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Review of potential areas for global harmonization of risk assessment protocols for Food Contact Materials (FCMs)

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A B S T R A C T

Food Contact Materials (FCMs) are produced and marketed worldwide global value in excess of 400.20 billion dollars. All FCMs have to be safe and guarantee the safety and security of food in contact with them. Specific regulations, which establish the rules for all materials, exist in different regions, which implies that the same material has to comply with different limits depending on the region in which it is distributed and marketed. This paper reviews differences and similarities between the FDA, EU, MERCOSUR, India, China, Japan and Thailand. Various areas essential for a risk assessment are compared. Requirements for testing substances or materials is an area where there are divergencies or commonalities. Harmonization of regulations and procedures is needed, as humans are the same, independently of where they live, and the substances released by the FCMs are the same. The same protocols and procedures are not applied worldwide, but the results are essential for the risk assessment of FCMs. Examining the approaches of different regions showed that there is room for harmonization in many areas, to obtain a more harmonized risk assessment and facilitate subsequent risk management. This review establishes the main areas of risk assessment of FCMs, compares the main regulations in different regions and discusses the essential areas that influence their global risk assessment and provides a guide to help to the development of the relevant research field and industry. Some examples and proposals for the main areas for harmonising risk assessment globally, are given.

Glossary

Abbreviation	Full name
ANVISA	National Agency of Sanitary Surveillance of Ministry of Health – Brazil - The Brazilian Health Regulatory Agency
ASEAN	Association of Southeast Asian Nations
BW	Body Weight

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Abbreviation	Full name
BfR	German Federal Institute for Risk Assessment
CDC	Cumulative Dietary Concentration
CEDI	Cumulative Exposure
CEFIC-FCA	European Chemical Industry Council - Food Contact Additives Sector Group
CF	Consumption Factor
CFR	Code of Federal Regulations
CFSA	China National Centre for Food Safety Risk Assessment
CoE	Council of Europe
CONAL	Comisión Nacional de Alimentos - Argentina
DC	Dietary Concentration
DF	Food Distribution Factors - Japan
DGSante	Directorate General for Health
DNA	Deoxyribonucleic acid
DSS	Department of Science Service – Thailand
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
FACET	Flavours, Additives, Contaminants Exposure Task
FBO	Food Business Operator – India
FCAs	Food Contact Articles
FCM	Food Contact Material
FCMs	Food Contact Materials
FCN	Food Contact Notification
FCS	Food Contact Substance
FD&C Act	Federal Food, Drug, and Cosmetic Act - USA
FDA	Food and Drug Administration
FSCJ	The Food Safety Commission of Japan
FSSAI	Food Safety and Standards Authority of India
f_T	Food-type Distribution Factors
GB standards	Guobiao Standards – China
GHP	Good Hygiene Practices
GC-MS	Gas Chromatography - Mass Spectroscopy
GMC	MERCOSUR Regulations
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
IAS	Intentionally Added Substance
INAL	(Food National Institute) for imported FCMs - Argentina
INV	INV (National Institute of Viti viniculture) (FCMs for wines) - Argentina
JECFA (FAO/WHO)	Joint FAO/WHO Expert Committee on Food Additives (JECFA)
JRC	Joint Research Centre - EU
LATAM	Latin America
LC-HRMS	Liquid Chromatography with High Resolution Mass Spectroscopy
LC-MS	Liquid Chromatography with Mass Spectroscopy
LOD	Limit Of Detection
MHLW	Ministry of Health, Labour and Welfare - Japan
MPOH	Ministry of Public Health - Thailand
MPPO	Modified Polyphenylene Oxide
NAMs	New Approach Methodologies
NHC	National Health Commission – China
NIAS	Non-Intentionally Added Substances
OECD	Organisation for Economic Co-operation and Development
OML	Overall Migration Limit
P&B	Paper & Board
QM or QMA	Quantitative Amount in the Material
rPET	Recycled Polyethylene Terephthalate
SAMR	State Administration for Market Regulation - China
SENASA	(National Service of Agrarian Health and Quality) for FCMs used to package animal and vegetable foodstuffs - Argentina
SML	Specific Migration Limit
SNVS	Brazilian Health Regulatory System
TDI	Tolerable Daily Intake (TDI)
ToR	Threshold of Regulation
TFDA	Thai Food and Drug Administration
TNE	Total Non-Volatile Extractives Overall Migration - USA
TPE	Thermoplastic elastomers
TTC	Threshold of Toxicological Concern
USFDA	United States Food and Drug Administration – see FDA
WHO	World Health Organisation

1. Introduction

Food contact materials (FCMs) play an essential role in ensuring the safety and security of the food supply chain ensuring the protection of food from chemical, microbiological and physical damage, increasing shelf life and enabling transport over long distances. Packaging and labelling are necessary to provide consumers with ingredient and nutritional information (Dupouy, 2023, pp. 320–328; Marsh & Bugusu, 2007). FCMs include not only packaging and articles, but, food processing equipment, bulk food storage, tableware, kitchenware, etc. With any products resulting in exogenous chemicals entering the food chain, the safety assessment of FCMs is essential, whether in a linear or circular economy. Unfortunately, requirements for such assessments are not harmonized across materials or regions, nor between single-use and reusable materials, recycled or not. There are different regional regulatory approaches to ensuring the safety of FCMs. However, food safety remains a common goal that can be supported by mutually recognized principles, including testing, hazard and risk assessment. As the hazard will not vary across regions, there is no scientific reason why approaches to hazard characterization should differ and hence it should be possible to harmonise them. Risk characterization may need to vary from region to region, due to differences in exposure scenarios or at-risk populations, although the principles should be the same. Harmonization of approaches has many advantages, despite the many hurdles needed to be overcome, benefiting consumers in global foodstuff markets., by ensuring that foodstuffs consumed have similar safety standards, simplifying rules for regulators, especially for imported foodstuffs and benefiting industry, as the number of different tests and approaches required by different regions are reduced. It facilitates world trade, with associated socioeconomic and food security benefits. Finally, animal testing would be reduced, with one set of results being accepted by all.

Harmonization is difficult to achieve, even within a geographic region. In the EU harmonization is refers to differences across the EU and Member States, as outlined in the JRC baseline study (Simoneau et al., 2016).

ILSI Europe tried to understand the differences in testing requirements for FCMs, and examine ways in which the underlying principles on which they are based can be harmonized. Following an initial workshop, it became clear that global harmonization is a long-term objective, unlikely to be achieved without there being evolution in various aspects of FCM assessment, with each needing to be harmonized. The workshop agreed that global acceptance of the key principles underlying the regional guidelines was a worthwhile goal.

The workshop highlighted numerous issues that need resolving, with some requiring significantly more time than others, and identified obstacles that needed to be overcome. Therefore, it was decided to approach this task in a stepwise manner, many requiring cooperation between the different authorities and a willingness for them to consider harmonising their approaches and accepting those of others.

1.1. FCMs regulators and their risk assessment and approval process

There is a fundamental difference between the approaches taken by the EU and United States Food and Drug Administration (USFDA).The USFDA considers the food contact substance (FCS) whereas the EU considers both the manufactured FCMs and their constituents. The EU Framework Regulation (EC 1935/2004) establishes criteria for materials in contact with food Whilst food contact regulations in different regions share common goals, they differ significantly in their approaches, regulatory frameworks, and enforcement mechanisms. Seven major regions are compared below:

1.1.1. United States

The Food and Drug Administration (FDA) is the primary regulatory authority for FCMs and operates under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The FDA's regulation is based on the concept

of Generally Recognized as Safe (GRAS) and premarket clearance for new FCSs. The use of certain materials must be approved by the FDA, either through a Food Contact Notification (FCN) or inclusion in the inventory of approved substances.

The FDA conducts risk assessments based on available scientific data and exposure estimates.

1.1.2. European union

The European Commission (EC) – specifically Directorate General for Health (DGSante) is the main regulatory body for FCMs. Regulations are based on the Framework Regulation (EC) No 1935/2004, and specific measures, such as Regulation (EU) No 10/2011 for plastic materials. The risk assessor is the European Food Safety Authority (EFSA) and DGSante implements their opinions into law. The EU employs a positive list for plastics, where only substances in the Union list can be used in plastic FCMs. Specific measures for different materials (e.g., ceramics, coatings, silicones, paper and board) exist at national levels.

For 'harmonized' FCMs, EFSA conducts risk assessments based on toxicological studies and exposure data. Substances are added to the positive list by DGSante. For non-harmonized FCMs, Member State National Regulations apply, if they exist.

1.1.3. China

The National Health Commission (NHC) and the State Administration for Market Regulation (SAMR) oversee FCMs. China's regulations are encapsulated in the Food Safety Law and the Guobiao standards (GB standards), with GB 4806.1–2016 being the framework standard for FCMs. China follows a positive list approach with mandatory GB standards listing approved substances and migration limits. The China National Centre for Food Safety Risk Assessment (CFSA) is responsible for the risk assessment of new substances, often requiring comprehensive toxicological data. Once approved, substances are listed in the relevant GB standards.

1.1.4. India

The Food Safety and Standards Authority of India (FSSAI) regulates FCSs. Food Safety and Standards (Packaging) Regulations (FSSAI, 2018), prescribes an overall migration limit (OML), and "specific migration limit". For any chemical noticed by FSSAI, existing toxicity data with mode of action is reviewed, and a risk assessment performed. In the absence of data, the Food Business Operator (FBO) has to generate toxicity data based upon dietary exposure. Toxicity data requirements are similar to those of EU-EFSA.

