Recent advances in assessing xenobiotics migrating from packaging material – a review

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Abstract: Migration of potentially toxic xenobiotics and their transformation products from packaging materials needs continuous monitoring efforts. This task requires utilizing both instrumental and biological methods as more and more novel materials reach market every year to serve consumers and reduce production costs. Unfortunately, these materials very often sneak past our legal regulations on their composition and emission of contaminants due to contact with the materials or products stored. For these reasons, more and more novel, holistic and multi-tier approaches must be elaborated to uncompromisingly assure safety of these materials to living creatures. In the work presented, a review of methods enabling performing studies on extraction, leaching, qualitative and quantitative determination of xenobiotics and their combined effect on certain biological endpoints is given. Additionally, a basic approach guiding end-users and scientists to elaborate such studies is presented in the form of a basic scheme, and advantages and disadvantages of these methods are summarized.

Keywords: Food Contact Materials, extraction, food quality, novel packaging materials

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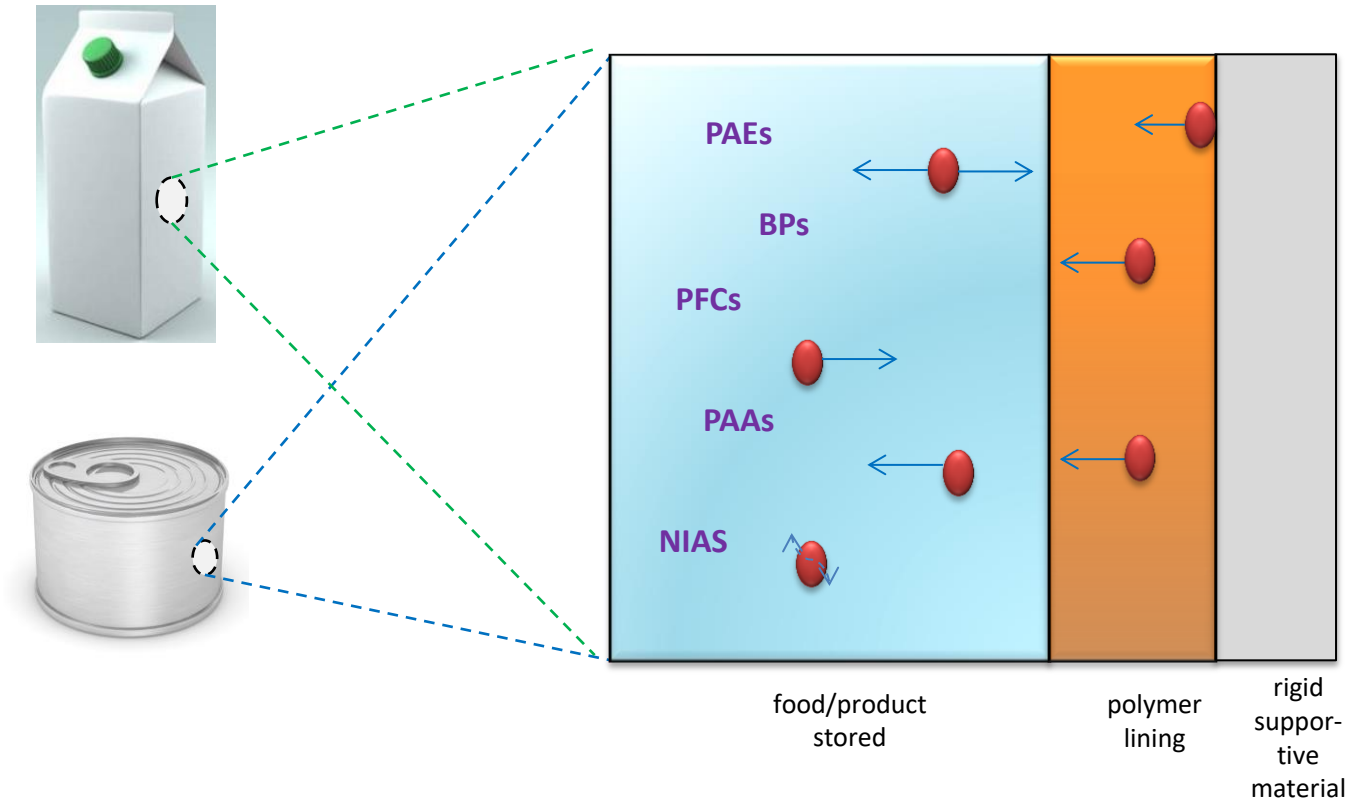
*Graphical Abstract



1. Introduction

Development of human civilization since the XX century is undoubtedly connected with more efficient food distribution chaining processes as chronic lack of time in highly developed societies resulted in changes in their lifestyles and in patterns of consumption. As even brief data evaluation shows, highly developed countries feature almost 98% of widely used products, especially food products, sold in various types of packaging consisting of plastics, paper, glass, metal and composite materials [1]. The main assumptions at the stage of designing and production of packaging materials destined for the storage of food products are mainly related to ensuring the best protection of the products, having an influence on maintaining all of their health properties and prolonging their shelf life (while keeping the price of the product as low as possible). The packaging is supposed to be a certain barrier, protecting the food against the influence of various external factors, including chemical, biological and physical protection. The missing gap in this design process can be identified as the lack of using all available diagnostic techniques (including biological and instrumental ones) and impact of artificial complex fluids mimicking advanced extraction media in a chronic manner.

In addition to protecting food from damage, the packaging fulfills an informative role and has a marketing function. Data placed on the packaging provide the consumers with valuable information on the quantitative and qualitative composition of the product, as well as appropriate usage and its use-by-date. In addition, as provided in studies aimed at understanding the consumer behaviors and preferences, the visual attractiveness of the packaging as well as its functionality are the main factors influencing purchase of the given product. Due to the diversity of the functions of packaging and the various physicochemical properties of products stored in the packaging, the choice of appropriate packaging materials is a very complex issue, requiring scientific knowledge of a wide range of materials [1]. Currently, materials used as packaging can be divided into the classic categories such as glass, paper, cardboard or metal, as well as those packaging materials that are obtained through chemical synthesis such as polymer sand composite materials [2,3]. It is extremely difficult to

unequivocally state which of the accessible materials is characterized by the best qualities as an Food Contact Materials (FCM), as it is determined by numerous factors, both directly related to food storage itself, and the economic factors related to production costs, as well as environmental factors, related to the environmental nuisance resulting from the production of the packaging, as well as its disposal.

Undoubtedly, the current world production of packaging materials is based mainly on the use of polymer materials. The wide areas of applicability of synthetic materials, the ease of modification and the low cost of production (in comparison to other materials) have contributed to the great success of this material [4]. Currently, different plastics are being used as packaging materials. Additionally, different types of additives such as antioxidants, stabilizers, lubricants, anti-static and anti-blocking agents have been developed to improve fabrication or use of the polymeric packaging materials [5].

Unfortunately, however, mass production and physicochemical properties of these materials have contributed to a significant increase in the amount of waste and, therefore, in both physical and chemical degradation of the environment. The will to prevent those adverse changes, as well as a growing care for the ecosystem, have become a factor stimulating the search for new pro-ecological solutions. It is currently of increasing importance to design, produce and use packaging in accordance with the sustainable development principles [6]. One of the pro-ecological solutions implemented in the packaging sector is the use of recycled materials. Approximately 59% of the paper and paperboard, 51% of the metals, 25% of the glass, and 9% of the plastics generated as containers and packaging are recovered [7]. Another solution is the use of biopolymers. The main advantage of these materials is their degradability, resulting from the activity of microorganisms, which solves the significant problem related to the management of an immense amount of waste. The products of this reaction of microorganisms, depending on the conditions under which the reaction occurs (aerobic/anaerobic), are oxygen, carbon dioxide, methane and biomass [8]. Eco-friendly materials,

applicable to the food packaging industry, can be categorized as three groups, depending on their origin as shown in the Fig. 1 [6,9].

Fig. 1.

To date, the results of research constitute a basis for the statement that these materials are fully degradable and may be classified as safe for food products, and their addition to non-degradable materials may increase the speed of their decomposition process. Unfortunately, despite the abovementioned advantages, eco-materials also have significant drawbacks, which currently make it impossible to replace the conventionally used materials with the eco-materials. The main limits of biopolymers are their poor mechanical and barrier properties and high permeability to water. In addition, biopolymers are characterized by a poor resistance to temperature and humidity, low resistance to prolonged technological operations, and brittleness [9,10].

While discussing issues related to the so-called new generation of packaging materials, it is impossible not to mention the intelligent packaging (IP) and the active packaging (AP). Intelligent packaging materials, also known as smart packaging, are "materials and articles that monitor the condition of packaged food or the environment surrounding the food" [11]. Indicators placed inside or outside the packaging provide information about the history of the packaging. The most commonly used indicators include gas leakage indicators, ripeness regulators and indicators, time-temperature monitors, bioprobes, radio frequency indicators and toxin indicators [3]. In Table 1, information on substances used as indicators for IP and AP is summarized.

Table 1.

As already mentioned, one of the key factors required for material to be a possible candidate for packaging is that it should not react with the products stored within. This assumption does not, however, concern active packaging. Active packaging is designed so that the surface layer of the packaging enters a strictly defined reaction to impede adverse effects (having an impact on the loss of health properties of food during its storage) and subsequently contributes to prolonging the

durability of the food [4]. Several active packaging systems such as CO_2/O_2 and ethylene scavengers and/or emitters, ethanol emitters, moisture regulators, antioxidant and antimicrobial controlled-release packages, and devices to control the release or adsorption of flavors, odors and colors have been widely reported in the literature [3,4].

