Directorate-General. *Guidelines of the Scientific Committee on Food for the Presentation of an Application for Safety Assessments of Substances to be Used in Food Contact Materials Prior to Its Authorization*; European Commission: Brussels, Belgium, 2001; pp. 1–6.
16. Bach, C.; Dauchy, X.; Severin, I.; Munoz, J.F.; Etienne, S.; Chagnon, M.C. Effect of temperature on the release of intentionally and non-intentionally added substances from polyethylene terephthalate (PET) bottles into water: Chemical analysis and potential toxicity. *Food Chem.* **2013**, *139*, 672–680. [CrossRef]
17. Carneado, S.; Hernández-Nataren, E.; Lypez-Sánchez, J.F.; Sahuquillo, A. Migration of antimony from polyethylene terephthalate used in mineral water bottles. *Food Chem.* **2016**, *166*, 544–550. [CrossRef]

18. Özlem, K.E. Acetaldehyde migration from polyethylene terephthalate bottles into carbonated beverages in Türkiye. *Int. J. Food Sci. Technol.* **2008**, *43*, 333–338. [CrossRef]
19. Eberhartinger, S.; Steiner, I.; Washüttl, J.; Kroyer, G. Study of the migration of acetaldehyde from PET bottles into soft drinks containing carbonic acid. *Z. Lebensm Unters* **1990**, *191*, 286–289. [CrossRef]
20. IARC. IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Agents Classified by the IARC Monographs, Vol. 1–124, International Agency for Research on Cancer, 2019. Available online: https://monographs.iarc.fr/agents-classified-by-the-iarc/ (accessed on 6 December 2023).
21. Paine, A.J.; Dayan, A.D. Defining a tolerable concentration of methanol in alcoholic drinks. *Hum. Exp. Toxicol.* **2001**, *20*, 563–568. [CrossRef]
22. Lachenmeier, D.W.; Haupt, S.; Schulz, K. Defining maximum levels of higher alcohols in alcoholic beverages and surrogate alcohol products. *Regul. Toxicol. Pharmacol.* **2008**, *50*, 313–321. [CrossRef]
23. Lachenmeier, D.W.; Rehm, J. What is the main source of human exposure to higher alcohols and is there a link to immunotoxicity? *Immunopharmacol. Immunotoxicol.* **2013**, *35*, 451–453. [CrossRef] [PubMed]
24. Park, Y.S.; Lee, Y.J.; Lee, K.T. Analysis of formaldehyde and acetaldehyde in alcoholic beverage. *J. Korean Soc. Food Sci. Nutr.* **2006**, *35*, 1412–1419. [CrossRef]
25. Gehring, C.; Welle, F. Migration of Acetaldehyde Scavengers From PET Bottles. In *Reference Module in Food Science*; Elsevier: Amsterdam, The Netherlands, 2017. [CrossRef]
26. Welle, F. Migration of Acetaldehyde From PET Bottles Into Natural Mineral Water. In *Reference Module in Food Science*; Elsevier: Amsterdam, The Netherlands, 2018. [CrossRef]
27. Chapa-Martínez, C.A.; Hinojosa-Reyes, L.; Hernández-Ramírez, A.; Ruiz-Ruiz, E.; Maya Treviño, L.; Guzmán-Mar, J.L. An evaluation of the migration of antimony from polyethylene terephthalate (PET) plastic used for bottled drinking water. *Sci. Total Environ.* **2016**, *565*, 511–518. [CrossRef] [PubMed]
28. Fang, H.; Wang, J.; Lynch, R.A. Migration of di(2-ethylhexyl)phthalate (DEHP) and di-nbutylphthalate (DBP) from polypropylene food containers. *Food Control* **2017**, *73*, 1298–1302. [CrossRef]