1.1.5. Thailand

Food Act B.E.,2522 (Ministry of Public Health, 2022) is the fundamental law covering FCMs in Thailand and FCM importers need to register their products using a USFDA number (Nishimura, 2022) . The importer should register with Thai Customs for custom clearance procedure (Department of Science Service Thailand). The ASEAN (Association of Southeast Asian Nations) Centre for Food Contact Materials Testing is the governmental laboratory under the Division of Food Products and Food Contact Materials, Department of Science Service (DSS), Ministry of Science and Technology, Thailand and leads in collecting FCM standards and regulations among ASEAN member states (Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam).

1.1.6. Japan

Japan regulates FCMs through the Food Sanitation Act (Food Sanitation, 1947) and a positive list system, which establishes the basic requirements for the safety and quality of FCMs and food. A Positive list system was introduced in 2020 and will be fully enforced by 2025. Only evaluated substances on the positive list can be used in FCMs. The positive list covers materials polymeric resins, food contact additives, and starting substances (Food Sanitation Act No. 233 of 1947, 1947).

1.1.7. MERCOSUR

South America is mainly covered by MERCOSUR. Members are Argentina, Bolivia Brazil, Paraguay and Uruguay. Venezuela is currently suspended. Associate members are Chile, Colombia, Ecuador, Guyana, Peru, Surinam (Kenny, 2016).

MERCOSUR reviews USFDA, EU, German BfR regulations and the Council of Europe Recommendations, but approvals cannot be relied on, as substances must be on MERCOSUR Positive lists. MERCOSUR resolutions require transposition into national legislation and differences can exist in implementation and interpretation.

GMC Resolution No. 02/12 (GMC/RES No 02/12, 1992), "Technical Regulation on Positive List of Monomers, Other Starting Substances and Polymers Authorized for the Manufacture of Plastic Packaging and Equipment that Come into Contact with Food" is the resolution that has to be transposed into National Legislation:

- List of monomers and other starting substances with usage restrictions, composition limits and specific migration limits (SMLs); - based upon EU Regulation 10/2011
- Positive list of polymers based on US 21 CFR Parts 175 and 177 (U.S. Food and Drug Administration)

Argentina and Brazil implemented this resolution.

- Argentina Resolución Conjunta 168/2013 y 229/2013 of 5 June 2013 (Official Gazette of the Republic of Argentina, 2013)
- Brazil Anvisa Resolution RDC 56 of 16 November 2012 (National Health Surveillance Agency (National Health Surveillance Agency, 2012)

In Argentina, the Baseline Food Law Argentine Food Code (Código Alimentario Argentino) – Law 18284/1969 as amended applies (Government of Argentina, 1969). The responsible agencies are:

- INAL (Food National Institute) for imported FCMs
- SENASA (National Service of Agrarian Health and Quality) for FCMs used to package animal and vegetable foodstuffs
- INV (National Institute of Viti viniculture) (FCMs for wines)

FCMs are regulated by the Argentine Food Code, Chapter IV. In Brazil there is a Baseline Food Law, but no framework law, instead regulation is achieved through multiple Resolutions. The responsible agency –National Agency of Sanitary Surveillance (ANVISA) of Ministry of Health, publishes food packaging material resolutions according to the type of packaging materials.

Table 1 contains an overview of the different regulatory situations in the above countries.

1.2. Risk assessment, communication and management of FCMs

This manuscript considers FCMs and areas where there could be opportunities for harmonization in their risk assessment and analysis protocols. There are a number of areas that could be harmonized in their approach, even though they may differ quantitatively, reflecting the differences between regions. Some areas will be easier to harmonise than others, in theory at least. Different areas for harmonization are reviewed later. However, as a first step some background information is provided to illustrate how close or far apart the different approaches are. This document considers three aspects of risk analysis, all of which need to be harmonized. Each will be considered in turn along with potential areas for harmonization.

1.2.1. Risk assessment

To undertake a robust risk assessment it is necessary to approach it in a structured manner. Data needed for risk assessment can be collected through information/documents from the suppliers, found in literature

Table 1
Overview of regulatory situation in EU, USA, China, India, Thailand, Japan and MERCOSUR (Southern Common Market of South America).

	EU	USA	China	India	Thailand	Japan	MERCOSUR
Regulatory framework	EU Framework Regulation (EC) No. 1935/2004: Establishes general safety requirements for all (FCMs).	FDA (Federal Food, Drug, and Cosmetic Act): Establishes general safety requirements for FCMs under Title 21 of the CFR (Code of Federal Regulations).	Food Safety Law and GB Standards Established general safety requirements for FCMs under the National Standard GB 4806 series. |	Food Safety and Standards Authority of India (FSSAI) regulates safety requirements for FCM through Food Safety and Standards (Packaging) Regulations, 2018, and Bureau of Indian Standards regulation & specification.	Overarching law is the Food Act of 1979 which sets out the framework requirements for FCM. The Thai Food and Drug Administration (TFDA) enforces the Food Act and is responsible for ensuring the safety and quality of FCMs. For specific materials, the Ministry of Public Health (MOPH) has issued three notices.	The Food Sanitation Act (Act No. 233 of 1947) is the supreme law for the hygiene and safety of food and FCMs. Japan also has a positive list system.	Framework Regulation (GMC Res 3/92) Establishes general safety requirements for all FCMs and Food contact articles (FCAs).
General Safety Principle	FCMs should not release harmful substances in quantities that could endanger human health.	FCMs must be safe and not adulterate food.	The level of substance migrating from FCMs and articles into foods should not impose harm to human health.	FCMs should not exceed the Overall Limits or Specific limits prescribed, as the case may be, to ensure food safety to the consumer.	FCMs should be safe and of adequate quality by meeting an the appropriate standards of the FDA	Restrictions on the migration of the FCM into food; which are not in the positive List. From June 1, 2025, any FCM substances not listed in the finalised positive list may not be used.	FCMs should not release harmful substances in quantities that could endanger human health.
Good Manufacturing Practices (GMP)	Regulation (EC) No. 2023/2006 requires compliance with GMP for the production of FCMs.	21 CFR Part 110 (Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food) requires compliance with GMP.	GB 31603-2015 - National Food Safety Standard for GMP for FCMs.	FSSAI requires food businesses to follow Good Manufacturing Practices (GMP) and Good Hygiene Practices (GHP).	FDA and GMP certifications are indispensable for Thailand's pharmaceutical and food industries to ensure the production of safe, high-quality products.	In accordance with Article 50, Paragraph 3 and 4 of the Food Sanitation Act, manufactures must comply with the GMP, and are obligated to convey material compliance information to downstream customers.	GMC Resolution No. 03/92 requires all FCMs to be manufactured under GMP.
Migration limits	Specific Migration Limits (SMLs) established for substances in harmonized FCMs (e.g., Plastics Regulation (EU) No. 10/2011). OML at 60 mg/kg or 10 mg/dm^2 is also applicable. Quantitative amount in the material (QM or QMA) also exists in some situations.	Threshold of Regulation (ToR) sets migration limits based on risk assessments. GRAS is also applicable. For some substances and/or materials extractive limits exist.	SMLs set for substances in FCMs (e.g., GB 9685). For some substances and/or materials extractive limits exist.	OMLs and SMLs are set. All packaging materials of plastic origin shall pass the prescribed OML of 60 mg/kg or 10 mg/dm^2.	OML $\leq$10mg/dm^2. Specific migration for 19 heavy metals have been prescribed. For specific migration limit of 22 Primary Aromatic Amines(PAA), a limit has been prescribed as ND (LOD-0.002 mg/kg) (Notification of Ministry of Public Health(No.435) B.E. 2565(2022) Issued under Food Act,B.E 2522., 2022).	The OML for FCMs in Japan is 60 mg/kg of food or 10 mg/dm2 of the contact material Migration limit of 0.01 mg/kg food for all other polymer resins and additives not on the positive list.	The OML is standardized to 10 mg/dm^2.
Risk Assessment	(EFSA) conducts risk assessments for substances used in FCMs.	FDA conducts risk assessments for FCS which are not considered GRAS.	CFSA conducts Risk Assessments for FCMs.	FSSAI conducts risk assessments for FCMs.	The Risk Assessment of FCMs is undertaken by the Food and Drug Administration	Under the Food Sanitation Act, the Ministry of Health, Labour and Welfare (MHLW) conducts Risk Assessment.	ANVISA is the coordinator of the Brazilian Health Regulatory System (SNVS), The Argentinian COMISIÓN NACIONAL

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Table 1 (*continued*)

	EU	USA	China	India	Thailand	Japan	MERCOSUR
Risk Management	European Commission DG Sante are risk managers and not EFSA who are risk assessors.	FDA are both risk assessors and risk managers.	SAMR are risk managers.	FSSAI are risk assessors and risk managers.	The Food Committee and its sub-committee are responsible for food safety risk management. TFDA is responsible for enforcing the Food Act and ensuring the safety and quality of FCMs.	The Food Safety Commission of Japan (FSCJ) who is responsible for establishing guidelines for risk assessment of FCMs, is also responsible for risk management.	DE ALIMENTOS (CONAL) is responsible for the tasks of advising, supporting and monitoring the National Food Control System Ministry of Health in the individual countries

when already published (official opinions, scientific publications etc), or generated with new experimental data.

Testing may then also be required. There are number of different approaches to testing available and in practice a combination of these will be used, as appropriate. For hazard identification and characterization, the migrant(s) that could be present in the foodstuffs consumed need to be identified and quantified and these need to be considered in any subsequent assessment. It is then necessary to determine the toxicity of migrating substances with experimental data or *in silico* approaches.

For the exposure assessment, it is necessary to define the intended use of the FCS and/or FCM and the different foodstuffs with which it may come into contact. This will enable an estimate of exposure to the migrant by estimating levels of migrants in food and subsequently estimating dietary exposure.