Although the market is currently dominated by traditional packaging, it may be assumed that in the near future, modern types of food packaging will be registered in the European Union countries, and we will face real revolution in this area of interest. No doubt that packaging currently plays a major role both in the everyday life of societies and in the various branches of industry. Despite numerous advantages, packaging may be a source of contamination of food and thus may constitute a source of consumer exposure to various types of xenobiotics [27]. As the fact, a wide range of materials is used in the production of packaging (metals and alloys, polymers, nano-compounds, stabilizers, colorants, *etc.*), the ingredients of which may be transferred into food. In the literature, the transfer process of chemicals from the packaging to the food is known as migration [28]. Considering that digestion is a process causing the liberation of the largest amounts of contamination to be transferred and absorbed into the body, this situation may result in a disruption of the balance of a living organism. In this sense, digestion greatly contributes to the occurrence and progression of many diseases and dysfunctions [29]. Therefore, it is crucial to constantly monitor the influence of the packaging material on the quality of the products stored in it, as well as to intensify the efforts to develop new analytical tools, enabling the detection, identification and quantitative determination of a wide range of analytes. In this paper, we describe methods for assessing streams of xenobiotic migration from packaging materials, starting from the extraction of the packaging materials using different chemical and biological methods and the final determination methods. Based on all of the information mentioned above the objective of work presented is to comprehensively present information on known properties and methods of analyses of packaging materials including utilization of biological methods at the stage of the exposure assessment and

artificial body fluids at the extraction process. A scheme representing suggestions on selecting extraction media, sample preparation and determination methods is also presented.

2. Migration process and possibilities for testing

The phenomenon of migration of hazardous chemical substances from packaging materials was scientifically observed at the beginning of the 1980s [5]. From that moment, many research centers all over the world have intensified their efforts to better understand the mechanism of the transport of substances and the factors contributing most significantly to the intensification of this transfer process. According to the results of numerous research observations, the migration process is a very complex phenomenon. Detailed information on the migration process as well as factors influencing its intensity are described in the paper of Arvanitoyannis and Kotsanopoulos [28].

Deeper understanding these dependencies has allowed the development of various mathematical models enabling the estimation of the degree of the migration and the assessment of the changes in the qualitative properties of the packaging material. For example, the Weibull model was applied to describe the migration of phthalates into Tenax® from paper and paperboard [30]. In another paper, the authors used the Crank's mathematical model to evaluate the migration of butylated hydroxytoluene (BHT) from polypropylene film [31]. The use of advanced numerical techniques (as tools for developing a better understanding of migration processes) has many advantages, and their future role in ensuring FCM quality will probably increase. Decisions about accepting or rejecting packaging materials are currently made mainly based on the results of experimental research.

The issue of safety of food packaging is subjected to EU and national legislation. The basic legal act is Regulation (EC) No. 1935/2004, which establishes general safety requirements for the manufacturing, processing and distribution of all possible FCMs [11]. Regulation 2023/2006 describes good manufacturing practices (GMPs) that industry should follow to protect the interests of customers [32]. In addition to the general provisions, detailed legal regulations have been set forth

for some packaging: (i) provisions concerning materials and products made of plastics - Commission Regulation (EU) No. 10/2011 [33], (ii) recycled plastics - Commission Regulation (EC) No. 282/2008 [34], (iii) packaging materials made of ceramics - Council Directive 84/500/EEC [35], (iv) regenerated cellulose film - Commission Directive 2007/42/EC [36], and (v) active and intelligent packaging - Commission Regulation 450/2009. Those documents contain exact guidelines, including a list of substances that are permitted for use both in the production process and the processing of materials (the positive list), border values of admissible global migration limits (overall migration limit – OML) and of specific migration (specific migration limit – SML) defined for appropriate substances, migration research methods and conditions, as well as admissible values of the substance content in the final product [33].

The basic research for packaging materials destined for contact with food is based on determining the values of so-called overall migration and specific migration [37]. The overall migration is the most unspecific measurement of migration that results in the determination of migration of all non- and medium-volatile migrants from the packaging material and not of a specific migrant. There is no identification of the migrants and hence no toxicological conclusions based on single species can be drawn [37]. By contrast, in the case of the specific migration, the actions are focused on quantitative determination of strictly defined analytes [37,38]. Because a vast diversity of food products and their mixtures is currently available on the market, it is impossible to perform research with the use of all the food products in their real conditions of usage. That is why properly chosen food simulants (FSs) are used in laboratory practice, imitating a defined type of food. The simulants are either liquid or solid substances that have a simple and known composition and facilitate and ameliorate test interpretations. In the aforementioned legal regulations and in the EN 13130 standard, both the criteria for the choice of food simulants and for research methods and conditions were described in detail to best mimic the conditions of real usage. In addition, information was provided on both the size and geometry of the material subject to analysis, and the method of sampling after a given time of contact with the packaging [39]. Samples taken at a later

stage of the analysis are subjected to instrumental analysis to qualitatively and quantitatively determine the analytes released.

3. Substances migrating from FCMs

There are hundreds of compounds that can migrate from food contact materials to food or food stimulants, from substances such as plasticizers, antioxidants, light and thermal stabilizers, slip compounds, antistatic agents, lubricants, monomers, residual solvent, and degradation products to heavy metals and nanoparticles [40–42]. In this review, we have focused on some relevant families of organic and inorganic compounds, which are classified by European Food Safety Agency (EFSA) as endocrine disrupting compounds (EDCs) [43], the migration of which from the packaging surface may be particularly dangerous to consumers. These are among other: bisphenols and related compounds, phthalates, perfluorinated compounds (PFCs), Primary aromatic amines (PAAs), UV-photoindicators and substances included to NIAS (non-intentionally added substances). The characteristics of each of the aforementioned family of compounds are thoroughly described in the works of Gallart -Ayala et al. [44] and Sanchis et al. [45]. However, in order to supplement the information included in the studies. Table 2 presents the data on the harmful effects caused by these compounds and the permitted values of TDI (Tolerable Daily Intake) and SML. Unfortunately, analogues of BPA, namely bisphenol S (BPS), bisphenol F (BPF), bisphenol AP (BPAP), and bisphenol AF (BPAF) (that were developed for various industrial applications), also pose estrogenic activity and potential toxicity when compared with BPA. Some of them were found to be even more resistant to biodegradation than BPA [46–48].

Table 2.

4. Instrumental methods used to evaluate different migrants from food packaging materials

Identification and quantitative determination of analytes released from the packaging material is undoubtedly a difficult and tricky task, requiring the chemical analyst to develop an individual approach to obtain reliable analytical information. During the past few years, numerous tools have been developed, allowing the identification and quantitative determination of most analytes. Unfortunately, it is still challenging for scientists to determine substances at trace or even ultra-trace levels in samples characterized by a very complex, and often variable, matrix composition [74]. In such cases, a condition necessary for obtaining reliable information is the choice of an approach allowing the isolation and the enrichment of analytes, as well as the choice of an appropriate technique for final determination. Among threats related to the migration of low molecular weight compounds from the packaging surface, three main areas of scientific interest may be distinguished. The first area is the determination of the quantity of analytes in FCMs. The second is the determination of harmful substances in simulant samples. The third area of research is focused on the determination of target analytes in food samples [45]. The designated matrix composition of the sample analyzed determines further steps in the analytical process. Figure 2 schematically shows the most common analytical approaches for the determination of analytes in samples with different matrix compositions.

Fig. 2.

Typical steps in analytical procedures for sample preparation include sampling, sample pretreatment (homogenization or cutting), extraction, cleanup and pre-concentration prior to instrumental analysis. A review of the literature indicates that the most common techniques used for the extraction of analytes from FCMs surface primarily include solvent methods such as Soxhlet extraction, solid-liquid extraction (SLE), and liquid-liquid extraction (LLE) [45,74]. The Soxhlet method has been used for extracting phthalates from films of food packaging and bags for food freezing [75]. In another study, researchers used this technique for the extraction of BPA and phthalates from

recycled paper and paperboard packaging. The use of this method allowed the development of a methodological approach, assuring the acquisition of 101-108% recoveries [7]. However, when the purpose is to extract more polar compounds from the matrix, the SLE technique is often used. A factor having the greatest impact on the efficiency of the extraction process is, in this case, the choice of an appropriate solvent, which should depend on the physicochemical properties of both the analytes and the matrix [76]. Methanol, sodium hydroxide in methanol solutions, acetonitrile and ethyl acetate are most commonly used for the extraction of BPA and PFCs. In addition to the solvents mentioned above, mixtures of solvents are also used, e.g., dichloromethane-cyclohexane, acetonitrile-hexane, acetone-hexane, and acetonitrile-acetone [44].

To improve the efficiency of the extraction process, a variety of supporting factors are additionally used. Ultrasound assisted extraction (USE), pressurized liquid extraction (PLE) or microwave-assisted extraction (MAE) have been applied for the extraction of target compounds from packaging materials [77]. The main drawbacks related to the use of such conventional methods are the necessity of a significant amount of toxic organic solvent as well as the long duration of the process. An additional disadvantage is the fact that, due to a limited selectivity, an additional cleanup stage is necessary prior to instrumental analysis [44]. Incontestable progress was made during the past years regarding the development of the techniques of preparation of samples for analysis, as well as an increasing focus on introducing the 12 principles of green chemistry to laboratory practice, resulting in the so-called modern extraction techniques being more often used in research practices. Solid Phase Extraction (SPE), Solid Phase Microextraction (SPME), Stir Bar Sorptive Extraction (SBSE), Hallow-Fiber Liquid Phase Microextraction (HFLPME), QuECHERS (Quick, Easy, Cheap, Effective, Rugged, and Safe), Dispersive Liquid–Liquid Microextraction (DLLME) or Focused Ultrasonic Solid–Liquid Extraction (FUSLE) have been successfully applied to extract FCM contaminants from foodstuffs and packaging [78–81]. SPE is usually used for isolation of nonvolatile analytes. Among the most commonly used sorbents, a distinction can be made between those commercially available in the market and those referred to as modern sorbents. Molecularly imprinted polymer (MIP) sorbent

was applied to isolate and pre-concentrate BPA and related compounds from canned energy drink samples [49]. In another study, scientists used a highly specific reaction between an antibody and an antigen for isolation of BPA from canned food [82]. In the case of the volatile or semivolatile compound analysis with gas chromatography, SPME is the most commonly used. The process of analyte extraction using the SPME technique may be conducted in two modes: an extraction fiber is placed in the gas or liquid medium which is the subject of analysis (DI-SPME) or the analytes are collected from the headspace (HS-SPME). The first technique has been successfully used for the extraction of plasticizers migrating from plastic bags to meat [80]. While the second one, Has been applied to identification and determination of volatile compounds released from wrapping films [81]. Like the technique described above, both conventional and modern sorption materials are used to cover the fibers. MIP and single-walled carbon nanotubes (SWCNT) have been used as a sorption material for BPA and BPF isolation and enrichment from canned food samples [84,85]. A review of the literature concerning issues related to NIAS determination indicates that SPME is the most commonly used technique for this type of analysis. The main quality supporting the choice of this technique is the fact that analytes are collected directly from the sample, which minimizes the risk of cross contamination from glassware and solvents [45,86]. Additionally, it should be noted that in this technique it is not necessary to use organic solvents, which is undoubtedly an advantage that gives the green character to this technique.