29. Ohno, K.; Azuma, Y.; Nakano, S.; Kobayashi, T.; Hirano, S.; Nobuhara, Y.; Yamada, T. Assessment of styrene oligomers eluted from polystyrene-made food containers for estrogenic effects in in vitro assays. *Food Chem. Toxicol.* **2001**, *39*, 1233–1241. [CrossRef]
30. Yang, Y.-P.; Hu, C.-Y.; Zhong, H.N.; Wang, Z.-Y.; Zeng, G.-F. Degradation of Irgafos 168 and determination of its degradation products. *Modern Food Sci. Technol.* **2016**, *32*, 304–309. [CrossRef]
31. Marcato, B.; Guerra, S.; Vianello, M.; Scalia, S. Migration of antioxidant additives from various polyolefinic plastics into oleaginous vehicles. *Int. J. Pharm.* **2003**, *257*, 217–225. [CrossRef] [PubMed]
32. Geueke, B. *Dossier-Bioplastics as Food Contact Materials*; Food Packaging Forum: Zurich, Switzerland, 2014. [CrossRef]
33. Guo, R.; Du, Y.; Zheng, F.; Wang, J.; Wang, Z.; Ji, R.; Chen, J. Bioaccumulation and elimination of bisphenol a (BPA) in the alga Chlorella pyrenoidosa and the potential for trophic transfer to the rotifer Brachionus calyciflorus. *Environ. Pollut.* **2017**, *227*, 460–467. [CrossRef] [PubMed]
34. Flint, S.; Markle, T.; Thompson, S.; Wallace, E. Bisphenol A exposure, effects, and policy: A wildlife perspective. *J. Environ. Manage.* **2012**, *104*, 19–34. [CrossRef] [PubMed]
35. Vega-Morales, T.; Sosa-Ferrera, Z.; Santana-Rodríguez, J.J. Determination of alkylphenol polyethoxylates, bisphenol-A, 17α-ethynylestradiol and 17β-estradiol and its metabolites in sewage samples by SPE and LC/MS/MS. *J. Hazard. Mater.* **2010**, *183*, 701–711. [CrossRef] [PubMed]
36. Klečka, G.M.; Gonsior, S.J.; West, R.J.; Goodwin, P.A.; Markham, D.A. Biodegradation of bisphenol a in aquatic environments: River die-away. *Environ. Toxicol. Chem. Int. J.* **2001**, *20*, 2725–2735.
37. Munguia-Lopez, E.M.; Gerardo-Lugo, S.; Peralta, E.; Bolumen, S.; Soto-Valdez, H. Migration of bisphenol A (BPA) from can coatings into a fatty-food simulant and tuna fish. *Food Addit. Contam.* **2005**, *22*, 892–898. [CrossRef]
38. Munguia-Lopez, E.M.; Peralta, E.; Gonzalez-Leon, A.; Vargas-Requena, C.; Soto-Valdez, H. Migration of bisphenol A (BPA) from epoxy can coatings to jalapeno peppers and an acid food simulant. *J. Agric. Food Chem.* **2002**, *50*, 7299–7302. [CrossRef]
39. Errico, S.; Bianco, M.; Mita, L.; Migliaccio, M.; Rossi, S.; Nicolucci, C.; Menale, C.; Portaccio, M.; Gallo, P.; Mita, D.G.; et al. Migration of bisphenol A into canned tomatoes produced in Italy: Dependence on temperature and storage conditions. *Food Chem.* **2014**, *160*, 157–164. [CrossRef]
40. Goodson, A.; Robin, H.; Summerfield, W.; Cooper, I. Migration of bisphenol A from can coatings—Effects of damage, storage conditions and heating. *Food Addit. Contam.* **2004**, *21*, 1015–1026. [CrossRef]
41. Dodds, E.C.; Lawson, W. Synthetic strogenic agents without the phenanthrene nucleus. *Nature* **1936**, *137*, 996. [CrossRef]
42. Dodds, E.C.; Lawson, W. 1938 Molecular structure in relation to oestrogenic activity. Compounds without a phenanthrene nucleus. *Proc. Royal Soc. B* **1938**, *125*, 222–232. [CrossRef]
43. Krishnan, A.V.; Stathis, P.; Permuth, S.F.; Tokes, L. Bisphenol-A: An Estrogenic Substance is Released from Polycarbonate Flasks During Autoclaving. *Endocrinology* **1993**, *132*, 2279–2286. [CrossRef]