For the risk characterization, it is possible to:

- compare the reference value for the toxicity of the substance and the estimated level of exposure based on migration levels and dietary consumption (including margin of exposure if needed)
- gather information that would help inform the magnitude and relevance of risk, such as dependence on duration of exposure, dose, route of exposure and mode of action (e.g. how relevant is skin toxicity to risk from oral ingestion).
- Identify and consider any potentially susceptible sub-groups, such as infants or toddlers.

1.2.2. Risk communication

Having undertaken the above it is necessary to communicate the outcome. Risk communication must ensure that not only scientists are aware of any conclusions on safety, including how and why they were reached, but also non-scientists, in order to allay unnecessary, or unjustified concerns, where a clear, non-specialised explanation would be of value. Risk communication sits between risk assessment and risk management and together these comprise risk analysis (World Health Organization, 2009).

1.2.3. Risk management

Based on the above it is necessary to implement risk management measures necessary to ensure the acceptable use of the FCM, including setting limits for exposure to the substances. Risk management measures are unlikely to be harmonized due to differences across regions in socio-economic circumstances. Risk management is not in the scope of this document, as it is the responsibility of individual countries/regions and includes considerations beyond scientific ones.

1.3. Stateof the art of differences in risk assessment

The description of differences in risk assessment has been divided into two parts: the protocols for testing and the approach applied for the risk assessment.

1.3.1. Differences in protocols for testing

1.3.1.1. Migration testing. Information on the identity and the concentration of a migrant in a foodstuff are both needed for a comprehensive risk assessment. The first step relies on an extraction from the material or migration testing. For migration testing, obviously, it is impractical for this to be obtained using every foodstuff consumed, so substitutes, called simulants, are used to represent different groups of foodstuffs, and various conditions of time and temperature are selected to simulate the intended use. For migration testing, there are a number of factors that need to be considered, including:

1. Choice of suitable food simulant(s)
2. Time for exposure to simulant(s)

3. Temperature for exposure to simulant(s)
4. Recognition that different FCMs may require different and not frequently used test methods.
5. Application of state-of-the-art analysis including scientifically accepted qualitative and quantitative methods, particularly because some regions (e.g. EU) are revising their FCM regulations. Taking account of these changes will be essential for any upcoming requirements for analysis

A limited range of simulants are used by different regimes to determine the potential concentration of a substance that could migrate into particular foodstuffs. Different regimes use some simulants in common and others that are different. Table 2 contains information on the different simulants used in the different regions and this is an area which could potentially benefit from some degree of harmonization. The durations and temperatures of exposure differ, being adapted to the actual foodstuffs, processing temperatures and shelf lives. For further details refer to the relevant regulations. However, the conditions used by some regimes will be varied depending on the nature of the packaging, such as differentiating between single and repeated use FCMs.

Although there are many similarities among regions (Table 2), there are subtle differences that would benefit from harmonization.

The reasons for the differences in choice of food simulants are not clear and could not be determined from the literature. Some differences are marginal, such as the use of 3 % acetic acid versus 4 % acetic acid. Nevertheless, the different testing conditions impose a huge burden for industry to obtain worldwide approval.

Besides variations in analytical method, the variation in sample preparation needs to be reduced. By "fixing" the simulants in a harmonized way as given below, variation could be reduced, especially for non-plastic based materials. The concept of using food simulants is accepted mainly only for plastics. For paper & board (P&B) as an example, the simulant concept does not really work as P&B has low resistance to liquid simulants. In addition, some simulants cannot be used for some materials, e.g. 95 % ethanol for silicones and TPEs (Thermoplastic elastomers) – leading to non-realistic swelling effects. In other words, for non-plastic materials harmonization of simulants would also lead to better data for assessments.

The above food simulants are applicable mainly to plastic based materials. For final FCAs, they are not ideally suited, especially if the plastic is not a barrier or the final article is not made from plastic, e.g. paper & board, silicone rubber, new plant-based materials.

Generally, simulation is based on liquids with the exception of modified polyphenylene oxide (MPPO), a simulant for dry foods, which is not accepted in all countries. For example, China has proposed using a liquid, such as ethanol, as a simulant for dry foods. However, most foodstuffs, except for beverages, are not liquid. They are either solid or semi-solid. A revised approach might be needed. The rationale is demonstrated with, as an example, a plastic layer (food contact side) and printed (non-food contact side) paper. If the layer is thin PE (polyethylene), which is not a barrier, a liquid simulant will pass through the PE layer, thereby coming into contact with the paper. This leads to a migration of paper-based substance, which appear in a Non-Intentionally Added Substances (NIAS) screening. However, in reality solid food will never pass the PE layer. If the PE layer is stressed over 10d at 60 °C, as used for long term storage simulation, this effect causes issues. Once the liquid simulant has passed the PE coating, it will also initiate migration of the ink-related substances through the paper.

This simple example shows that for final FCM articles the migration/extraction conditions laid down in EU and/or US-FDA guidelines are a long way from reflecting reality. In some cases regulations also allow the use of reduction factors to reduce the amount of migrant experimentally analysed in order to compensate for the amount in the simulant being larger than that in the foodstuff represented by the simulant. One example is the "simulant D2 reduction factor" (Commission Regulation, 2011; Hoekstra et al., 2011).

In Europe, it is in theory, possible to override results from tests with food simulants, by testing the actual foodstuff. However, this approach is often not practical, as separate testing of each type of foodstuff would be required. Testing of foodstuffs instead of simulants is technically challenging and not practically possible for NIAS analysis.

As long as the focus is on monomers and additives in the plastic world, the current approach can be seen as feasible, albeit worst case. For NIAS determination, it does not work and needs to be revised.

1.3.1.2. Analytical methods to identify and quantify migrating substances. The identification of a substance relies on different strategies based on the level of knowledge available of the potential substances. The knowledge will differ depending on whether the substances are used in the preparation of the FCM (Intentionally Added Substances or IAS) or are present incidentally (NIAS).

IAS in FCMs include monomers and special additives used to manufacture FCMs and FCAs. NIAS, which are often of unknown origin, include impurities present in the IAS or degradation or reaction products created during the synthetic process (Koster et al., 2015). One of the first problems in the task of comprehensively identifying and quantifying the migrants that might be present is the lack of harmonization of the analytical procedures, as depending on the analytical technique used and the procedure applied, different results can be obtained. While for the IAS and predictable NIAS, standard molecules can be used to confirm/verify the presence of the declared migrating substances in a targeted analysis, a non-targeted screening is required for NIAS that cannot be predicted. In a non-targeted screening, libraries of structures are needed to identify the substances.

There are a series of scientific publications (Driffield et al., 2018; García Ibarra et al., 2019; Hoppe et al., 2016; Martínez-Bueno et al., 2019; Nerín et al., 2022; Omer et al., 2018; Peters et al., 2019; Schymanski & Williams, 2017; Song et al., 2019; Su et al., 2019; Tsochatzis et al., 2020; Ubeda et al., 2018; Vera et al., 2018, 2019) and documents (Oldring et al., 2023) describing the different approaches and providing recommendations for achieving the goal, but even then, the libraries used by the different operators and laboratories are not the same and thus the identification of migrants is not comparable. Based on the very wide number of chemicals to analyse (thousands) and the huge range of concentrations that can be present, ranging from less than 0.1 ppb to 60 ppm, that have to be confirmed in food or food simulants, such harmonization is very challenging and not a question of recommending only one analytical procedure. As methods for the analysis of all individual substances that might be present are not available, the modern trend is to run non-targeted screening, preferably based on high-resolution mass spectrometry. Due to a lack of harmonized procedures, the comparability of non-targeted screening results between different laboratories is low. Improving the comparability of screening results is one possible area for harmonization, by defining methods, including clear requirements for e.g. analytical temperature, solvent gradients, mass range. This means that harmonization will need to be step by step, where one important priority step is the use of a single unique library for identification of the unknown compounds, which are mainly NIAS. Development of such a unique and public library for identification of substances, either volatile, semi-volatile and non-volatile, is in progress and will be published soon. The direct analysis of FCMs, either by exhaustive extraction with the appropriate solvent or by headspace HS-GC-MS or GC-MS or LC-MS allows the identification of potential migrants and the final concentration in the food to be estimated. For the non-volatile substances, LC-MS operated in high resolution mode is required for identification purposes and the use of the correct library and experience play an important role.

If the concentration extracted exceeds any limit then it's necessary to run migration tests using relevant simulants. A critical step when doing the specific migration analysis is the sample treatment procedure, which depends on the FCM, the simulant and whether it is a targeted or an

Table 2
Simulants representing Foodstuffs for different Regimes.