Another green technique used for the determination of packaging contaminants is dispersive liquid-liquid phase microextraction (DLLME). This approach was undertaken to determine three compounds from the EDC group in samples of paper and plastic packaging. Ionic liquids, also known as eco-friendly "green" extraction solvents, were used as medium sorption agents. Compared to conventional extraction methods, this method has reduced both the time and cost of the entire analysis and, most importantly, significantly improved the analytes enrichment coefficients [79]. In other studies, in both the extraction and the cleanup stages, researchers utilized the QeECHERS approach. This technique is known above all due to its use for determining pesticide residue in fruit

and vegetable samples. However, its scope of application keeps increasing with time. It was recently used for the extraction of BPA and BPB from canned seafood [81] and BADGE from canned fish [86]. The growing popularity of this method is above all because it is characterized by low sample and reagent volume/amount usage, as well as its simplicity, since the procedure implies only shaking and swirling of the sample, which significantly reduces the costs of the entire analysis. According to researchers, its only drawback, which is unfortunately quite significant, is its low enrichment factor. To overcome this limitation, some authors proposed a DLLME step after QuEChERS extraction.

Recently, there is more and more information in the literature on the use of LPME with hallow fibers in order to isolate and enrich the analytes. This technique is gaining more and more popularity mainly due to its high selectivity, cheapness, versatility and high potential for miniaturization and automation and it provides high analyte enrichments and low consumption of hazardous organic solvents [88,89]. An additional advantage is that the acceptor solution can be directly analyzed by gas chromatography or by capillary electrophoresis. Hallow fiber based LPME can be carried out in two or three-phase mode [88]. A fully automated HFLPME was successfully applied to determination of 43 compounds migrating from active food packaging containing essential oils [89].

One of the techniques particularly worth considering (only recently starting to be used for analysis of packaging materials) is focused ultrasonic solid–liquid extraction (FUSLE). This method is a relatively new and very fast (the process takes from a few seconds up to a few minutes) and low-cost based on the cavitation phenomenon. Numerous research results indicate that it is more reproducible and efficient than traditional ultrasonic bath extraction (USE) due to its 100 times higher ultrasonic power and the immersion of the ultrasound microtip directly in the extracting solution [90,91]. FUSLE was successfully applied to the determination of BPA and related compounds in food-contact recycled-paper materials [78], UV-filters in different packaging [90] and perfluorinated alkyl acids in corn, popcorn and popcorn bags [91]. The recoveries obtained with all experiments were close to or slightly higher than 100% for most analytes, except for bis-

ethylhexyloxyphenol methoxyphenyltriazine (58%) and butyl methoxydibenzoylmethane (78%) [78,90,91]. One of the newest techniques used for the isolation of analytes from liquid samples is fabric phase sorptive extraction (FPSE). FPSE, like the method described above, is a new technique, developed in 2014 by Kabir and Furton [92]. FPSE addresses the majority of the shortcomings related to conventional sorptive sample preparation techniques. In this approach, the analytes are adsorbed on the surface of the natural or synthetic fabric. The surface of the fibers can be modified with various functional groups, ensuring the desired sorption properties of the fabric [92]. Compared to the sorbent loading in a typical SPME fiber, FPSE media can contain approximately 400 times higher sorbent loading. However, unlike stir bar sorptive extraction, the extraction sorbent is distributed uniformly on the surface of nanometer size cellulose microfibrils of FPSE [93]. This technique is becoming increasingly popular in environmental research, most importantly for studies focused on determination of estrogens or non-steroidal anti-inflammatory drugs in various samples [93,94], primarily because the use of this technique conditions the acquisition of high analyte recoveries, while it remains cheap and fast and requires low sample and reagent usage. In 2016, FPSE was used in the analysis of a wide range of analytes that are used for the production of packaging materials, such as plasticizers, antioxidants, UV absorbers and antistatic agents [92].

Tab. 4.

The content of analytes in the analyzed packaging material and in food samples or the model extraction liquid can be determined, e.g., with MS, MS/MS, TOFMS and other instrumentation by separation with gas chromatography (GC) and liquid chromatography (LC). The choice of an appropriate method for separation and final determination is closely related to the properties of the target compounds. GC is used primarily for the analysis of volatile compounds with lower polarity (mostly phthalates). LC is used for analysis of more polar and less volatile compounds (PFCs, PAAs, photoindicators, NIASs). In the case of determination of BPA and related compounds where a clear tendency cannot be determined, both LC and GC are used [45]. Table 3 summarizes key information

about techniques and types of detectors used for analysis of FCM contaminants. The data in the table conclusively indicate that the MS detector is most commonly used for both LC and GC. The main advantages of this detector are its high selectivity, high sensitivity and universality. In case of non-target analysis (like in case of NIAS analysis) one of the most powerful tool is mass spectrometry detector with a quadrupole-time-of-flight analyzer (QTOF–MS). The QTOF-MS detector provides sufficiently accurate mass measurements of precursor ion and precursor ions, what is excellent structural information and assures the correct identification of unknown compounds [95,96]. For the most commonly used columns, polar columns are the most popular for determination of volatile compounds (usually 5% phenyl-95% dimethylpolysiloxane), whereas the use of columns with sorbent C_8 or C_{18} is preferred for nonvolatile compounds [44,45].

For the determination of trace quantities of nonorganic compounds migrating from the packaging to the product, the most common are atomic absorption spectrometry (AAS), inductively coupled plasma atomic emission spectroscopy (ICP-AES) or mass spectrometry (ICP-MS), inductively coupled plasma-optical emission spectrometry (ICP-OES) and high performance capillary electrophoresis (HPCE) [42,97,98].

Despite the accessibility of highly selective determination methods, characterized with proper metrological parameters, acquiring reliable information on content levels of FCM contaminants is an extremely difficult task for chemical analysts. This task is so difficult mainly because trace amounts of plasticizers may be present in laboratory vessels, solvents, plastic products and the laboratory environment. This situation makes it more difficult to develop an analytical methodology characterized by a high sensitivity and a good reproducibility of results. The latest literature reports indicate that trace amounts of phthalates and BPA were identified in samples of commercially available high-purity organic solvents, as well as in ultra-high-quality water. BPA has been found at concentrations of 20-200 ng/L in ultra-pure water, with DEHP and DBP at a level of 100 ug/L in hexane [44,99]. The probable cause of the presence of such contaminants is washing the plasticizers out of plastics used for the production and storage of those solvents [99]. In addition to

solvents, another contamination source is all the utensils commonly used in laboratories, such as plastic Pasteur pipettes, SPE columns, and plastic cups [99].

For the reasons mentioned above, it was necessary to develop procedures minimizing the risk of the occurrence of background signals. Most importantly, the use of glassware is recommended for each stage related to both the sample preparation and its storage. Information concerning appropriate preparation methods for glassware can also be found in the literature, starting from heating the glassware at high temperatures (4 h at 450 °C) and ending with washing the glassware with ultra-pure water, methanol, acetone or hexane. Many papers also indicate that the use of gloves is not recommended [49,66,100]. This considerable number of potential sources for sample contamination may result in a significant effort to obtain the final results of the analysis. The utmost effort must be made to eliminate potential sources of sample contamination.

Table 3.

The data presented above on the methodologies used in the field of research on packaging provide primarily information on the content of xenobiotics in the packaging material and their amounts that can be released into the model liquid or the product. Based on this knowledge, it is possible to estimate the health risk resulting from exposure to given harmful compounds. However, taking into account the multitude of processes occurring in the human body and its complexity, this risk may be subject to a significant error. The solution to this problem seems to be the use of artificial body fluids in the research. This approach has recently been the object of increasing interest of chemist analysts mainly due to the fact that it allows to estimate the bioaccessibility of xenobiotics, i.e. the amount of a compound that is solubilized from food through the action of body fluids and can be absorbed by the body [101]. Currently, this approach is mainly used to determine the bioavailability of heavy metals, PAH group compounds and various types of plasticizers e.g. rice [102], seafood [103], dust, air [104], soil [105]. So far, little information can be found about the use of this approach when examining packaging or food stored in it. To our knowledge, only two such studies have been conducted using the *in vitro* digestion model. The purpose of the first research

was to estimate the bioavailability of ethyl lauroyl arginate (LAE), a potent antibacterial compound used as active compound in active packaging using the simulated gastrointestinal digestion process. Analysis of digestion solutions showed no presence of LAE and degradation products in the bioaccessible fraction. Moreover, no new toxic compounds have been found [96]. In the second approach, a more complex procedure was applied. In studies assessing the bioavailability of BPA in canned seafood as many as four digestion fluids were used (salivary, gastric, duodenal and bile). The obtained results indicated that the average of BPA bioaccessibility at the end of *in vitro* digestion was 81%. It was additionally found out that BPA bioaccessibility in the small intestine was higher than in gastric (stomach) or mouth conditions [106]. Considering the amount of information that can be obtained in research by using the model of liquids imitating the natural physiological liquids, it seems that this direction will be increasingly used and dynamically developed in the following years. Therefore, we decided to collect information on both the properties and the possibilities of using Simulated Body Fluids.