44. Vom Saal, F.S.; Hughes, C. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. *Environ. Health Perspect.* **2005**, *113*, 926–933. [CrossRef] [PubMed]
45. Myers, J.P.; vom Saal, F.S.; Taylor, J.A.; Akingbemi, B.T.; Arizono, K.; Belcher, S.; Colborn, T.; Chahoud, I. Good laboratory practices: Myers et al. respond. *Environ. Health Perspect.* **2009**, *117*, A483–A484. [CrossRef]

46. Wolstenholme, J.T.; Rissman, E.F.; Connelly, J.J. The role of Bisphenol A in shaping the brain, epigenome and behavior. *Horm. Behav.* **2011**, *59*, 296–305. [CrossRef] [PubMed]
47. Bergman, Å.; Heindel, J.J.; Jobling, S.; Kidd, K.; Zoeller, T.R. *World Health Organisation. State of the Science of Endocrine Disrupting Chemicals 2012*; World Health Organisation: Geneva, Switzerland, 2013; ISBN 978 92 4 150503 1.
48. Silva, B.S.; Bertasso, I.M.; Pietrobon, C.B.; Lopes, B.P.; Santos, T.R.; Peixoto-Silva, N.; Carvalho, J.C.; Claudio-Neto, S.; Manhaes, A.C.; Cabral, S.S.; et al. Effects of maternal bisphenol A on behavior, sex steroid and thyroid hormones levels in the adult rat offspring. *Life Sci.* **2019**, *218*, 253–264. [CrossRef] [PubMed]
49. Nesan, D.; Sewell, L.C.; Kurrasch, D.M. Opening the black box of endocrine disruption of brain development: Lessons from the characterization of Bisphenol A. *Horm. Behav.* **2018**, *101*, 50–58. [CrossRef] [PubMed]
50. European Union. Regulation (EC) No. 1895/2005. *Off. J. Eur. Union* **2005**, *L302*, 28–32.
51. European Union. Regulation (EU) No. 2018/213. *Off. J. Eur. Union* **2018**, *L41*, 6–12.
52. Cabado, A.G.; Aldea, S.; Porro, C.; Ojea, G.; Lago, J.; Sobrado, C.; Vieites, J.M. Migration of BADGE (bisphenol A diglycidyl-ether) and BFDGE (bisphenol F diglycidyl-ether) in canned seafood. *Food Chem. Toxicol.* **2008**, *46*, 1674–1680. [CrossRef]
53. Theobald, A.; Simoneau, C.; Hannaert, P.; Roncari, P.; Roncari, A.; Rudolph, T.; Anklam, E. Occurrence of bisphenol-F-diglycidyl ether (BFDGE) in fish canned in oil. *Food Addit. Contam.* **2000**, *17*, 881–887. [CrossRef]
54. Paseiro-Cerrato, R.; DeVries, J.; Begley, T.H. Evaluation of Short-term and long-termmigration testing fromcan coatings into food simulants: Epoxy and acrylic−phenolic coatings. *J. Agric. Food Chem.* **2017**, *65*, 2594–2602. [CrossRef]
55. Gallart-Ayala, H.; Moyano, E.; Galceran, M.T. Fast liquid chromatography–tandem mass spectrometry for the analysis of bisphenol A-diglycidyl ether, bisphenol F-diglycidyl ether and their derivatives in canned food and beverages. *J. Chromatogr. A* **2011**, *1218*, 1603–1610. [CrossRef]
56. Gallo, P.; Pisciottano, I.D.M.; Esposito, F.; Fasano, E.; Scognamiglio, G.; Mita, G.D.; Cirillo, T. Determination of BPA, BPB, BPF, BADGE and BFDGE in canned energy drinks by molecularly imprinted polymer cleaning up and UPLC with fluorescence detection. *Food Chem.* **2017**, *220*, 406–412. [CrossRef] [PubMed]
57. Zech, J.; Manowski, A.; Malchow, S.; Rettberg, N.; Garbe, L.A. Determination of bisphenols, bisphenol A diglycidyl ether (BADGE), BADGE chloro-hydrins and hydrates from canned beer by high-performance liquid chromatography- tandem mass spectrometry. *Brew. Sci.* **2015**, *68*, 102–109.