Food Categories	China	EU	FDA	South America	Japan	S-Korea	Thailand	India
non-acidic aqueous foods pH > 4.5	Water 10 % Ethanol	– 10 % Ethanol	Water (pH > 5) 10 % Ethanol (alcohol content <10 %)	Water –	Water –	Water –	Water 10 % Ethanol	Water (pH > 5) 10 % Ethanol (alcohol content <10 %)
Acidic Food pH < 4.5	4 % Acetic Acid	3 % Acetic Acid	–	3 % Acetic Acid	4 % Acetic Acid	4 % Acetic Acid	3 % Acetic Acid	3 % Acetic Acid (pH < 5)
Alcoholic Food	20 % Ethanol	20 % Ethanol	8 % Ethanol	20 % Ethanol (alcohol content >10 %)	20 % Ethanol (alcohol content >1 %)	–	20 % Ethanol (alcohol content <20 %)	–
Dairy Products	50 % Ethanol	50 % Ethanol	50 % Ethanol	50 % Ethanol	50 % Ethanol (fat content <20 %)	–	50 % Ethanol	50 % ethanol (alcohol >10 % and <50 %
Fatty Food	Vegetable Oil	Vegetable Oil	–	Vegetable Oil	Vegetable Oil Fat content >20 %	–	Vegetable Oil	–
Fatty Food - alternatives	95 % Ethanol – –	95 % Ethanol Isooctane –	– – Heptane	95 % Ethanol Isooctane –	95 % Ethanol Isooctane Heptane	– – Heptane	– – –	– – Heptane
Dry Food	10 % Ethanol (depends on other ingredients too)	Tenax[a]		Tenax	Tenax (water content <20 %)	–	Tenax	–

- not applicable.
[a] Tenax = poly(2,6-diphenylphenylene oxide).

untargeted analysis. In any case, the selection of the analytical technique and procedures critically depends upon the substances to be detected and the required limits of detection (LOD). This approach is widely accepted and the upcoming 18th amendment of Regulation (EU) 10/2011 lays down clear criteria for method performances. Details about the different analytical techniques, recommendations and useful information can be obtained elsewhere (Nerín et al., 2022; Oldring et al., 2023). Use of such a harmonized approach does not exclude the use of other analytical approaches, but in an FCM analysis report the results from the harmonized method should always appear. Results from any additional analytical approaches can be added. One good example of the consequences of this lack of harmonization is the migration of benzene from recycled PET. When applying 200 °C for 1 h to rPET there is degradation. If traces of PVC are present in rPET, benzene appears under these conditions, but this is unrealistic in the use of rPET in FCMs, as PET will never be subject to 200 °C for 1 h.

1.3.1.3. Toxicity testing. The extent of (estimated) dietary exposure tends to dictate the type of toxicity testing required. Toxicity testing can be either *in-vitro* or *in-vivo*. For low levels of exposure, *in-vitro* might suffice, primarily for genotoxicity, but for higher levels it is necessary to confirm *in-vitro* data by *in-vivo* testing, to supplement the initial data. At higher exposure levels, more test data are required by all authorities.

There are new approach methodologies (NAMs) emerging or established, such as *in-vitro* assays, *in silico* tools, and read across, but in general their fitness-for-purpose needs to be established, before they can be used routinely to replace animal testing. OECD may be able to assist as a basis for mutual acceptance of protocols for NAMs.

Different regimes have different requirements for the extent of toxicity testing needed on the basis of the level of dietary exposure. As an example, in Table 3 the differences between USFDA, EFSA and other regions are shown.

At first sight, there appears to be a lot of commonality for the different regimes, but the details may differ. As a first step towards harmonization, it would be constructive for experts from the different regimes, along with expert toxicologists and regulators, to try and ascertain what is essential and what is an over-cautious requirement. Following advice from its Scientific Committee in 2011 (EFSA Scientific Committee, 2011), EFSA concluded that the genotoxicity of chemicals in food could be reliably assessed using only 2 *in vitro* tests, namely an Ames bacterial toxicity test and typically an *in vitro* mammalian cell micronucleus test. An *in vivo* test would be necessary only when there was some ambiguity from *in vitro* testing. This could be considered as a first step towards harmonization between EU, USA and elsewhere.

OECD (Organisation for Economic Co-operation and Development) could play a pivotal role in harmonising the acceptance of data on genotoxicity in different regimes.

1.3.2. Differences in the approaches applied in risk assessment

1.3.2.1. Hazard characterization in the absence of testing data. When analysing an FCM it is common to find NIAS, for which no or very limited toxicological data are available. It is impossible to perform a comprehensive set of experimental toxicity studies for every identified substance. To facilitate the risk assessment, a predictive approach is usually applied, based on the chemical structure and likely exposure.

The Threshold of Toxicological Concern (TTC) concept provides a pragmatic, science-based approach to prioritize and manage safety evaluations of substances with no or limited toxicological data. In their guidance on the TTC, the EFSA defines 5 different groups of chemicals summarized in Table A1, for which different thresholds were assigned by statistical analysis of a large set of toxicological data (More et al., 2019; Kroes et al., 2004).

Chemicals, with a few exceptions, can be classified into these five classes, depending on chemical structure. A maximum estimated daily intake (EDI) has been assigned to each class, based on the toxicity threshold for that class (Barlow, 2005; Barlow et al., 2001).

Providing that the substances found are not potential DNA reactive carcinogens or mutagens, or organophosphates or carbamates, the maximum concentration for the highest toxicity class is 90 μg/kg food (based on TTC for Cramer class III substance and consumption of 1 kg of food per day, all of which is contact with the FCM). This value has often been set as the maximum acceptable concentration of potentially toxic substances found in migration studies.

Typically, the TTC for DNA-reactive mutagens and/or carcinogens is applied to substances with unknown structure, if genotoxicity of the substance cannot be ruled out e.g. by combining formulation data, analytical data and bioassay results. It is also necessary for a reasonable case to be made that the substance does not belong to one of the chemical classes excluded from the TTC approach (e.g. dioxins, nitrosamines) (Schilter 2019).

A different approach, that also aims to facilitate the risk assessment for substances with limited toxicological data is the "Threshold of Regulation (ToR)" concept, which is implemented by the FDA. The ToR is applicable when the estimated dietary exposure to the substance is less than 0.5 ppb in food (referring to a daily exposure of 1.5 μg per person per day for the FDA assumption of a daily food consumption of 3 kg). Below this daily exposure the risk is generally considered as acceptable (Food and Drug Administration, 1995). Carcinogens, compounds that are predicted to be genotoxic and all substances on an exemption list published by the FDA (Threshold of Regulation Exemptions for Substances Used in Food-contact Articles | FDA) are excluded from the ToR. However, in contrast to the TTC concept in the EU, the FDA does not generally assume that all unknown or uncharacterized contaminants are carcinogens, but accepts the ToR limit as a pragmatic threshold for unknown contaminants.

Therefore, for unknown contaminant FDA's ToR of 1.5 μg/day is considerably higher, than the European approach of using the TTC for DNA-reactive mutagens and/or carcinogens, which refers to a daily intake of 0.15 μg per person per day for the default assumption of a 60 kg person consuming 1 kg of food per day. This difference between the ToR and the TTC based concept for the evaluation of unknown contaminants can get considerably higher for exposure scenarios for other than a 60 kg adult. The FDA also does not distinguish between people of different bodyweight for the ToR, the threshold of 0.5 ppb is applied for infants as well as for adults.

Once a NIAS has been detected, even though it maybe tentative (either from a structural or concentration point of view), it is necessary to review any existing data on its toxicity and its mode of action, if known. Assuming that any hazard associated with the substance would apply to all situations, regardless of exposure. This is considered inappropriately conservative. For example, the toxicity of some substances is route-specific, so that a skin sensitiser should not be considered a hazard following dietary ingestion (oral) on just this basis. The mode of action or adverse outcome pathway and potency need to be taken into account, as this information can be used to determine whether and how to extrapolate to different routes of exposure. The hazard of the starting materials for FCMs will not necessarily dictate any hazard from the resulting FCM. For example, monomers are by design reactive chemicals. However, when polymerised their functionality and potential hazard are much reduced and the toxicity of the finished FCM should be assessed, rather than that of the starting monomer, and this would depend upon residual level and systemic exposure – namely, if it is not bioavailable, it is not hazardous (other than possibly locally).

It is not possible to harmonise approaches to assessing all hazards at the same time. As a first step, it is suggested that assessment of genotoxicity and endocrine disruption should be prioritised.

Bioassays have traditionally been used for testing single substances, but with the newer requirements, particularly from the EU, for NIAS to be evaluated, bioassays are increasingly being used to test mixtures of migrants in what has been termed a 'Migrant Soup'. Even though there is no specific regulatory requirement for bioassay data for the complex mixture of migrants, this information can help to support a safety assessment of NIAS, as bioassays can specifically detect substance groups with critical toxicological effects, e.g. mutagenicity, oestrogenicity, including currently unknown chemicals, as described by Schilter et al. (2019).

Whilst the current level of biological detection is inadequate to cover the very stringent requirements for demonstrating the absence of DNA reactive genotoxic substances, these techniques have much to offer in combination with analytical data. A recent Inter-laboratory study demonstrated that bioassay testing of FCM migrates gives reproducible

Table 3
Toxicity testing requirements vs level of migration for petitioning IAS to different regulatory authorities (FDA, 2021, Lambré et al., 2024; Anvisa 2012).

Region	Level of substance in diet [mg/kg food]									
	<0.0005	≥0.0005	≥0.005	≥0.01	≥0.05	≥0.5	≥1	≥5	≥10	≥60
EU[a]	*in-vitro* Genotoxicity (minimum 2 Tests)									
					90 day feeding study (1 species)					
								ADME Study		
								Comprehensive Studies		
US/FDA[b]	*In-silico*									
			in-vitro Genotoxicity (minimum 2 Tests)							
						in-vivo Genotoxicity				
						90 day feeding study (2 species)				
									Comprehensive Studies	
China [a]	*In-silico*									
				in-vitro Genotoxicity						
					90 day feeding study (2 species)					
								Comprehensive Studies		
Japan [b]	*In-silico*									
			in-vitro Genotoxicity							
					in-vivo Genotoxicity					
					90 day feeding study (2 species)					
					ADME Study					
					Comprehensive Studies					
MERCOSUR[a]		*in-vitro* Genotoxicity (minimum 3 Tests)								
					90 day feeding study (2 species)					
					ADME Study					
								Comprehensive Studies		

In India data required for the risk assessment are considered on a case-by-case basis.
"Comprehensive Studies": higher tier in-vivo tests such as carcinogenicity studies and reproductive toxicity tests, often has to be discussed case by case with authorities (e.g. with FDA).
[a] This is based upon migration data, normally into simulants, but migration into food overrides simulant data.
[b] This is based on the CDC (Cumulative Dietary Concentration).

results if well conducted, even though it could benefit from further standardization of test protocols (Marin-Kuan et al., 2023). Bioassay testing of the complex mixture in a migrate can support a toxicological risk assessment of NIAS, but it is not a substitute for toxicological testing of IAS or chemical analysis of migrants.