5. Model liquids imitating natural physiological liquids

Liquids imitating natural body fluids are referred to as Simulated Body Fluids (SBFs), and these liquids simulate secretions of human body. They can be useful to determine the impact of respective chemical species on objects (samples) of interest. Depending on the type of studies performed, research is conducted to reflect the impact of a compound of interest prior to reaching the internal organs (contact with external barriers) of the body and afterwards. These model liquids have found application not only in assessing the toxicity of pure chemicals but also in experiments performed in pharmaceutical industry research units (details are given in electronic supplementary materials). Artificial body fluids used as the extraction agents in analytical studies are:

- artificial sweat: the composition of human sweat is individually variable (age, diet, gender, origin, season of year, cosmetics used, and physical activity are only several factors impacting the composition and pH of sweat of a given individual [115, 116]. Artificial sweat solutions have

found applicability in assessing the impact of objects in contact with the skin such as gloves, locks, clothes, jewelry, and implants (details on some compositions of artificial sweat are presented in electronic supplementary Table 1.) [117];

- artificial saliva: the composition of human saliva depends on the individual person and the type of experiment is decisive at the stage of selecting an extraction medium due to organic content. Initial optimization of the composition of saliva was done by Darvell and Leung, who tried to obtain the most suitable formulae for *in vivo* studies (details on some compositions of artificial sweat are presented in electronic supplementary Table 2.) [118-120];
- stomach fluid: is characterized by highest variability of pH. To reflect all possible conditions occurring in the stomach of a healthy person, 4 media formulae have been suggested, namely: FaSSGF (fasted-state stomach gastric fluid) and early/middle/late FeSSGF (fed-state stomach gastric fluid). In supplementary Table 3 the basic composition of selected digestive fluids is given.
- gastrointestinal liquid: also known as intestinal juice, is an isotonic liquid, also containing digestive enzymes and exfoliated intestinal cells. Examples of its composition are briefly given in supplementary Table 4.

Fluids simulating body excretions are used in numerous experiments performed by scientists (not only on package xenobiotics extraction processes), and selected information on these studies is depicted in Table 4 in order to present and confirm importance of utilizing the GI liquids in toxicological studies of different objects. As can be easily notified applicability of different BFs in environmental and exposure studies is performed in different operational modes in numerous scientific centers however there is lack of unified procedures and international standards guiding such scientific research pointing importance of undertaking actions that, after interlaboratory and proficiency testing, could lead to issuing such standards.

Table 4.

6. Biological methods in migration studies

Instrumental analyses have undoubted advantages in learning novel information about processes occurring in samples of FCM from contact with different media stored. Still, no holistic information on the impact of packaging on food quality can be gained without using biological systems to respond to a given packaging. As presented in Table 3, there are available methods (however still imperfect ones) that help scientists assess the toxicological impact of packaging extract on products stored. Table 5 summarizes information on biological methods used for the determination of the toxic effect of migrants. Most of the studies performed include extraction of paper and plastic materials with respective food simulants followed by estrogenicity or genotoxicity studies. Most of endocrine potential work includes utilization of CALUX (Chemical Activated LUciferase gene eXpression) and YES/YAS (yeast androgen/estrogen screen) assays. However, most often, signals of the androgenic activity of extracts were observable. In the case of DNA damage studies, only the results of a few experimental studies are available in the literature, although these studies confirm cyto- and genotoxicity of paper and paperboard packaging. Based on the quick review of data presented, one can conclude that mostly cytotoxicity tests and ones of endocrine potential were performed for aqueous or solid phase extracts. Unfortunately, these studies constitute only a small fraction of overall packaging studies, and future trends must focus on combining versatile analytical and bioanalytical methods starting from extraction with model solutions of simulants (gases, liquids), performing proper treatment of packaging material to reflect its real life-cycle and conducting final instrumental and biological studies. It proves the necessity of utilizing other cell lines (e.g. liver, stomach, kidney, nervous) in holistic studies on impact of xenobiotics and their metabolites when absorbed from food. Unified holistic models should be elaborated to assist package producers to model behavior of different plausibly toxic substances migrating from packaging materials under varying storage and production conditions. In this way food products will be free of ingredients of scientifically proved toxic potential.

Table 5.

Even brief review of literature data indicates how many tasks must still be done to deliver "safer" packaging materials to customers and societies all over the world. The complementary rule and Green Chemistry tools should help researchers: design, synthesize, determine physicochemical properties, study acute and chronic impact on living organisms and entire ecosystems, continuously study and improve (if necessary) quality of product to reduce both environmental "fingerprinting" and impact on health status of biota from cradle to grave. Certainly, this goal cannot be achieved without asking specialist from different branches and origins (e.g. chemists, toxicologists, physiologists, biologists, chemometricians, material science specialists, etc.) into cooperation. This holistic approach is presented schematically in Fig. 3. Biological endpoints, including molecular level endpoints, as well as hormonal, cytotoxic and mutagenic bioassays, should be implemented in the detection steps of a migration stream from the FCM. Certainly, this goal cannot be accomplished without utilizing artificial body fluids as the extraction/simulation media prior to performing both instrumental and biological studies.

Fig. 3.

7. Conclusions

Packaging has played and will play a crucial role in the development of modern societies, independent of its historical role. Unfortunately, for decades, efforts were undertaken only to analyze rheological properties, and price was a major factor in the selection of proper material even when FCM were considered. It is a matter of approximately 20 years since more comprehensive studies on studying the migration ratio of xenobiotics from packaging materials have been undertaken. Following the sequential extraction methods (e.g., BCR or Tessier's) in this field of research, procedures are being developed to give an answer to the problem of assessing the magnitude of the xenobiotic leachable stream. Bioassays are relevant powerful tools to study hazard assessment of FCM extracts. Some bioassays are already standardized and validated. Application of SBFs with instrumental and biological methods are fortunately becoming routine screening methods,

enabling assessment of the package material impact on the quality of the product stored within. Such a holistic approach helps to overcome some problems such as troubles with identifying package contaminants, their degradation and transformation products, their combined impact on living organisms (synergy/antagonism), performing studies *in situ*, and confirming the quality of the FCM production process. The results of biological studies may aid in complying with the regulations on FCM, especially regarding NIAS, and may contribute to a more conscious choice of food products and to the use of preventive measures to minimize the level of threat posed by xenobiotics.

Based on data collected and presented it can be concluded that future trends in packaging materials development are, next to elaborating novel composite materials, establishing unified extraction procedures (for all packaging material candidates) that could be internationally checked and compared, using artificial body fluids of organisms of different trophic levels at the extraction stage at different abiotic conditions and, most importantly, utilizing both biological and instrumental methods at the evaluation of packaging material candidates.

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Figures captions:

Figure 1. Basic classification of the biopolymers

Figure 2. Analytical approaches used in packaging studies

Figure 3. Scheme presenting suggestions on extraction media and determination methods selection

Table 1

Table 1. Information on the intelligent packaging (IP) and the active packaging (AP)

Type of packaging	Purpose	Mediator used	Application	Ref.
Intelligent packaging	Time-temperature indicator	curcumin (Cur) into a tara gum (TG)/polyvinyl alcohol (PVA) film	Monitor shrimp spoilage	[13]
		chitosan-based films with anthocyanins from red cabbage	Monitor milk spoilage	[14]
		aqueous suspensions of triangular silver nanoplates	Monitor milk spoilage	[15]
		gelatine – template gold nanopraticles	Monitor frozen storage	[16]
	pH indicator	chitosan film containing anthocyanins	Monitor changes chemical composition in food	[17]
		Bauhinia blakeana Dunn dye immobilized in chitosan	Sensor for pork and fish freshness	[18]
Active packaging	Antimicrobial agent	wheat gluten/nanocellulose/titanium dioxide nanocomposites	Coated paper	[19]
		chitosan coatings onto polyethylene terephthalate	Polyethylene terephthalate (PET) film	[20]
		titanium oxide, zinc oxide, magnesium oxide, calcium oxide	Prolonged the shelf life of products	[21]
	Oxygen scavenger	nanoscale iron	Prolonged the shelf life of products	[22]
		powder iron oxide, ferrous carbonate and metallic platinum, ascorbic acid, glucose oxidase, ethanol oxidase, polyunsaturated fatty acid, sulphites	Packaging of dried food, beverages, pasta, meats, cheese	[23]
	Carbon dioxide scavenger	powder of calcium hydroxide, sodium carbonate, sodium glycinate, activated carbon, zeolite	Packaging of coffee, fresh meat and fish, nuts	[24]
	Antioxidant agent	α-tocopherol, quercetin, Vitamin E, Vitamin B12, tea phenol, L-ascorbic acid, L-tyrosin, rosmarine extracts	Packaging of meat, grain products	[25]
		butylated hydroxyanisole, butylated hydroxytoluene (BHT), propyl gallate	Packaging of meat products	[26]

Table 2

Table 2. Information of results of selected studies on xenobiotics identification methods in case of their extraction from packaging materials

Compound	Acronym	Application in FCM	Harmful effect	TDI [mg/kg of Body Weight]	SML [mg/kg]	Ref.
Bisphenol A	BPA	Monomer in the production of polycarbonate plastics and epoxy resins	- moderate estrogenic activity - disrupt thyroid hormone action -proliferation of human prostate cancer cells and block of testosterone synthesis - genotoxic and carcinogenic potency and effects on metabolism and oxidative stress	4 ug/kg	0.05	[49,50]
Bisphenol F	BPF	Substitute of BPA (especially for systems needing increased thickness and durability)	- moderate-to-slight acute toxicity - cytotoxity for HepG2 cells - estrogenic activity similar to BPA - cause of significant increase secretion of 17 β-estradiol in H295R cells	not regulated	not regulated	[42,45]
Bisphenol S	BPS	Substitute of BPA	- low acute toxicity to *Daphnia magna* - estrogenic activity higher than BPA - suspected to indicate of obesity and steatosis - suspected to alter brain function in mammals	not regulated	not regulated	[54]
Bisphenol A diglycidyl ether	BADGE	Substrate to produce epoxy resins	- moderate-to-slight acute toxicity - causes gene mutation in bacterial and mammalian cell -estrogenic activity and androgen antagonist activity - suspected to carcinogenic effects - can induce adipogenic differentiation in both stromal stem cells and preadipocytes at low nano-molar concentrations.	15	9 (for the sum of BADGE and their hydrolyzed derivatives) 1 (for BADGE and their chydroxyxhlorinated derivative)	[55–57]
Bisphenol F diglycidyl ether	BFDGE	additives for organosol coatings of metal cans	- cytotoxicity for HepG2 cells - mutagenic effects in bacterial strains	1	completely banned since 1st January 2005	[51,58,59]
Bis(2-ethylhexyl) adipate	DEHA	Used to produce polyvinyl chloride (PVC)	- classified as a possible human carcinogen - moderate acute toxicity in mammals - reproductive and development toxicity	0.3	1.5	[50,60]
Di-butylphthalate	DBP	Additive, plasticizer in repeated use materials/articles for non-fatty foods	- low to moderate acute toxicity in mammals - reproductive and development toxicity - inhibits testosterone synthesis - induces apoptosis and neurotoxicity	0.01	0.3	[50,61,62]
Benzyl-butylphthalate	BBP	Additive, plasticizer in repeated use materials/articles for non-fatty foods	-low acute toxicity, -classified as a possible human carcinogen - can adversely affect development, - causes reduced sperm counts,	0.5	30	[43][63]