58. Cirillo, T.; Esposito, F.; Fasano, E.; Scognamiglio, G.; Di Marco Pisciottano, I.; Mita, G.D.; Gallo, P. BPA, BPB, BPF, BADGE-andBFDGEin canned beers fromthe Italian market. *Food Addit. Contam. Part B* **2019**, *12*, 268–274. [CrossRef] [PubMed]
59. Cacho, J.I.; Campillo, N.; Vinas, P.; Hernandez-Cordoba, M. Stir bar sorptive extraction coupled to gas chromatography–mass spectrometry for the determination of bisphenols in canned beverages and filling liquids of canned vegetables. *J. Chromatogr. A* **2012**, *1247*, 146–153. [CrossRef] [PubMed]
60. Cunha, S.C.; Fernandes, J.O. Assessment of bisphenols A and bisphenol B in canned vegetables and fruits by gas chromatography–mass spectrometry after QuEChERS and dispersive liquid–liquid microextraction. *Food Control* **2013**, *33*, 549–555. [CrossRef]
61. Summerfield, W.; Goodson, A.; Cooper, I. Survey of bisphenol a diglycidyl ether (BADGE) in canned foods. *Food Addit. Contam.* **1998**, *15*, 818–830. [CrossRef] [PubMed]
62. Hammarling, L.; Gustavsson, H.; Svensson, K.; Oskarsson, A. Migration of bisphenol-A diglycidyl ether (BADGE) and its reaction products in canned foods. *Food Addit. Contam.* **2000**, *17*, 937–943. [CrossRef] [PubMed]
63. Biedermann, S.; Zurfluh, M.; Grob, K.; Vedani, A.; Bruschweiler, B.J. Migration of cyclo-diBA from coatings into canned food: Method of analysis, concentration determined in a survey and in silico hazard profiling. *Food Chem. Toxicol.* **2013**, *58*, 107–115. [CrossRef]
64. EFSA. Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA J.* **2015**, *13*, 3978. [CrossRef]
65. EFSA. Opinion of the scientific panel AFC related to bisphenols A diglycidyl ether (BADGE). *EFSA J.* **2004**, *86*, 1–40.
66. Marqueno, A.; Perez-Albaladejo, E.; Flores, C.; Moyano, E.; Porte, C. Toxic effects of bisphenol A diglycidyl ether and derivatives in human placental cells. *Environ. Pollut.* **2019**, *244*, 513–521. [CrossRef] [PubMed]
67. Zhang, N.; Scarsella, J.B.; Hartman, T.G. Identification and quantitation studies of migrants from BPA alternative food-contact metal can coatings. *Polymers* **2020**, *12*, 2846. [CrossRef] [PubMed]
68. Chen, M.Y.; Ike, M.; Fujita, M. Acute toxicity, mutagenicity, and estrogenicity of bisphenol-A and other bisphenols. *Environ. Toxicol.* **2002**, *17*, 80–86. [CrossRef]
69. Maćczak, A.; Cyrkler, M.; Bukowska, B.; Michałowicz, J. Bisphenol, A, bisphenol S, bisphenol F and bisphenol AF induce different oxidative stress and damage in human red blood cells (in vitro study). *Toxicol. Vitr.* **2017**, *41*, 143–149. [CrossRef] [PubMed]
70. Huang, M.; Liu, S.; Fu, L.; Jiang, X.; Yang, M. Bisphenol A and its analogues bisphenol S, bisphenol F and bisphenol AF induce oxidative stress and biomacromolecular damage in human granulosa KGN cells. *Chemosphere* **2020**, *253*, 126707. [CrossRef] [PubMed]
71. Jacobson, M.H.; Woodward, M.; Bao, W.; Liu, B.; Trasande, L. Urinary bisphenols and obesity prevalence among US children and adolescents. *J. Endocr. Soc.* **2019**, *3*, 1715–1726. [CrossRef] [PubMed]
72. Horan, T.S.; Pulcastro, H.; Lawson, C.; Gerona, R.; Martin, S.; Gieske, M.C.; Sartain, C.V.; Hunt, P.A. Replacement bisphenols adversely affect mouse gametogenesis with consequences for subsequent generations. *Curr. Biol.* **2018**, *28*, 2948–2954. [CrossRef]