1.3.2.2. Exposure assessment

1.3.2.2.1. Concentration of migrants. There are two basic approaches for estimating the concentration of a substance or substances in the migrate from an FCM, namely physically measuring it in the actual foodstuff or a food simulant or by calculation based on worst-case assumptions of 100 % migration of a substance present in an FCM or migration modelling. Of course, previous identification of the substances involved is required for applying migration modelling.

In the EU, in addition to modelling or measurement of migration into simulants of foodstuffs, it is possible to use worst case assumptions to estimate exposure, but it should be borne in mind that the EU treats infants, toddlers and adults differently. In the revised guidance for the safety assessment of recycled PET, EFSA recently defined new worst-case exposure scenarios for different groups of food, specifically considering infants (for water and infant formula) and toddlers (e.g. for milk and non-alcoholic drinks) (EFSA Panel on FCMs). One hundred per cent of a substance in an article is assumed to migrate and if the resulting exposure estimate does not give cause for concern, then there is no need for further testing. The concentration of the substance in an article can be obtained from either the concentration initially present in (added to) the FCM or that obtained by experimental exhaustive extraction.

Mathematical modelling is an accepted approach for evaluating the potential migration of specific substances, but it is not applicable for overall migration assessments. Modelling involves mathematical reasoning based on mass balance, mass transfer, and polymer science, constructed to ensure that the estimated values are as conservative as test results. The numerical models used are increasingly simulating the entire migration process, including redistribution of the substance before food contact, accelerated mass transfer during heating, and specific interactions with food.

Two regulatory guides have been produced, developed at different times, when the dominant plastics varied and by different authorities. These guides are not contradictory but emphasize different phenomena not mutually recognized in both.

The US guidance (Schwope et al., 1990) focuses on partitioning effects and coupling with reactions, particularly hydrolysis, which the European guidance (Hoekstra, 2015) largely does not consider. The European guidance provides rough estimates of partition coefficients and details overestimations of diffusivities based on molecular mass. Both guides have remained static for years and do not explicitly integrate multilayer and multi-material considerations. This lack of harmonization, along with the absence of open property databases and safety margin evaluations, limits developments, unlike other fields using quantitative structure property relationships. Despite their imperfections, these models are very useful as they reduce testing costs and the testing capacity needed. Although they predate the circular economy, they are extensively used to assess the safety of recycled materials post-decontamination, ensuring substances do not migrate above the genotoxic TTC. However, these models are unsuitable for optimizing recycled material decontamination, necessitating more realistic models that integrate cross-mass transfer, outgassing, etc.

There is no standard for reporting migration modelling results in the EU or US. The models are not unified, typically relying on 1D approximations with variable boundary layer implementations and capacities to handle chained operations, barrier layers, and food/simulant interactions under variable conditions. Reviewing these approaches in complex cases is challenging. Advanced modelling techniques, such as 3D, multiscale, and probabilistic, are often neglected or limited to complex industrial cases. For recycled materials, early-stage modelling directly on pellets rather than finished products could be advantageous (CosPaTox Consortium).

1.3.2.2.2. Dietary exposure. The current EU dietary exposure model generally leads to arguably over-precautionary estimates. Different regimes use different methods/rules to estimate exposure to migrants. The EU regulation for plastics requires use of the actual area to volume ratio, but in several defined cases, the area to volume ratio of 1 dm edge cube, total surface 6 dm2, in contact with 1 kg/foodstuff can be used. (Commission Regulation 10/2011).

The USFDA use a dietary consumption of food and beverage of 3 kg per person per day, whereas DGSante (EU) and EFSA use 1 kg/per person per day for an adult. However, in the EU, it is assumed that all of the food consumed is packaged in the same material and migration is at the maximum level. Whereas, in the USA food consumption and packaging usage factors, which modify the estimation of the amount of a substance ingested, based on use patterns, are used. The adoption of a similar approach for the EU would be a major step forward, even though the numerical values may differ.

To illustrate this, consider the following, extracted from FDA guidelines (FDA, 2006).

The US dietary exposure (EDI estimated daily intake) is obtained by combining a number of factors, which are derived from actual survey data. These factors are:

- Consumption factor
- Food-type distribution
- Concentration in the diet
- Cumulative exposure

In addition to the above, there are approaches for modelling exposure.

Consumption factor

The term “Consumption Factor" (CF) describes the fraction of the daily diet expected to contact specific packaging materials. The CF represents the ratio of the weight of all food contacting a specific packaging material to the weight of all food packaged. CF values for both packaging categories (e.g., metal, glass, polymer and paper) and specific food-contact polymers are summarized for USA and Japan in Table 4 These values were derived using information on the types of food consumed, the types of food contacting each packaging surface, the number of food packaging units in each food packaging category, the distribution of container sizes, and the ratio of the weight of food packaged to the weight of the package. This, of course, would require an extensive effort by the non-US agencies and industry input would be needed. In reality, differences between the EU and US would be expected to be minimal, but this would require confirmation. EU industry data need to be collected and compiled in order to obtain a better benchmark. It is also important for risk assessment to consider differences between actual amounts in foodstuff and concentrations in simulants or worst-case calculations/modelling.

Food-type distribution factor

Before migration levels can be combined with CF values to derive estimates of probable exposure, the nature of the food that will likely contact the food-contact article containing the FCS must be known. Migration into a fatty-food simulant, for example, will be of little use in estimating probable exposure if the FCS is used exclusively in, or for, articles in contact with aqueous food. To account for the variable nature of food contacting each food-contact article, FDA has calculated “food-type distribution factors" (f_T) for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic and fatty. Appropriate f_T values for both packaging categories and polymer types are given in Table 5 (USFDA) and Table 6 (Japan).

Concentration in the daily diet and EDI

FDA uses the following approach for calculating the concentration of the FCS in the daily diet. The concentration of the FCS in food contacting the food-contact article, is derived by multiplying the appropriate f_T

values by the migration values, M_i, for simulants representing the four food types. This, in effect, scales the migration value from each simulant according to the actual fraction of food of each type that will contact the food-contact article.

$$C = \left(f_{aqueous} + f_{acidic}\right)\left(M_{10\%ethanol}\right) + f_{alcohol}\left(M_{50\%ethanol}\right) + f_{fatty}\left(M_{fatty}\right)$$

where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant.

The concentration of the FCS in the diet is obtained by multiplying by CF. The EDI is then determined by multiplying the dietary concentration by the total weight of food consumed by an individual per day. The USFDA assumes that an individual consumes 3 kg of food (solid and liquid) per day.

EDI = 3 kg food/person/day x CF x C.

Cumulative exposure (CEDI)

If an FCS already regulated for other uses by the USFDA (in 21 CFR 170–199) has been exempted from the need for specific regulation, under the Threshold of Regulation (21 CFR 170.39), or has been the subject of previous effective FCNs, it is necessary for the sponsor to estimate the cumulative exposure to the FCS from the proposed and permitted uses.

Dietary Concentration for Japan.

Table 6 shows food distribution factors in Japan used for the below calculation.

Modelling exposure

Consumer exposure modelling varies between the US and Europe. In the US, exposure is modelled realistically for materials with multiple applications, assuming a diet of 3 kg/day. In Europe, a more conservative model assumes that 1 kg of food is consumed daily, and that all of it is in contact with the same material. Both approaches lack detailed geometric considerations of packaging (e.g. 6 dm^2 packaging/kg food).

These different interpretations of the precautionary approach and consumption profiles lead to different outcomes. The US approach calculates a maximum exposure to a FCS, based on information on substance occurrence in FCMs, material representativeness, and consumption profiles, maintained by a trusted authority. Verification of compliance is straightforward. In contrast, the European approach bases estimates on maximum exposure on the assumption that all food consumed is in contact with the FCM, independent of material or food, requiring testing or conservative calculations to ensure limits are not exceeded. This necessitates known substance concentrations in materials and re-evaluation for new applications. Calculation helps manage complexity, but for recycled materials, where concentration and prevalence are unknown, assumptions may be overly conservative, unless believing that highly toxic substances are always probable and such conservatism is necessary.

As FCM producers often don't know the final food filled in their FCM, there is often insufficient knowledge on the final packed food to calculate exposure based on the food consumption database. EFSA also published a guidance with selected default values in 2012, which simplifies risk assessment in cases where no detailed knowledge on the final packed food is available (EFSA Scientific Committee, 2012). However, more recent risk assessments by EFSA use stricter worst-case assumptions on bodyweight and food consumption, then proposed in the original EFSA guidance of 2024 (More et al., 2024).

CEFIC-FCA (the European Chemical Industry Council Food Contact Additives Sector Group) are proposing a more realistic approach (Position of PlasticsEurope on the 2nd Reading) for assessing exposure for the EU in its forthcoming revision of the Framework Regulation. This will be based on the results of the FACET project (Castle et al., 2012; Oldring et al., 2009, 2013) in which dietary surveys were used from 6 representative European countries. The EFSA concise dietary database could also be used. In FACET, there are 18 food classifications at Tier 1 of 4 tiers. In the FACET project data were obtained for the different types of packaging for each foodstuff. The proposal is to use the actual consumption data along with packaging usage to obtain a more realistic estimate of exposure for foodstuffs which are not consumed at the EU assumption of 1 Kg/day. This significantly reduces the estimates of exposure depending upon the foodstuffs consumed.