			- weakly bound to estrogen receptors,			
Di-ethylhexylphthalate	DEHP	Additive, plasticizer in repeated use materials/articles for non-fatty foods	- low acute toxicity, - classified as a carcinogenic, - interfere with the endocrine function (decreased testosterone output), - toxic to reproduction	0.05	1.5	[50,61,64]
Di-isononylphthalate	DiNP	Additive, plasticizer in repeated use materials/articles for non-fatty foods	- carcinogenic to the rodent - reproductive and development toxicity - and androgen antagonist activity	0.15	9	[65,66]
Di-isododecylphthalate	DiDP	Additive, plasticizer in repeated use materials/articles for non-fatty foods	- reproductive and development toxicity, - androgen antagonist activity,	0.15	9	[65,66]
Perfluorooctanesulfonic acid	PFOS	Used in the production of cookware, as a paper coatings, Used in dyes production	- moderate acute toxicity, - causes neurotoxicity and behavior defects, - carcinogenic, -reproductive and development toxicity,	0.00015	not regulated	[64,65]
Perfluorooctanoic acid	PFOA		- moderate acute toxicity, - causes neurotoxicity and behavior defects, - carcinogenic, - reproductive and development toxicity,	0.0015	not regulated	[67,69]
Benzidine		Used in production of kitchen utensils, plastic laminates	- classification of carcinogenicity, - cytogenetic effect,	0.003	0.01 (for sum of PAAs)	[65]
Aniline			- high acute toxicity, - classification of carcinogenicity reproductive and development toxicity	0.007		[65]
Toluidine		Used in production of kitchen utensils, plastic laminates	- low to moderate acute toxicity, - characterization as a potential cancerogenic			[70]
Chromium	Cr	Component of alloys, cans, used in dyes	- suspected to indicate lung cancer, - respiratory effects, - allergic dermatitis	0.3	0.25	[71]
Cadmium	Cd	Used as a pigment and stabilizers in plastic materials, pigments in enamels	- causes kidney damage, - suspected to indicate lung cancer, - bone disorders	0.0025 (weekly intake)	0.005	[71]
Lead	Pb	Used in printing inks and pigment in ceramic glazes	- causes neurological and reproductive disorders - causes damage of hepatopoietic system	0.025 (weekly intake)	0.01	[71,72]
Cobalt	Co	Used as a colorant in enamels and ceramics	- causes problems with heart	0.0014	0.02	[71]

Tin	Sn	Used in a steel cans, antioxidant	organic compounds – cause neurological effects	14 (weekly intake)	100	[71]
Nonylphenol	NP	Additive degradation product	- high acute toxicity, - shows estrogenic activity, - facilitator of human breast cancer, - reproductive and development toxicity	0.5	not regulated	[65]
4-tert-octylphenol	OP		- low acute toxicity, - shows estrogenic activity, - reproductive and development toxicity	not regulated	not regulated	[73]

TDI – Tolerable Daily Intake [mg/kg of Body Weight], SML – Specific Migration Limit [mg/kg]

Table 3

Table 3. Selected information on procedures and techniques used in analysis of FCM contaminants

Sample	Analytes	Sample Size	Sample Preparation	Final Determination	Recovery [%]	LOD	LOQ	Ref.
Food contact materials								
Recycled paper and paperboard packaging	BPA, DEHP, NMP, NDP	1 g	1) cutting into small pieces, 2) Soxhlet extraction (in acetone–hexane, 6 h), 3) adding anhydrous sodium sulfate, evaporation until nearly dry and recovery with 10 mL of hexane 4) centrifugation	GC/MS Column: Supelco SLB-5ms type (5% polysilarylene–95% polydimethylsiloxane; 30 m x 0.25 mm i.d. x 0.25 µm film thickness).	101-108	0.017-0.033 mg/L	0.005-0.1 mg/L	[7]
Recycled paper packaging	BPA, BPF, BADGE, BFDGE	0.5 g	1) homogenization 2) FULSE extraction adding 20 mL of methanol and stored in ice–water bath 3) ultrasonic irradiation 4) centrifugation 5) evaporation of liquid extract to 1 mL and dilution to 5 mL with methanol 6) filtration with Teflon filter	UPLC–Q-TOF with ESI Column: BEH C18 column (1.7 µm x 50 x 2.1 mm)	72-97	0.16-0.65 µg/g		[78]
Films for food packaging and bags for food freezing	phthalates	1 g	1) Soxhlet extraction (ethyl acetate, high temperature, 3 h 20 min)	GC-FID, Column: Supelco MDN-5 (95% dimethyl-5% diphenyl silicone), 30 m, 0.25 mm I.D.	95±10	13.88-14.,41 mg/L	0.07-0.71 mg/L	[75]
Cardboard, Tetra brick, Plastic	phthalates	1 cm^2	1) cutting into small pieces, 2) extraction with 40 mL of hexane in ultrasonic bath 3) solvent exchange to 20 mL of dichloromethane 4) evaporation to 1 mL under nitrogen stream	GC/MS with ESI Column: DB-XLB (60 m x 0.25 mm x 0.25 µm film thickness with a non-polar stationary phase)	82-99		0.1-1.5 ng/cm^2	[66]
Packaging made of paper and/or aluminum	PFBA, PFDA, PFOS and related compounds	2 g	1) cutting into small pieces, 2) PLE (80 °C, pressure 1500 psi) 3) SPE (glass column containing 1.5 mg of florisil, 1 g of basic alumina, 1	LC-MS/MS with ESI Column: Hypersil GOLD C8 (150 mmx 2.1 mm i.d, 3 µm)	60-90	0.20-0.94 ng/g	0.54-2.83 ng/g	[107]

			g of anhydrous Na_2SO_4), conditioning: 5 mL of MeOH + 5 mL of petroleum ether, washing: 10 mL of petroleum ether, 8 mL of petroleum ether:MeOH 90:10; elution: 8 mL of MeOH 4) evaporation to dryness 5) reconstitution in mobile phase					
Packaging made of paper and plastic	PFSAs, PFPAs, PFOSA, PAPs, FTCAs, FTUCAs	0.5 g	1) cutting into small pieces 2) UPAE (sample + 7 mL of MeOH (1% HOAc), 0 °C in an ice-water bath. 3) filtration (polyamide filter) 4) evaporation to dryness 5) reconstitution in MeOH 6) filtration (polypropylene filter)	LC-QqQ-MS/MS with ESI and APCI Column: ACEUltra Core 2.5 Super C18 (2.1 mm x 50 mm, 2.5 µm)	66-117	0.001-0.7 ng/mL	0.005-2.3 ng/mL	[77]
Multilayer films PET, oriented polyamide (OPA), cast PP (CPP), PE and PE/ethyl vinyl alcohol PE(EVOH)	benzidine, 4,4-diaminodiphenylethe, *o*-anisidine, and related compounds	80 mL	1) thermally sealed bags filled with 3% acetic acid solution 2) SPE (tubes with cation exchanger) 3) elution: 2 mL of 5% solution of NH_3 in methanol (w/v) (80:20 v/v).	UHPLC–MS/MS with ESI Column: Acquity UPLC BEH C18(2.1 × 100 mm and 1.7 µm)		0.002-0.013 ng/g	0.007-0.042 ng/g	[86]
Different types of Honey containers	BPA and analogous	10 mL of food simulant	1) dilution to 50 mL of purified water 2) SPE extraction (Oasis HLB sorbent) 3) conditioning: mL of EtAc, 3 mL of ACN, 15 mL of MeOH elution: 0.5 mL of ACN and 3 mL of EtAc 3 mL 4) evaporation remaining solvent 5) derivatization	GC/MS Column: DB-5 MS (30 m × 0.25 mm × 0.25 µm)	19.5-98.6	0.0101-0.0907 ng/mL	0.0346-0.191 ng/mL	[108]
Paper and plastic containers	BPA, BPAF, BPAP	2 g	1) cutting into small pieces 2) shaking with ethanol (24 h) 3) evaporation to 0.5-1 mL and	HPLC-DAD Column: XDB-C18 (150 mm x 4.6 mm x 5 µm)	97.8-103.1	0.5-1.5 ng/mL	1.65-4.85 ng/mL	[79]

			dissolved to 10 mL with water 4) filtration 5) IL-DLLME extraction addition of 200 µL [C8MIM][PF6]) to sample and sonification separation by centrifugation, removing upper phase and dissolved ionic liquid phase in methanol					
Multilayer packaging materials	toluene, hexanal, styrene, naphthalene and related compounds	1 g	1) cutting into small pieces 2) placing in Petri dishes and covering with Tenax® 3) extraction with 3.4 mL of acetone 4) evaporation to 200 µL under nitrogen stream	GC–O–MS Column: BP-20 (30 m x 0.25 mm x 0.25 µm)		0.01-25.7 µg/dm^2	0.02-85.6 µg/dm^2	[109]
Bread bags, fast food boxes, milk bags	phthalates	2 g	1) cutting into small pieces, 2) adding 50 mL *n*-hexane and sonification, 3) evaporation to dryness and dissolving in 5 mL methanol	EKC-UV with Polymeric pseudo-stationary phase P(SMA-co-MAA) Column: Uncoated fused silica capillary with 50 x 65 cm x 50 µm	81-118	0.8-2.6 mg/L		[110]
Active food packaging containing essensial oils	terpens, alkanes, plastic additives, etc	3 cm x 4 cm ractangles	1)cutting into small pieces, 2)immersed in 20 ml of stimulant liquids 3)stored in thermostatic oven 4)HFLPME 5)extractionwith 50 µl of toluen	GC-FID Column: SLB-5ms (30m×0.25mm, 0.25 µm)		<0,01 µg/kg	0,02-0,04 µg/kg	[89]
Plastic packaging	Cd	0.5 g	1) cutting into small pieces 2) adding 5 mL of sulfuric acid, 5 mL of nitric acid and 5 mL of perchloric acid (heated 1 h) 3) diluting with water 4) adding 0.15 mL of 10^{-3} mol/L 5-Br-PADAP solution, 0.4 mL of 5% (w/v) Triton X-100, 0.4 mL of 2 mol buffer solution and 0.7 g of [C4 mim][PF6]	FAAS	98-102	6 ng/g		[111]
Ceramic	Al, B, Ba, Cd, Co, Cr,		1) Filling with the stimulants and	ICP-OES				[98]