73. European Union. Regulation (EC) No. 1935/2004. *Off. J. Eur. Union* **2004**, *L338*, 4–17.

74. Geueke, B.; Wagner, C.C.; Muncke, J. Food contact substances and chemicals of concern: A comparison of inventories. *Food Addit. Contam. Part A* **2014**, *31*, 1438–1450. [CrossRef]
75. Yang, F.; Mao, Y.; Zhang, X.; Ma, Z.; Zhang, X. LC-MS/MS method for the determination of melamine in rat plasma: Toxicokinetic study in Sprague–Dawley rats. *J. Sep. Sci.* **2009**, *32*, 2974–2978. [CrossRef] [PubMed]
76. Baynes, R.E.; Smith, G.; Mason, S.E.; Barrett, E.; Barlow, B.M.; Riviere, J.E. Pharmacokinetics of melamine in pigs following intravenous administration. *Food Chem. Toxicol.* **2008**, *46*, 1196–1200. [CrossRef]
77. Wu, C.F.; Hsieh, T.J.; Chen, B.H.; Liu, C.C.; Wu, M.T. A crossover study of noodle soup consumption in melamine bowls and total melamine excretion in urine. *JAMA Intern. Med.* **2013**, *173*, 317–319. [CrossRef] [PubMed]
78. Zheng, X.; Zhao, A.; Xie, G.; Chi, Y.; Zhao, L.; Li, H.; Wang, C.; Bao, Y.; Jia, W.; Luther, M.; et al. Melamine-induced renal toxicity is mediated by the gut microbiota. *Sci. Transl. Med.* **2013**, *5*, 172ra22. [CrossRef]
79. Xu, S.; Zhang, Y.; Sims, A.; Bernards, M.; Hu, Z. Fate and toxicity of melamine in activated sludge treatment systems after a long-term sludge adaptation. *Water Res.* **2013**, *47*, 2307–2314. [CrossRef]
80. REIHEY CHEM, Melamine: A Guide to its Applications in Plastics and Coatings. 2023. Available online: https://reiheychem.com (accessed on 9 January 2024).
81. WHO. Toxicological and Health Aspects of Melamine and Cyanuric Acid. In *Report of a WHO Expert Meeting in Collaboration with FAO*; Health Canada: Ottawa, Canada; WHO: Geneva, Switzerland, 2008.