Table 4
US and Japan Consumption factors.

Classification	Material	Consumption Factor (CF)	
		USA	Japan
General	Glass	0.1	–
	Adhesives	0.14	–
	Metal polymer Coated	0.17	–
	Metal uncoated	0.03	–
	Retort Pouch	0.0004	–
	Microwave susceptor	0.001	–
	Paper- Polymer coated	0.2	–
	All Polymer [a]	0.8	–
	Paper- Uncoated and clay-coated	0.1	–
	Polymer/Polymers with Ball pressure >150 °C	0.4	0.05
Polymer	Polyolefins	0.35 [b]	–
	- LDPE	0.12	0.25
	- LLDPE	0.06	–
	- HDPE	0.13	–
	- PP	0.04	0.16
	Polystyrene	0.14	0.07
	EVA	0.02	–
	Cellophane	0.01	–
	PVC	0.1	0.05
	- rigid/semirigid	0.05	–
	- plasticized	0.05	–
	PET [c,d]	0.16	0.22
	Other Polyester	0.05	–
	Nylons	0.02	–
	Acrylics, phenolics	0.15	–
	All other [e] (PA)	0.05	0.05

[a] Originates from adding CFs for metal-polymer coated, paper-polymer coated, and polymer (0.17 + 0.2 + 0.4 = 0.8).
[b] Polyolefin films, 0.17 (HDPE films, 0.006; LDPE films, 0.065; LLDPE films, 0.060; and PP films, 0.037).
[c] PET-coated board, 0.013; thermoformed PET, 0.0071; PET carbonated soft drink bottles, 0.082; custom PET, 0.056; crystalline PET, 0.0023; PET films, 0.03.
[d] A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").
[e] As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

Worst-case exposure scenarios for vulnerable groups with low bodyweight can lead to far lower thresholds, even if the same toxicological thresholds per kg bodyweight are applied.

Harmonising realistic exposure for low, medium, and high consumers would benefit industries and consumers by identifying substances warranting reduced exposure. Any evolution must estimate safe exposure margins to identify potential protection gaps in new systems and unreasonable over-protectiveness in old systems. Any harmonization should be in mg/ug per kg body weight (World Health Organization, 2009).

1.3.2.3. Risk characterization. Risk characterization is a step in the risk assessment process that integrates information from exposure and hazard characterization to provide a basis for understanding the possible implications of the results for human health. It consists of a qualitative estimate in terms of low, moderate, high, and/or quantitative/numerical estimation of the probability of occurrence and the severity of an adverse effect (World Health Organization, 2009) (known or potential) in a certain population. Risk characterization is the final step of risk assessment that derives from the analysis of data and evidence collected

Table 5
Food type distribution factors used by USFDA.

	Package Category	Food-Type Distribution (fT)			
		Aqueous[a]	Acidic[a]	Alcoholic	Fatty
A. General	Glass	0.08	0.36	0.47	0.09
	Metal- Polymer coated	0.16	0.35	0.40	0.09
	Metal- Uncoated	0.54	0.25	0.01[b]	0.20
	Paper- Polymer coated	0.55	0.04	0.01[b]	0.40
	Paper- Uncoated and clay-coated	0.57	0.01[b]	0.01[b]	0.41
	Polymer	0.49	0.16	0.01[b]	0.34
B. Polymer	Polyolefins	0.67	0.01[b]	0.01[b]	0.31
	Polystyrene	0.67	0.01[b]	0.01[b]	0.31
	-impact	0.85	0.01[b]	0.04	0.10
	-nonimpact	0.51	0.01	0.01	0.47
	Acrylics, phenolics, *etc.*	0.17	0.40	0.31	0.12
	PVC	0.01[b]	0.23	0.27	0.49
	Polyacrylonitrile, ionomers, PVDC	0.01[b]	0.01[b]	0.01[b]	0.97
	Polycarbonates	0.97	0.01[b]	0.01[b]	0.01[b]
	Polyesters	0.01[b]	0.97	0.01[b]	0.01[b]
	Polyamides (nylons)	0.10	0.10	0.05	0.75
	EVA	0.30	0.28	0.28	0.14
	Wax	0.47	0.01[b]	0.01[b]	0.51
	Cellophane	0.05	0.01[b]	0.01[b]	0.93

[a] For 10 % ethanol as the food simulant for aqueous and acidic foods, the food-type distribution factors should be summed.
[b] 1 % or less.

Table 6
Japan food distribution factors (DF).

Resin	Distribution Factor					
	Water [non-acidic aqueous foods pH > 4.5 - ordinary food]	Tenax [Dry Food - water content <20 %]	3 % Acetic Acid [acidic aqueous foods pH < 4.5]	20 % ethanol [alcohol content >1 %]	50 % Ethanol [fat content <20 %]	Veg. Oil [Fat content >20 %]
	D1	D1sub	D2	D3	D4	D5
Polymers with Basll pressure >150 °C	DF of the food category with the largest maximum quantity of migration is 0.96 and that of others is 0.01					
PS	0.38	0.02	0.27	0.01	0.11	0.23
PA	0.92	0.01	0.01	0.01	0.01	0.05
PVC	0.93	0.01	0.01	0.01	0.01	0.01
PE	0.88	0.03	0.04	0.01	0.02	0.05
PP	0.80	0.05	0.05	0.01	0.02	0.12
PET	0.86	001	0.09	0.01	0.01	0.03

Dietary Concentration (DC) is calculated by providing the maximum quantity (Qi) and Distribution Factor (DFi) of food category and Consumption Factor (CF) or relevant synthetic resin group as follows.
DC = {(Q1xDF1)+ (Q2xDF2)+ (Q3xDF3)+ (Q4xDF4)+ (Q5xDF5)}*CF.

in previous steps of chemical risk assessment, assessors' reflections, and conclusions. Risk characterization takes into account and acknowledges the overall uncertainties in the interpretation related to data limitation, time limitation, sampling and extrapolation, etc. When characterizing risk, uncertainty should be considered (World Health Organization, 2009), the assessors may use qualitative expressions of probability, such as "likely"/"unlikely." Science- and evidence-based risk characterization are key for effective risk communication and decisions on risk management options (Dupouy, 2023).There are different approaches between different regions of the globe based upon different policy considerations, which mandate the default assumptions to use in risk characterization. For reactive substances such as butyl acrylate, a monomer for some acrylic resins, different rules apply in different parts of the world as shown in Table A2.

In EU, for plastics, reactive starting substances are listed under the Monomers section of (EU)10/2011. Restrictions can be assigned, under the form of QM or QMA or SMLs into food. The SML has been derived from toxicological data, assuming daily intake at the level of the SML from any type of food or packaging.

While many FCM types have no harmonized regulations and therefore, there is no EU harmonized positive list, SMLs of monomers which are allowed for plastics are usually used as limits for all FCMs made using the substance. Polymers can usually be made by reacting together any monomers from the positive lists, as long as the final material meets the SML requirements.

In the US, polymers are authorized to be used only for certain types of FCM, in certain types of materials. However, there is usually no requirement regarding specific migration. The only migration limit to meet is total non-volatile extractives overall migration (TNE). To illustrate this difference, consider BADGE (bisphenol A diglycidyl ether - CAS No 1675-54-3) or styrene (CAS No 100-42-5). In the EU, each can be used in any FCM whatever the packaging type or end use, as long as the applicable SMLs are met into the food.

In contrast, in the US, BADGE or styrene can each be used only for certain polymer applications, and a BADGE-styrene co-polymer would be allowed only for the FCMs where they are both listed in the same section of CFR 175. An example of differences between the US and EU, approaches for recycled plastics are shown in Table A3.

The difference between the EU and FDA is due to the fact that the EFSA have a different dietary intake for infants compared to adults, whilst the FDA use 3 kg irrespective of age.

1.4. Risk communication

Communication is probably the most challenging part of any exercise to harmonise risk assessment and risk management to different audiences. It should be assumed that ZERO risk doesn't exist in any activity or environment, as life is a constant state of conflicting risks at different levels, and while minimizing the risk is always a key objective, there can be competing factors. Hence, there is a need for estimates of risk as accurate as appropriate to the problem at hand. Having conducted a risk assessment, it is necessary to communicate the results objectively, while reflecting the confidence in the assessment (uncertainty) and this could be best achieved by targeting two separate groups, namely:

1. Scientific communication for technicians and scientists
2. Non-scientific communication for politicians, journalists and the general public.
   Notwithstanding the differences between the intended audiences including any regional differences, there are many common themes. Table 7 summarises the main elements to be considered in any risk communication exercise.

"Risk communication for FCM" includes explaining the assessment process, uncertainties, areas of likely conservatism, and potential consequences of exposure to chemicals migrating from FCMs to food. Communicating risks early on in the assessment process allows informed decision-making and potential mitigation actions. Qualitative information about the nature of the risk and the weight of evidence should be provided, but there are inherent difficulties in communicating the quantitative aspects of a risk assessment (Spiegelhalter, 2017).

Contradictory views based on misinformation or different value judgements inhibit effective consumer actions. Industry and regulators should work together and consider being proactive about the benefits and risks of packaging. Imagine the world without FCMs, where food would be exposed to bacteria and viruses, as well as to natural decay, where food waste would increase exponentially, especially under warm and hot weather, where fresh food can stand only a few hours. Then, the risk associated to these situations would be very high and would undoubtably affect our lives. Are the available alternatives effective and are they objectively safer?