packaging	Cu, Fe, Mn, Ni, Pb, Sb, Sn, Sr, Ti, V, Zn, Zr		heated 2) sampling after 30, 60, 90, 120 and 180 min.					
Active packaging	Nano-silver particles	50 mL food stimulant	1) filling containers with two simulants: ethanol (EtOH) 50% v/v and acetic acid (HAc) 3% v/v 2) sonication for 5 min of migration solutions	ICP-MS				[112]
Food samples								
Canned energy drinks	BPA, BPB, BPF, BADGE, BFDGE	5 mL	1) degasification in ultrasonic bath 2) adding 1 mL of 0.2 M aqueous ammonium acetate, adjust pH to approximately 4.0 3) SPE (with molecularly imprinted polymer sorbent) Conditioning: 3 mL of 2% acetic acid solution in methanol, 3 mL of acetonitrile and 3 mL of MilliQ water Washing: 9 mL of MilliQ water, 6 mL of MilliQ water/acetonitrile 60/40 v/v Elution: 3 mL of methanol and 3 mL of acetonitrile 4) evaporation to dryness 5) reconstitution in MeOH	UPLC- FD Column: Acsentis Express (RP-Amide, 75 x 4.6 mm, 2,7 µm)	78-94	0.15 ng/mL	0.5 ng/mL	[49]
Sugar, Salt	BPA, DEHP, NMP, NDP	10 g	1) shaking with methanol (30 min) 2) filtration through a paper filter and 1 g of anhydrous sodium sulfate 3) evaporation until nearly dry and recovered with 10 mL of methanol 4) centrifugation	GC/MS Column: Supelco SLB-5ms type (5% polysilarylene-95% polydimethylsiloxane; 30 m x 0.25 mm i.d. x 0.25 µm film thickness).	91-106 79-106	0.015-0.033 mg/L	0.05-0.1 mg/L	[7]
Meat and fish products	Phthalates	10 g	1) homogenization 2) shaking with acetone/*n*-hexane (1:1)	GC/MS with ESI Column: DB-XLB (60 m x 0.25 mm x 0.25 µm film thickness	93-100	5-145 µg/kg		[66]

			3) dissolving fat residue in 2 mL of dichloromethane 4) cleaning-up by gel permeation chromatography 5) evaporation to 1 mL under nitrogen stream	with a non-polar stationary phase)				
Canned food (bean, corn, peas, tomato paste, tuna)	BPA	1 g	1) homogenization 2) adding 1 mL of acetonitrile and shaking 3) filtration of supernatant through a glass microfiber filter 4) cleaning-up with immunoaffinity column, washing: 5 mL of acetonitrile/water (10:90, v/v) Eluting: 4 mL of acetonitrile/water (40:60, v/v).	HPLC-DAD Column: Inertsil ODS (4.6x 250 mm, 3.5 µm)				[82]
Canned seafood (sardines, squid, octopi, mussels, anchovies)	BPA, BPB	10 g	1) homogenization 2) QuECHERS extraction Added 5 mL of *n*-heptane and 10 mL of deionized water and centrifugation Removal of supernatant added 10 mL of MeCN, 4 g of anhydrous $MgSO_4$ and 1 g of NaCl and centrifugation Added MeCN extract to 1.2 g of $MgSO_4$, 120 mg of C18 and 50 mg of GCB, centrifugation 3) DLLME procedure Adding 1 mL of the MeCN to 5% K_2CO_3 solution and 50 µL of T4CE and 125 µL of acetic anhydride and centrifugation	GC/MS Column DB-5MS (30 m × 0.25 mm I.D. × 0.25 µm)	71-107	0.2 µg/kg 0.4 µg/kg	1 µg/kg	[81]
Honey	BPA and analogues	10 g	1) homogenization 2) dilution in 100 mL of purified water and filtered through glass-	GC/MS Column: DB-5 MS (30 m × 0.25 mm × 0.25 µm)	24.6-99	0.00338-0.147 ng/g	0.00199-0.489 ng/g	[108]

			microfiber filters 3) SPE extraction (Oasis HLB sorbent) conditioning: mL of EtAc, 3 mL of ACN, 15 mL of MeOH washing with 6 mL of 20% MeOH elution: 0.5 mL of ACN and 3 mL of EtAc 4) evaporation of remaining solvent 5) derivatization					
Canned vegetables and beverages	BPA, BPF, BPZ	2 mL	1) degassing 2) dilution to 10 mL with water 3) derivatization 4) SBSE extraction (PDMS) 5) thermal desorption	GC/MS Column: HP-5MS (5% diphenyl–95% dimethylpolysiloxane, (30 m × 0.25 mm I.D., 0.25 µm)	86-122	0.9-2.5 ng/L	3.1-8.4 ng/L	[100]
Canned tomato paste and corn	BPA, BPF	10 g	1) homogenization 2) extraction with 15 mL ACN:water (90:10 v/v) 3) preconcentration: HS-SPME (SWCNT) 4) derivatization	GC/MS with ESI Column: HP-5MS (30 M x 0,25 mm, 0,25 µm)	79-86	0.1 ng/g	0.3 ng/g	[84]
Meat roasted in plastic bags	phthalates	13 g	1) cutting into small pieces and added 80 mL of water 2) CF-SPME extraction (85 µm polyacrylate fiber)	GC/MS Column: HP-5MS (30 m x 0.25 mm x 0.25 µm)		0.01-0.18 µg/kg	0.07-0.26 µg/kg	[80]
Chicken soup	DBP, DEHP		1) filtration with paper filter 2) extraction with magnetic MWCNTs-PVA cryogel-l-SPE sorbent 3) magnetic separation 4) evaporated until dryness and dissolved with ethyl acetate	GC-FID Column: B-5 fused silica capillary column (30 m x 0.25 mm I.D. x 0.25 µm)	70 ± 9 – 118 ± 10	36.4 ± 0.5 ng/mL 26.3 ± 0.3 ng/mL	121 ± 2 ng/mL 88 ± 1 ng/mL	[113]
Canned fish (sardines, mackerels, tuna)	BADGE and related compounds	2 g	1) extraction with 20 mL of 1:1 v/v acetonitrile:*n*-hexane solution 2) stirring and centrifugation, 3) solvent evaporation to 1 ml 4) reconstitution in ammonium formate (0,01 M)	LC-MS/MS with ESI Column: Synergy MAX-RP (100 x 2.0 mm x 2.5 µm)	89.9 - 109.5	0.5-3.1 µg/kg	1.8-10.3 µg/kg	[74]

Corn and popcorn	PFAAs	1.5 g	1) removal of salt and sugar from corn 2) grounding and sieving 3) FUSLE extraction 4) evaporation to dryness under nitrogen stream 5) reconstitution with 1 mL of MeOH and filtration through nylon filter	UHPLC-MS/MS Column: Acquity BEH C18 50 mm × 2.1 mm x 1.7 µm	90-106	0.2-0.5 ng/g	0.6-2 ng/g	[91]
Canned food (orange juice, mango pulp, baked beans in tomato sauce, sweet corn)	Al, Fe, Mn, Si, Sn	5 g	1) homogenization, 2) digestion with 10 mL of concentrated nitric acid and 2 mL of concentrated H_2O_2, using microwave digestion system 3) dilution with water	ICP-AES	>95%			[114]

APCI - atmospheric pressure chemical ionization; DEHP - bis (2-ethylhexyl) phthalate; EKC- electrokinetic chromatography, ESI - electrospray Ionization; FAAS- flame atomic absorption spectrometry; FD - fluorescence detector; FID - flame ionization detector; GC - gas chromatography; GC–O–MS - gas chromatography–olfactometry and mass spectrometry; ICP-OES - Inductively Coupled Plasma Optical Emission Spectrometry; ICP-MS - Inductively Coupled Plasma–Mass Spectrometry; ICP-AES - inductively coupled plasma-atomic emission spectrophotometry; LC-QqQ-MS/MS - liquid-chromatography-triple quadrupole-tandem mass spectrometry, NMP - nonylphenol monoethoxylate, NDP - nonylphenol di-ethoxylate

Table 4

Table 4. Selected information on extraction studies conducted with utilization of artificial body fluids