82. Chien, C.Y.; Wu, C.F.; Liu, C.C.; Chen, B.H.; Huang, S.P.; Chou, Y.H.; Chang, A.W.; Lee, H.H.; Pan, C.H.; Wu, W.J.; et al. High melamine migration in daily-use melamine-made tableware. *J. Hazard. Mater.* **2011**, *188*, 350–356. [CrossRef]
83. Bradley, E.L.; Castle, L.; Day, J.S.; Ebner, I.; Ehlert, K.; Helling, R.; Koster, S.; Leak, J.; Pfaff, K. Comparison of the migration of melamine from melamine–formaldehyde plastics ('melaware') into various food simulants and foods themselves. *Food Addit. Contam. Part A* **2010**, *27*, 1755–1764. [CrossRef]
84. Bradley, E.L.; Castle, L.; Day, J.S.; Leak, J. Migration of melamine from can coatings cross-linked with melamine-based resins, into food simulants and foods. *Food Addit. Contam.* **2011**, *28*, 243–250. [CrossRef] [PubMed]
85. Poovarodom, N.; Junsrisuriyawong, K.; Sangmahamad, R.; Tangmongkollert, P. Effects of microwave heating on the migration of substances from melamine formaldehyde tableware. *Food Addit. Contam. Part A* **2014**, *31*, 1616–1624. [CrossRef]
86. Geueke, B. *Dossier-Per and Polyfluroalkyl Substances (PFASs)*; Food Packaging Forum: Zurich, Switzerland, 2016. [CrossRef]
87. Göteborgsposten. Stekpannor-Test. 2012. Available online: https://www.gp.se/livsstil/konsument/stekpannor-test-1.696573 (accessed on 25 November 2019).
88. Sinclair, E.; Kim, S.K.; Akinleye, H.B.; Kannan, K. Quantitation of gas-phase perfluoroalkyl surfactants and fluorotelomer alcohols released from nonstick cookware and microwave popcorn bags. *Environ. Sci. Technol.* **2007**, *41*, 1180–1185. [CrossRef]
89. Schlummer, M.; Sölch, C.; Meisel, T.; Still, M.; Gruber, L.; Wolz, G. Emission of perfluoroalkyl carboxylic acids (PFCA) from heated surfaces made of polytetrafluoroethylene (PTFE) applied in food contact materials and consumer products. *Chemosphere* **2015**, *129*, 46–53. [CrossRef]
90. Begley, T.H.; Hsu, W.; Noonan, G.; Diachenko, G. Migration of fluorochemical paper additives from food-contact paper into foods and food simulants. *Food Addit. Contam.* **2008**, *25*, 384–390. [CrossRef]
91. Still, M.; Schlummer, M.; Gruber, L.; Fiedler, D.; Wolz, G. Impact of industrial production and packaging processes on the concentration of per-and polyfluorinated compounds in milk and dairy products. *J. Agric. Food Chem.* **2013**, *61*, 9052–9062. [CrossRef] [PubMed]
92. Kannan, K.; Corsolini, S.; Falandysz, J.; Fillmann, G.; Kumar, K.S.; Loganathan, B.G.; Mustafa, A.M.; Olivero, J.; Wouwe, N.V.; Yang, J.H.; et al. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. *Environ. Sci. Technol.* **2004**, *38*, 4489–4495. [CrossRef] [PubMed]
93. Lau, C.; Anitole, K.; Hodes, C.; Lai, D.; Pfahles-Hutchens, A.; Seed, J. Perfluoroalkyl acids: A review of monitoring and toxicological findings. *Toxicol. Sci.* **2007**, *99*, 366–394. [CrossRef] [PubMed]
94. Olsen, G.W. PFAS biomonitoring in higher exposed populations. In *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*; Humana Press: Cham, Germany, 2015; pp. 77–125.