The following principles need to be kept in mind for risk communication.

For the non-scientific audience, individuals can perceive the risk from the same hazard very differently. Some of the public may disagree with risk assessors and managers regarding important hazard characteristics, the relative magnitude or severity of the risks associated with those hazards, the priority of risks, and other issues. Non-technical people should review proposed messages for clarity. Communicators should try to minimize the differences between themselves and the public and should address any uncertainties and subjective judgments involved in the risk analysis, both explicitly and clearly.

- Acknowledge potential anxieties about food safety and provide accurate information about the level of chemicals considered safe.
- Communicate the regulatory framework in place to ensure FCMs meet safety standards.
- Offer practical steps that consumers can take to minimize potential exposure to chemicals from FCMs should they wish to do so.

The use of analogy can be helpful. One potential strategy for general public communication, would be to use some examples of daily life, the risk associated with daily activities and the intrinsic assumption of such risk, e.g. walking in the street, driving a car, running in the park or the city, attending a crowded meeting such as a music festival or a sport tournament.

Scientific experts, as risk assessors, must be able to explain the concepts and processes of risk assessment. Regulatory agencies of governments at the national, regional and local levels, have a fundamental responsibility for risk communication. The public expects the government to play a leading role in managing public health risks. This is true in the case of FCMs, as the risk management decision involves regulatory or voluntary controls. The media also play an essential role in the communication process and, therefore, share a part of these responsibilities. Risk assessors include expert bodies such as EFSA (EU), FDA (USA), JECFA (FAO/WHO), CFSA (China), FSSAI (India). Risk managers are decision-makers responsible for implementing risk mitigation strategies such as EU Commission (DG SANTE), FDA (USA), Codex Alimentarius (International), State Administration for Market Regulation (China), FSSAI (India) based on the assessment. Food producers, manufacturers and suppliers of FCMs (raw materials and converted articles) need to understand regulatory requirements and communicate with consumers. Consumers are a key audience for risk communication, receiving information about potential risks and appropriate actions. Risk communication efforts and programmes need to be evaluated both regularly and systematically to determine their effectiveness and to provide change where needed. Communication aims and objectives need to be clearly stated, if an evaluation is to be effective. This could include the proportion of an at-risk population to be reached, adoption of appropriate risk reduction practices, and the extent of resolution of the concern. It is important to learn from both positive and negative risk communication experiences, in order to adjust and improve ongoing communication activities. Only through systematic evaluations, which are performed throughout the communication process, can that process be strengthened.

Table 7
Elements to be considered in risk communication.

The nature of the risk	The nature of the benefits	Uncertainties in risk assessment	Risk management options
The characteristics and importance of the hazard of concern.	The actual or expected benefits associated with each risk.	The methods used to assess the risk.	The action(s) taken to control or manage the risk.
The magnitude and severity of the risk.	Who benefits and in what ways.	The importance of each of the uncertainties.	The action individuals may take to reduce personal risk.
The urgency of the situation.	Where the balance point is between risks and benefits.	The weaknesses of, or inaccuracies in, the available data.	The justification for choosing a specific risk management option.
Whether the risk is becoming greater or smaller (trends).	The magnitude and importance of the benefits.	The assumptions on which estimates are based.	The effectiveness of a specific option.
The probability of exposure to the hazard.	The total benefit to all affected populations combined.	The sensitivity of the estimates to changes in assumptions.	The benefits of a specific option.
The distribution of exposure.		The effect of changes in the estimates on risk management decisions.	The cost of managing the risk, and who pays for it.
The amount of exposure that constitutes a significant risk.			The risks that remain after a risk management option is implemented.
The nature and size of the population at risk.			
Who is at the greatest risk.			

1.5. Proposals for areas for harmonization in risk assessment

Harmonization of protocols used in risk assessment would enable a more global communication about any associated risks. An issue which some face is that there are different rules/limits for different types of articles, for example common substances found in toys, drinking water and packaging and the question arises as to why. The reasons need to be clearly explained. This can give rise to situations where risk assessment, risk communication and risk management may differ for some substances. It would be beneficial for communicators to use a similar common vocabulary, so that regional differences are minimised. Due to the complexity of the current situation, it is suggested there are some areas that are more suitable for harmonization than others, including:

1. Foodstuff classifications and simulants
2. Migration testing conditions (time and temperature)
3. Analytical testing
4. Toxicity testing requirements, especially with the demand for reduced animal testing
5. Acceptability of bioassay testing
6. Adoption of universal allocation factors
7. Exposure assessments using packaging usage factors modelled on USFDA approach for Consumption Factors and food type distribution factors.
8. More realistic dietary exposure – amount of food consumed.

1.5.1. Foodstuff classifications and simulants

As a first step towards harmonization, alignment of the choice of simulants for migration studies would be a major step forward. There appears to be a consensus that ordinary food (neutral pH, part of fat, proteins, sugar and vegetables and non-alcoholic) needs to be considered separately from acidic food (pH value varies between 4.5 and 5). For alcoholic beverages the consensus lies in 20 % ethanol. More critical is the fat content. The Japanese approach is to fix this at 20 %, which is not that far away from the EU model with fat reduction factors. Fixed values have the advantage that it is easier to compare across systems (Commission Regulation, 2011; National Standard of the People's Republic of China, 2015; US-FDA).

The following approach for harmonization (this is only valid for plastics, see above) could be considered:

1) Ordinary food: 10 % ethanol (water seems to be too weak)
2) Acidic Food: 4 % Acetic Acid (the majority in Asia is following this approach)
3) 20 % Ethanol: Alcoholic food - mainly beverages (>1 % alcohol)
4) 50 % Ethanol: fat content below 20 % (in or outside – by weight)
5) Vegetable oil or 95 % ethanol or isooctane: fat content >20 % (in or outside – by weight)
6) Dry food: ordinary food with water content <20 % (in or outside – by weight) modified polyphenylene oxide (MPPO, tenax)

Examples of further areas where harmonization is needed:

- Paper&Board
  - Migration with simulants versus cold-/hot-water extractions
    Migration with liquid simulants lead to a kind of destruction of paper & board, whereas Tenax as powder may under-estimate the fat content.
  - Extraction with water (cold or hot) or solvents (95 % ethanol and/or isooctane) does not mimic any migration situation and over-estimates reality
  - As a solution, conventional model food defined could solve the problem as infant food powder etc.
- Printed or coated non-plastics
  - Extraction would also extract the printed/coated side, which leads to unrealistic findings – similar situation as for paper only. Single side migration is a possible solution
- Metals (coated/uncoated)
  - Applying 3 % or 4 % acetic acid as a simulant leads to rusting effects and should not be used for OM analysis. Citric acid as laid down in CoE Recommendation for Metal &Alloys might be an alternative, but it needs to be transferred into a harmonized migration Regulation
- Silicones
  - Silicones are qualitatively tested by stressing over 4h at 200 °C (CoE, F, CH, Germany). The loss in weight must be <0.5 %. However, this works only for well-tempered silicone. For silicones applied as a liquid and cured at lower temperature, e.g 0.160 °C the loss in weight will exceed 0.5 % even it is never used at these temperatures.
  - Using simulants, especially 95 % ethanol leads to swelling – a NIAS-Screening leads to overestimating results
- Wood, Textiles, plant-based materials
  - Currently no migration conditions are laid down. The inertness to liquid simulants as laid down in reg (EU) 10/2011 is not proven, especially when coated.

1.5.2. Migration and extraction testing conditions (time and temperature)

Having selected appropriate simulants, it is necessary to test for migration from the FCM. Different times and temperatures are used for different FCMs. Consult (Nerin et al., 2022) for further details.

This is a suggested topic for areas for further research.

1.5.3. Analytical approaches

Most analytical approaches are not regulated, especially for NIAS. There is a myriad of analytical techniques used for migrants from FCM's. In some cases, equipment is limited to a number of specialist laboratories, as well as there being a lack of staff experienced in interpreting and understanding the results. This is particularly true for NIAS. For many regulated starting substances with migration limits (SMLs) particularly in the EU, methodology is available. For a review of the analytical treatment for NIAS consult Nerin et al. (2022).

It is necessary to have techniques that will analyse for volatiles, semi-volatiles and non-volatiles with an agreed level of sensitivity. As a general rule, the more sensitive the more expensive the equipment. It is important that a wide range of laboratories are able to undertake NIAS testing. Each piece of equipment has its strengths and weaknesses. Different instruments may give different results. An agreed minimum level of detection, quantification and sensitivity as well as using common libraries is needed for identification purposes. For comparison of analytical results, standardized reporting is required, as an example highlighting critical parameters.

1.5.4. Toxicity testing requirements, especially with the demand for reduced animal testing

The acceptance of the TTC approach for risk assessment and risk management is urgently required.

Available OECD guidelines along with relevant Codex Alimentarius guidance should be used when trying to harmonise approaches to risk assessment and management.

Some substances identified in FCMs will have been evaluated separately in another context, for example as industrial chemicals, and a tolerable daily intake (TDI) may have been established. As this will have been based on a substantial amount of chemical-specific information, the TDI should be used to determine safe levels, rather than generic defaults.

1.5.5. Acceptability of bioassay testing

Bioassays for the complex mixture of an FCM extract or migrate, could be a promising approach to facilitate risk assessment in cases

where it is not possible to identify all substances reliably (Schilter 2019). Currently available in-vitro bioassays are in general not sensitive enough to meet the high requirements for detection limits for DNA reactive mutagens, but are considered as a potentially valuable tool in a weight-of-evidence approach, when bioassay data is combined with information from formulation data and analytical testing (Schilter 2019).