Type of Simulant	Simulant Composition	Type of Research and Methods Used	Research Objects	Conditions of Performing Process	Results of Studies	Ref.
Artificial sweat	According to ISO 105-E04: 1994	Studies on extensive kinetic migration with 5 simulation media at 3 temperatures (20 °C, 40 °C, 60 °C). Studies on polymeric material: toys – artificial saliva, skin contact materials – artificial sweat, FCM – water for water products, fatty food - Miglyol 840, dry food – Tenax®.	Eleven methacrylate material samples as FCM	Immersing samples in extraction media – typical volume/surface ratios were: 100 or 150 mL in 1 dm^2 or, in case of Tenax®, 4 g. Study at 3 different temperatures for 10 days. Glass vials with polytetrafluoroethylene septum were used.	Cutting samples to 0.5-g parts and dissolving in 5 mL of toluene. Analyses with GC/FID. Aluminum parts were cut into 1 cm × 6,5 cm strips. Analyses with GC/FID were performed for headspace. Acrylic materials used to produce rigid polymers show small diffusion degree, while polymer resins show slightly higher diffusion rates.	[121]
Artificial saliva	According to §35 LMBG (*Amtliche Sammlung von Untersuchungs-verfahren* § 35 LMBG - Germany) used to study toy quality					
Artificial sweat	According to DIN53 160 UE: 4.5 g NaCl, 0.3 g KCl, 0,3 g Na_2SO_4, 0,4 g NH_4Cl, 3 g of milk acid (90%), 0.2 g urea in 1 dm^3 H_20.	Studies on migration of toxic compounds (especially styrene) from toys made of ABS with application of SBF.	Eighteen commercially available toys were selected for this study.	The smooth side of toy was cut into pieces of 12 mm diameter and 1,3 mm thickness with mass = 0.167 ± 0.026. Wires with samples were immersed in calorimetric vial with artificial saliva or sweat (20 mL), and vortexed 100 rpm in a water bath at 37 °C for 10 min-120 h. Styrene was extracted with 3 mL of *n*-hexane.	Samples were analyzed with GC/MS and EI. Styrene was used to elaborate a new methodology for studying the migration of toxic substances. Fick's law was used to calculate diffusion and partition coefficients. Mathematical models were also evaluated.	[122]
Artificial saliva	According to DIN53 160 UE: 4.2 g $NaHCO_3$, 0,5 g NaCl, 0.2 g K_2CO_3 in 1 dm^3 H_20.					
Artificial saliva	4.2 g $NaHCO_3$, 0.5 g NaCl, 0.2 g K_2CO_3 (0.2 g) in 1 dm^3 H_20. pH = 8.9±0.1.	*In vitro* studies on hydrolysis of poly(1,2-propylene) adipinate with SBF to assess safety of plasticizers.	Reactivity of PPA-Ac2 and PPA was studied with special attention paid to hydrolysis products. Reaction mixtures were separated based on their acidity and polarity and subsequently analyzed.	Hydrolyses monitored with HP-SEC and NMR. Stomach hydrolysis: plasticizer (5 mg in 500 µL of 10 mg/ml acetonitrile) was added to 250 mL in a round bottom flask, and solvent was removed by vapor. Then, model liquid was added (100 mL) with sample and mixed at 37±0,5 °C for 4 h. Dichloromethane (20 mL) was added. Aqueous phase was separated, and again, 20 mL of dichloromethane was added. Organic phase was dried with $MgS0_4$. Residues were dissolved in $CDCl_3$ (0,4 mL) to perform NMR or in 100 mL of dichloromethane-cyclohexane 1:1, v/v,	High degree of hydrolysis was obtained with freshly prepared GI liquid. Size exclusion liquid chromatography confirmed total removal of plasticizer and short oligomers were created in 4 h. GC enabled confirmation that no conversion of free monomers occurred, while NMR showed that selective decomposition of primary ester bonds occurs. PNMR was used to assess total molecular weight of plasticizers and mean mass of hydrolysis products. In stomach fluid and saliva, the extract hydrolysis rate was <2%.	[123]
Stomach fluid	0,07 M HCl with pH 1,2±0,1					
GI	Containing pancreatin. 6.8 g KH_2PO_4 / 1 L of H_2O. Adding 0.2 M NaOH (190 mL), 0,5 g sodium taurocholate and 400 mL of H_20. pH 7.5±0.1 with NaOH (0.2 M)					

Table 4. Selected information on extraction studies conducted with utilization of artificial body fluids

Type of Simulant	Simulant Composition	Type of Research and Methods Used	Research Objects	Conditions of Performing Process	Results of Studies	Ref.
				to perform HP-SEC. GI extracts were also analyzed with GC.		
Stomach juice	2 g NaCl, 7 mL 37% HCl, 3.2 g pepsin/1 L H_2O pH=1.12	Study on emission from prototype composite polymer. Release of Cd was assessed as a result of extraction with a series of media and fluorescence decrease as marker of chemical CdSe/ZnS nanoparticles.	Two optical glass plates (borosilicate) with QD built in. QD were approximately 50/50 wt% CdSe/ZnS structures with cores of ~5 nm diameter. CdSe/ZnS QDs suspended in toluene were used as references. Eight environmental or body fluids were used.	Morphology was studied with AFM – samples were exposed to simulation media for 2 years then washed with deionized water. Selected samples were analyzed with UV-VIS and fluorescence in relation to native CdSe/ZnS QDs. QDs were mixed with MHRW and SHA at 0.5-1000 mg/L concentrations. After centrifuging at 60 rpm for 10 days, UV spectra were taken and fluorescence was measured at 490 nm excitation and 606 nm emission.	Cd release after 30 d exposure was assessed to reach 0.007 to 1.2 mg/g of polymer while these upper values are valid for model liquids of low pH (nitric acid or stomach juice). Ultrafiltration and ICP-MS were used to distinguish dissolved cadmium from solid particles. Lack of free nanoparticles confirmed that nanoproduct specificity is not impacted by leaching but dissolved cadmium can be present as in the case of conventional products.	[124]
Artificial sweat	0.9% NaCl in water	PFOA studies in textile samples due to contact with water, methanol and model fluids (artificial saliva, artificial sweat) with LC-MS/MS	Extraction for 2 h: 2 g of sample cut into pieces $1^n \times 1^n$ and placed in 50 mL vials. 25 mL of extraction medium were added, and the vials were closed and shaken. Extraction for 1 h at room temperature, and then for next 1 h of orbital rotation. Extracts were decanted.	Extracts prepared in 3 replicates and transferred to centrifuge (1.7 mL vials with internal standard ^{13}C-PFOA as 1,5 ng/mL). Shaking, 400 mL was transferred to clean vial and 1200 µL of acetonitrile were added. Samples were centrifuged for 20 min at 14 000 RCF and 25 °C. samples were evaporated to 300 µL and 1.25 mL ultrapure water was added. Analyses were done with LC/MS/MS.	Proper analytical methods were evaluated to quantitatively determine PFOA in every type of extractor used. Recovery for various samples and solvents reached 100±15% with application of isotope marked C-PFOA to correct for the matrix impact. PFOA content in different textiles is similar in cases of extraction with all media studied. Hand and pressurized fluid extraction at 2, 24 and 1.5 h times proved that extraction is the most efficient at 24 h of process run.	[125]
Artificial saliva	0.82 mM $MgCl_2$, 1 mM $CaCl_2$, 3.3 mM K_2HPO_4, 3.8 Mm K_2CO_3, 5.6 mM NaCl, 10 mM KCl, 1.6 g mucine/1 L H_2O; pH=6.8			Extracts prepared in 3 replicates and transferred to 1.7 mL centrifuge vials with internal standard ^{13}C-PFOA as 1,5 ng/mL. Shaking, 400 mL was transferred to clean vial and 1200 µL of acetonitrile were added. Samples were centrifuged for 20 min at 14 000 RCF and 25° C. samples were evaporated to 300 µL, and 1.25 mL of ultrapure water was added. Analyses were done with HPLC.		

Table 5

Table 5. Basic information on possible use of biological methods in studies on toxicity of packaging materials

Sample Type	Sample Treatment	Parameter Studied	Biological Detection Technique	Effect Observed	Ref.
carton and polypropylene packaging (PET, PE, PP, PS)	1) migration into food stimulants (10 days at 60^{o}C) 2) SPE (Oasis HLB columns)	estrogen and androgen activity	YES/YAS CALUX	- Estrogenic activity was detected in some samples (highest effect observed for paper/aluminum/PE composite film for fatty products sample YES EEQ = 59.6±29.3 ng/L). - In the yeast estrogen screen, antagonistic effects were noted for foil and carton for milk product extract. - None of the samples showed androgenic activity in either YAS or AR CALUX.	[126]
recycled and virgin paper kitchen rolls	1) extraction with ethanol 2) evaporation	estrogen activity	YES	- Estrogenic response was observed mainly for recycled paper extracts.	[127]
bottles (PET and glass)	1) migration into food stimulants (10 days at 40^{o}C or at 60^{o}C)	estrogen and androgen activity	Test with HELN, HG5LN cell line	- No hormone-like activities for samples were observed.	[128]
bottles (PET)	1) migration into water 2) SPE (C18-HD)	estrogen activity	E-Screen (human cancer cell Line)	- Most of the investigated products induced significant estrogenic effects in a human cancer cell line with proliferative effects from 19.8 to 50.2% compared to 17b-estradiol (1.9–12.2 pg EEQ/L)	[129]
nanocomposite materials with polylactic acid (PLA) and two modified clays	1) migration into food stimulants (10 days at 40^{o}C) 2) evaporation	cytotoxicity and mutagenicity	assay based on human intestinal Caco-2 and human liver HepG2 cells were studied using the Ames test	- No cytotoxic and mutagenic effects were observed.	[130]
PP films	1) migration into Isopropanol/cyclohexane mixture (92.5/7.5 v/v) (140°C for 20 min) 2) ASE extraction 3) evaporation to dryness 4) reconstitution in ethyl acetate	cytotoxicity genotoxicity	Assay based on measuring the RNA synthesis Inhibition (hepatoma cell line HepG2) Comet assay (line HepG2)	- No extracts were found to be genotoxic. - Non-cytotoxicity for polypropylene without additives samples was observed. - Strong cytotoxicity effect for samples with Irgafos 168 as an additive was noted.	[131]
paper and paperboard	1) extraction with methanol 2) filtration	genotoxicity	Rec-assay, comet assay	- DNA-damaging activity was observed mainly in recycled paper products.	[132]

packaging	3) extraction with dichloromethane 4) evaporated to dryness and reconstitution			- Weak genotoxic and cytotoxic effect was observed.	
plastic packaging	1) migration into food stimulants (10 days at 60^{o}C) 2) SPE (Oasis HLB columns) 3) evaporation	estrogen activity	YES	- The highest percentage of estrogen-positive samples was found in composite film extracts. - The highest estrogen activity determined for paper/aluminum/PE composite film for fatty products YES (EEQ = 59.6±29.3 ng/L). - None of the PP samples showed estrogenic activity.	[133]
paper and paperboard packaging	1) extraction with water and ethanol 2) filtration 3) evaporation	cytotoxicity and genotoxicity	Tests with human larynx carcinoma cell line (HEp-2) and metabolically competent mouse hepatoma cell line (Hepa–1c1c7) RNA-synthesis inhibition test with HepG2 cells Ames test Comet assay	- Samples showed marginal toxicity. - Some toxic responses, mainly in the RNA-synthesis inhibition assay measuring sublethal effects was observed. - Cytotoxicity in HEp-2 cells was observed for water extracts.	[134]
metal cans	1) migration into food stimulants (room temperature, 65^{o}C, 12^{o}C)	acute toxicity	Microtox ® (*Vibrio fischeri*)	- Extract samples where acetic acid was used as a stimulant showed highest toxicity. - Toxic effect was observed in most of the samples and increases in time and temperature during extraction.	[135]
bottles (PET and glass)	1) migration into food stimulants (10 days at 40^{o}C) 2) SPE (Sep-Pak Plus tC_{18} columns) 3) dissolved in DMSO	acute toxicity, genotoxicity	Microtox ® (*Vibrio fischeri*), Comet assay (human leukocyte cell line)	- No reduction of the bioluminescence of *V. fischeri* was observed. - DNA damage was observed in majority of samples studied. - Higher DNA damage in samples made of PET than glass was observed.	[136]