95. D'eon, J.C.; Crozier, P.W.; Furdui, V.I.; Reiner, E.J.; Libelo, E.L.; Mabury, S.A. Observation of a commercial fluorinated material, the polyfluoroalkyl phosphoric acid diesters, in human sera, wastewater treatment plant sludge, and paper fibers. *Environ. Sci. Technol.* **2009**, *43*, 4589–4594. [CrossRef] [PubMed]
96. Glynn, A.; Berger, U.; Bignert, A.; Ullah, S.; Aune, M.; Lignell, S.; Darnerud, P.O. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: Serial 75 sampling during pregnancy and nursing, and temporal trends 1996–2010. *Environ. Sci. Technol.* **2012**, *46*, 9071–9079. [CrossRef] [PubMed]
97. Kato, K.; Wong, L.Y.; Jia, L.T.; Kuklenyik, Z.; Calafat, A.M. Trends in exposure to polyfluoroalkyl chemicals in the US population: 1999–2008. *Environ. Sci. Technol.* **2011**, *45*, 8037–8045. [CrossRef] [PubMed]
98. Mamsen, L.S.; Björvang, R.D.; Mucs, D.; Vinnars, M.T.; Papadogiannakis, N.; Lindh, C.H.; Andersen, C.Y.; Damdimopoulou, P. Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies. *Environ. Int.* **2019**, *124*, 482–492. [CrossRef] [PubMed]

99. Haug, L.S.; Huber, S.; Becher, G.; Thomsen, C. Characterisation of human exposure pathways to perfluorinated compounds—Comparing exposure estimates with biomarkers of exposure. *Environ. Int.* **2011**, *37*, 687–693. [CrossRef] [PubMed]
100. Lindström, A.B.; Strynar, M.J.; Libelo, E.L. Polyfluorinated compounds: Past, present, and future. *Environ. Sci. Technol.* **2011**, *45*, 7954–7961. [CrossRef] [PubMed]
101. DeWitt, J.C.; Peden-Adams, M.M.; Keller, J.M.; Germolec, D.R. Immunotoxicity of perfluorinated compounds: Recent developments. *Toxicol. Pathol.* **2012**, *40*, 300–311. [CrossRef] [PubMed]
102. White, S.S.; Fenton, S.E.; Hines, E.P. Endocrine disrupting properties of perfluorooctanoic acid. *J. Steroid Biochem. Mol. Biol.* **2011**, *127*, 16–26. [CrossRef] [PubMed]
103. Gallo, V.; Leonardi, G.; Genser, B.; Lopez-Espinosa, M.J.; Frisbee, S.J.; Karlsson, L.; Ducatman, A.M.; Fletcher, T. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environ. Health Perspect.* **2012**, *120*, 655–660. [CrossRef]
104. Barry, V.; Winquist, A.; Steenland, K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ. Health Perspect.* **2013**, *121*, 1313–1318. [CrossRef]
105. Benbrahim-Tallaa, L.; Lauby-Secretan, B.; Loomis, D.; Guyton, K.Z.; Grosse, Y.; El Ghissassi, F.; Bouvard, V.; Guha, N.; Mattock, H.; Straif, K. Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1, 2-dichloropropane, and 1, 3-propane sultone. *Lancet Oncol.* **2014**, *15*, 924–925. [CrossRef]
106. Fitz-Simon, N.; Fletcher, T.; Luster, M.I.; Steenland, K.; Calafat, A.M.; Kato, K.; Armstrong, B. Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid. *Epidemiology* **2013**, *24*, 569–576. [CrossRef]
107. Steenland, K.; Zhao, L.; Winquist, A.; Parks, C. Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. *Environ. Health Perspect.* **2013**, *121*, 900–905. [CrossRef]
108. Grandjean, P.; Andersen, E.W.; Budtz-Jørgensen, E.; Nielsen, F.; Mølbak, K.; Weihe, P.; Heilmann, C. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA* **2012**, *307*, 391–397. [CrossRef] [PubMed]
109. Sunderland, E.M.; Hu, X.C.; Dassuncao, C.; Tokranov, A.K.; Wagner, C.C.; Allen, J.G. A review of the pathways of human exposure to poly-and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J. Expo. Sci. Environ. Epidemiol.* **2018**, *29*, 131–147. [CrossRef] [PubMed]
110. Blum, A.; Balan, S.A.; Scheringer, M.; Trier, X.; Goldenman, G.; Cousins, I.T.; Diamond, M.; Fletcher, T.; Haggins, C.; Lindeman, A.E.; et al. The Madrid statement on poly-and perfluoroalkyl substances (PFASs). *Environ. Health Perspect.* **2015**, *123*, A107–A111. [CrossRef] [PubMed]
111. Ritscher, A.; Wang, Z.; Scheringer, M.; Boucher, J.M.; Ahrens, L.; Berger, U.; Bintein, S.; Bopp, S.K.; Borg, D.; Buser, A.M.; et al. Zürich statement on future actions on per-and polyfluoroalkyl substances (PFASs). *Environ. Health Perspect.* **2018**, *126*, 084502. [CrossRef] [PubMed]
112. Goldenman, G.; Fernandes, M.; Holland, M.; Tugran, T.; Nordin, A.; Schoumacher, C.; McNeill, A. *The Cost of Inaction: A Socioeconomic Analysis of Environmental and Health Impacts Linked to Exposure to PFAS*; Nordic Council of Ministers: Copenhagen, Denmark, 2019.
113. Knutsen, H.K.; Alexander, J.; Barregård, L.; Bignami, M.; Brüschweiler, B.; Ceccatelli, S.; Cottrill, B.; Dinovi, M.; Edler, L.; Grasl-Kraupp, B.; et al. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. *EFSA J.* **2018**, *16*, e05194. [CrossRef]
114. Council of the European Union. UTCOME OF PROCEEDINGS, Brussels 26 June 2019. No. prev. doc.: 10279/19. Council Conclusions: Towards a Sustainable Chemicals Policy Strategy of the Union. Available online: https://www.consilium.europa.eu/en/documents-publications/ (accessed on 12 November 2023).
115. Fernández, M.A.; Gómara, B.; González, M.J. Occurrence of phthalates and their metabolites in the environment and human health implications. In *Emerging Organic Contaminants and Human Health*; Springer: Berlin/Heidelberg, Germany, 2011; pp. 307–336.
116. Katsikantami, I.; Sifakis, S.; Tzatzarakis, M.N.; Vakonaki, E.; Kalantzi, O.I.; Tsatsakis, A.M.; Rizos, A.K. A global assessment of phthalates burden and related links to health effects. *Environ. Int.* **2016**, *97*, 212–236. [CrossRef] [PubMed]
117. Fierens, T.; Servaes, K.; Van Holderbeke, M.; Geerts, L.; De Henauw, S.; Sioen, I.; Vanermen, G. Analysis of phthalates in food products and packaging materials sold on the Belgian market. *Food Chem. Toxicol.* **2012**, *50*, 2575–2583. [CrossRef]
118. Goulas, A.E.; Salpea, E.; Kontominas, M.G. Di(2-ethylhexyl) adipate migration from PVC cling film into packaged sea bream (Sparus aurata) and rainbow trout (Oncorhynchus mykiss) fillets: Kinetic study and control of compliance with EU specifications. *Eur. Food Res. Technol.* **2008**, *226*, 915–923. [CrossRef]
119. Goulas, A.E.; Zygoura, P.; Karatapanis, A.; Georgantelis, D.; Kontominas, M.G. Migration of di(2-ethylhexyl) adipate and acetyltributyl citrate plasticizers from food-grade PVC film into sweetened sesame paste (halawatehineh): Kinetic and penetration study. *Food Chem. Toxicol.* **2007**, *45*, 585–591. [CrossRef]
120. Coltro, L.; Pitta, J.B.; Costa, P.A.; Fávaro Perez, M.A.; Araújo, V.A.; Rodrigues, R. Migration of conventional and new plasticizers from PVC films into food simulants: A comparative study. *Food Control* **2014**, *44*, 118–129. [CrossRef]

121. Benjamin, S.; Masai, E.; Kamimura, N.; Takahashi, K.; Anderson, R.C.; Faisal, P.A. Phthalates impact human health: Epidemiological evidences and plausible mechanism of action. *J. Hazard. Mater.* **2017**, *340*, 360–383. [CrossRef] [PubMed]
122. Panou, A.; Karabagias, I.K. Biodegradable Packaging Materials for Foods Preservation: Sources, Advantages, Limitations, and Future Perspectives. *Coatings* **2023**, *13*, 1176. [CrossRef]