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Figure 1

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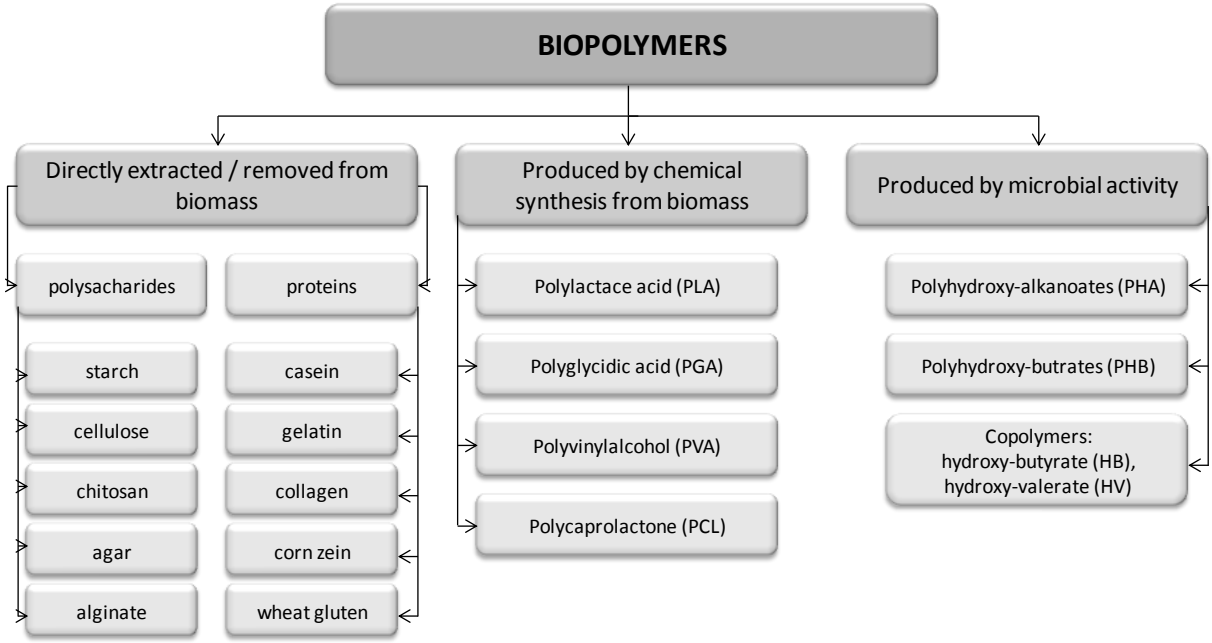

Fig. 1. Basic classification of the biopolymers

Figure 2
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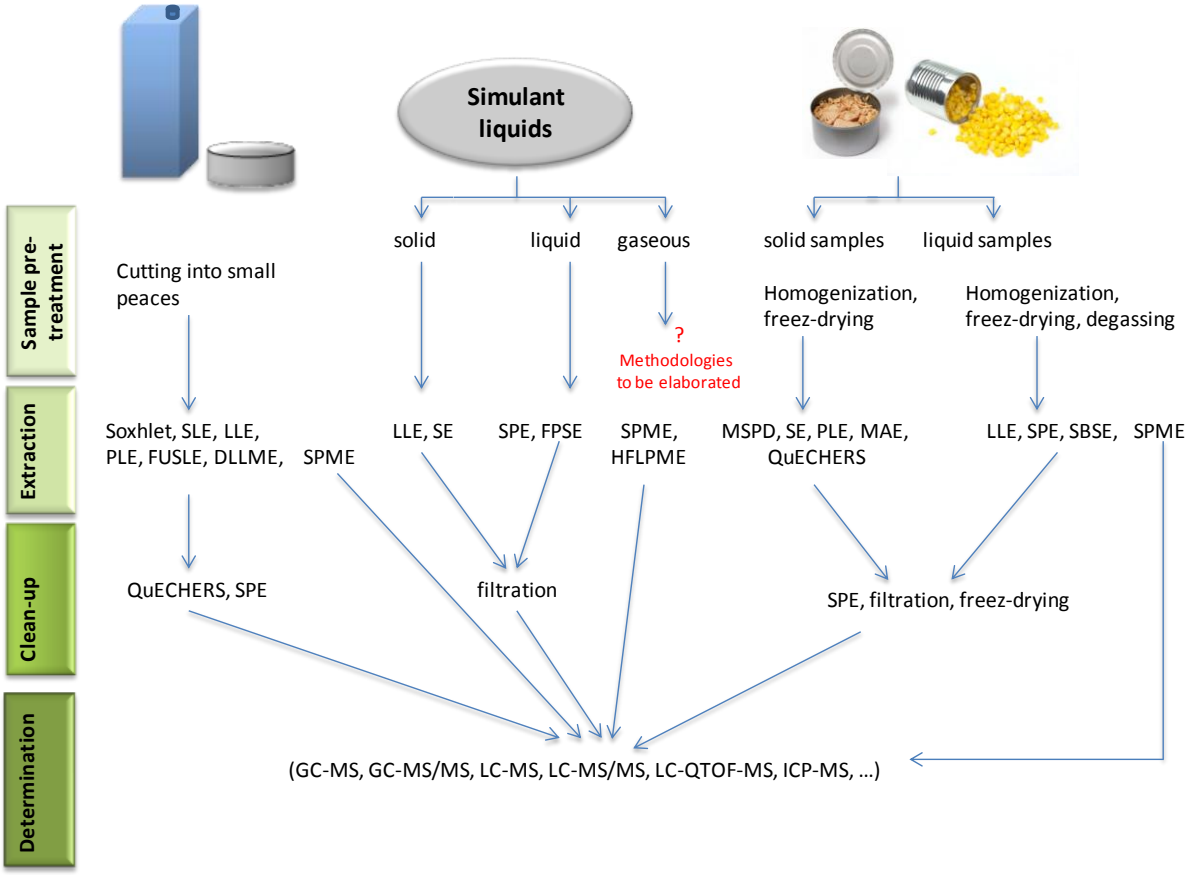

Figure 2. Analytical approaches used in packaging studies

Figure 3
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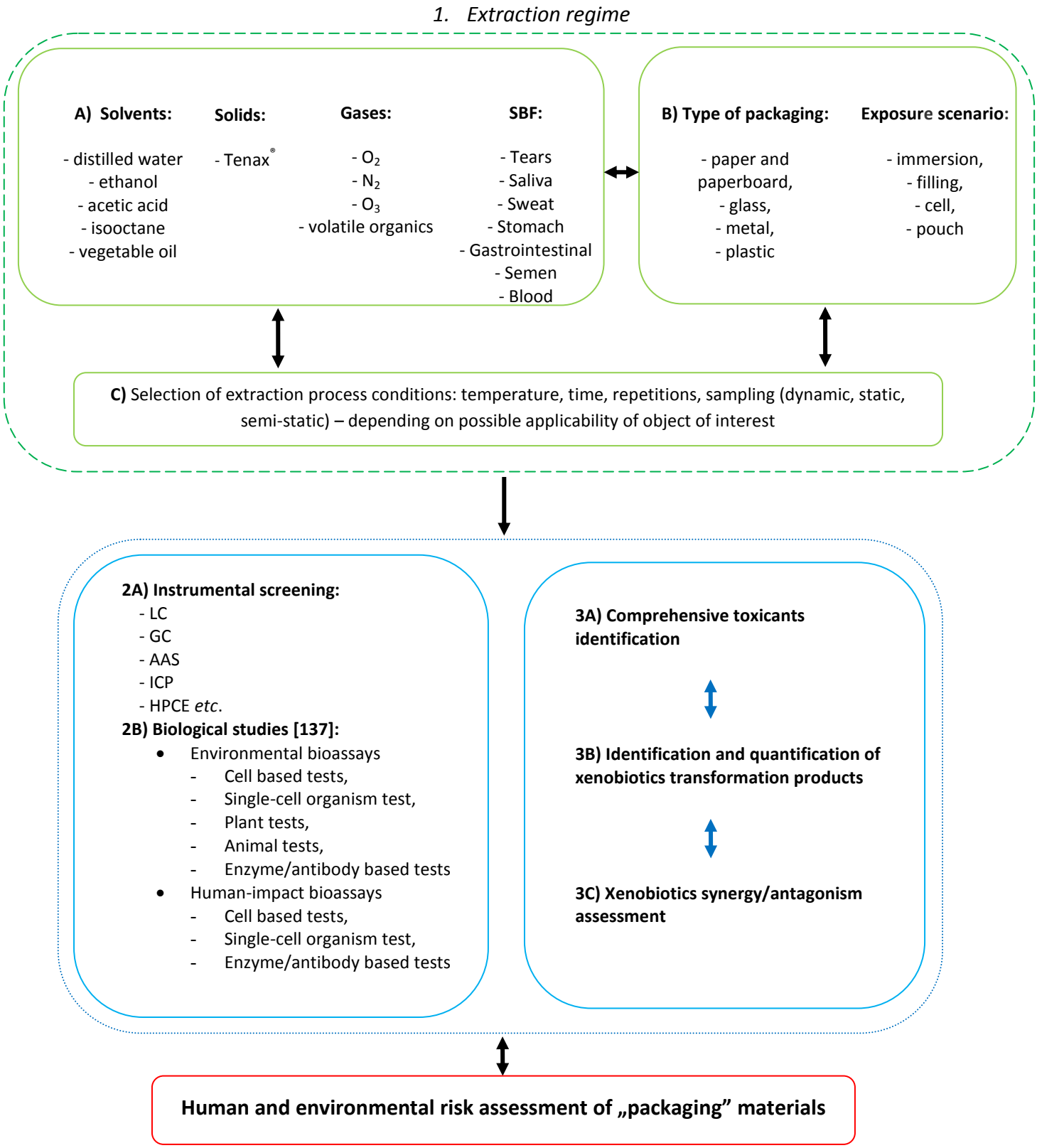

Fig. 3. Scheme presenting suggestions on extraction media and determination methods selection