From a regulatory point of view, it would be important that *in-vitro* bioassays, that are used as an additional analytical method as part of the NIAS analytics, are considered differently than toxicological tests for testing pure substances. Using bioassays as part of an analytical approach, requires different quality criteria (e.g. limit of detection, robustness of matrix effects) that are not considered in the guidance documents for the application on *in-vitro* bioassays for starting substances.

1.5.6. Adoption of universal allocation factors

Universal adoption of allocation factors would be beneficial for all involved. Currently the EU and China use fat reduction factors where the level of migration into a simulant is divided by a factor to better represent migration into the foodstuff the simulant is simulating.

For some substances in the EU, it is assumed that exposure to a substance of the consumer is not only by ingestion and allocation factors to the SML for the substance are used to reduce it, to allow for some exposure from other sources/routes.

1.5.7. Exposure

As above mentioned, consumption factors can be applied to the migration values in some regions (USA, Japan), while in EU such factors are not considered. This is an important area for harmonization. Packaging usage factors based on the USFDA approach for Consumption Factors and food type distribution factors would be a good starting point for harmonising exposure assessments. Today the required data are lacking in the EU, although there is a total diet survey available (Use of the EFSA, 2011). In the US there are regular surveys of foodstuffs consumed and their packaging.

1.5.8. More realistic dietary exposure

There is a need in certain regions, including EU, to use more realistic dietary exposure as the current defaults can be considered to be very over-protective. Use of actual dietary and packaging surveys could form the basis of this exercise.

1.5.9. Risk assessment and management

A harmonized approach, such as that given by Koster et al. (Koster et al., 2015) utilising the principles of Barlow (ILSI) (Barlow, 2005) should be a sound basis with today's technology, especially when assessing NIAS.

2. Conclusions

Food is a global issue, thus, there is no room for having different criteria for food safety and this involves FCMs, which play a critical role. This review emphasizes the similarities and differences between the criteria applied to FCMs in different regions, including testing, exposure and application of safety values. It is clear that harmonization of such criteria are necessary. It is also evident that such harmonization cannot be achieved immediately, and some discussions, reflexions and agreements will be necessary, involving legislators, researchers and industry. But, as the review highlighted, there are several areas which are closer to harmonization, such as analytical procedures, foodstuff classifications and simulants, migration testing conditions and acceptability of bioassay testing. Attempts of harmonization of some areas are in progress, whilst others require more time and further discussions, such as the application of consumption factors, already existing in some regions. FCM legislation is undergoing continuous changes and improvements. There are many scientific publications dealing with new analytical and bioassays procedures for testing FCMs and these can be the basis for proposing harmonized tools. All these tasks must be taken step by step, but the authors are confident that harmonized approaches to risk assessment will become available for many of them.

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Appendix

Table A1
Classification of Substances according to EFSA's guidance on the TTC.

Classification	TTC value in μg/person per day	TTC value in μg/kg BW per day [(a)]
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1800	30

TTC: Threshold of Toxicological Concern; BW: body weight.

Table A2
Comparison of regulations limits for butyl acrylate in different regions.

	Europe	US	China	Japan	MERCOSUR
FCM Regulation	Authorized in plastics with SML of 6 mg/kg	Authorized in polymers, paper and board, adhesives and coatings.	Authorized in adhesives, plastics, paper and board, coatings, inks and silicon rubber with SML of 6 mg/kg	Positive List For Utensils, Containers And Packaging: Appendix 1 Table 2 (Additives) (2023-11-30) with a use limit in polymer of 5 %.	Authorized in plastics with a SML of 6 mg/kg Authorized as processing aid substances with a max. limit at 5 % in the finished product Authorized in elastomeric materials

Table A3
A comparison of different approaches between USA and EU for recycled PET to illustrate some of the approaches with their inherent issues which will need harmonising. Unidentified post-consumer contaminant in rPET water bottle.

	EU (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), 2024)	FDA (FDA, 2021)
Toxicological Threshold	Worst-Case Assumption: unidentified contaminant is a DNA-reactive mutagen, Threshold of 0.0025 μg per kg BW per day according to the TTC	Threshold of Regulation: 1.5 μg/person/day
Daily food consumption	0.26 kg food/kg BW (based on the worst case assumption that a ≤16 week old baby is exclusively fed by infant formula prepared from bottled water)	3 kg food per person per day
Percentage of food consumption from the recycled PET bottle	100 % of food consumption from the recycled PET bottle, stored until end of shelf life	5 % of food consumed from recycled packaging (Food consumption factor 0.05)
Derived Safety Threshold in Food	0.0096 μg/kg food	10 μg/kg food

BW: Body weight.

Data availability

No data was used for the research described in the article.

References

Barlow, S. (2005). Threshold of toxicological concern (TTC) - a tool for assessing substances of unknown toxicity present at low levels in the diet. *International Life Science Institute Europe Concise Monograph Series*, 1–32.

Barlow, S. M., Kozianowski, G., Würtzen, G., & Schlatter, J. (2001). Threshold of toxicological concern for chemical substances present in the diet. *Food and Chemical Toxicology, 39*(9), 893–905. https://doi.org/10.1016/S0278-6915(01)00045-X

Castle, L., Kelly, J., Jickells, S. M., Johns, S. M., & Mountfort, K. A. (2012). Exploring the sensitivity of the zone of inhibition test for leachable biocides from paper and board food contact materials, and improvements thereof. *Food Additives & Contaminants Part A Chemistry, Analysis, Control, Exposure and Risk Assessment, 29*(1), 139–148. https://doi.org/10.1080/19440049.2011.616951

Commission Regulation 10/2011. (2011). Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Official Journal of the European Union.L 12, 15 January 2011, pp. 1–89.

Department of Science Service. *General Information*. Food Contact Materials. Retrieved 19.03.2025, from https://foodcontact.dss.go.th/index.php/en/about-us/general-information.

Driffield, M., Garcia-Lopez, M., Christy, J., Lloyd, A. S., Tarbin, J. A., Hough, P., Bradley, E. L., & Oldring, P. K. T. (2018). The determination of monomers and oligomers from polyester-based can coatings into foodstuffs over extended storage periods. *Food Additives & Contaminants: Part A, 35*(6), 1200–1213. https://doi.org/10.1080/19440049.2018.1440643

Dupouy, E. (2023). *Present knowledge in food safety, A risk-based approach through the food chain*. Elsevier. https://doi.org/10.1016/C2020-0-02174-5

EFSA Scientific Committee. (2011). Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. *EFSA Journal, 9*(9), 2379. https://doi.org/10.2903/j.efsa.2011.2379

EFSA Scientific Committee. (2012). Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. *EFSA Journal, 10*(3). https://doi.org/10.2903/j.efsa.2012.2579

FDA. (1995). 21CFR 170.39, Threshold of regulation for substances used in food-contact articles. *Federal Register, 60*(136), Article 36595.

FDA. (2006). *Guidance for Industry: Estimating Dietary Intake of Substances in Food.*, Article 2006. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-estimating-dietary-intake-substances-food.

FDA. (2021). Use of recycled plastics in food packaging (chemistry considerations): Guidance for industry. *S Department of Health and Human Services Food and Drug Administration Center for Food Safety and Applied Nutrition Available. Https://Www.Fda. Gov/Media/150792/Download*.

World Health Organization. (2009). *Considerations for the assessment of the safety of feed ingredients (IPCS)*. WHO. https://www.who.int/publications/i/item/9789241572408.

Food sanitation Act No. 233 of 1947.(1947).

FSSAI. (2018). Food safety and standards (packaging) regulations. https://www.fao.org/faolex/results/details/en/c/LEX-FAOC194990/.

García Ibarra, V., Rodríguez Bernaldo de Quirós, A., Paseiro Losada, P., & Sendón, R. (2019). Non-target analysis of intentionally and non intentionally added substances from plastic packaging materials and their migration into food simulants. *Food*

Packaging and Shelf Life, 21, Article 100325. https://doi.org/10.1016/j.fpsl.2019.100325

GMC/RES No 02/12. (1992). *Technical regulation on positive list of authorized monomers, other starting substances and polymers for the manufacturing of plastic food contact packaging and equipment*.

Government of Argentina. (1969). *Código Alimentario Argentino – law No. 18.284 of 1969*.

Hoekstra, E. J (2015). *Practical guidelines on the application of migration modelling for the estimation of specific migration*. European Commission. JRC Technical Reports.

Hoekstra, E. J., Petersen, J. H., & Bustos, J. (2011). *Guidance document on fat reduction factor, functional barrier concept, phthalates, and primary aromatic amines*. European Commission: Joint Research Centre. https://doi.org/10.2788/24439

Hoppe, M., de Voogt, P., & Franz, R. (2016). Identification and quantification of oligomers as potential migrants in plastics food contact materials with a focus in polycondensates – a review. *Trends in Food Science & Technology, 50*, 118–130. https://doi.org/10.1016/j.tifs.2016.01.018

Kenny, K.C. (2016). International conference food contact compliance. "Istituto Italiano Imballaggio''.

Koster, S., Bani-Estivals, M.-H., Bonuomo, M., Bradley, E., Chagnon, M.-C., Garcia, M. L., … Spack, L. (2015). *Guidance on best practices on the risk assessment of non-intentionally added substances (NIAS) in food contact materials and articles* (pp. 1–70). International Life Sciences Institute (ILSI). Retrieved from www.ilsi.eu.

Kroes, R., Renwick, A. G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J. G., & Würtzen, G. (2004). Structure-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet. *Food and Chemical Toxicology, 42*(1), 65–83. https://doi.org/10.1016/j.fct.2003.08.006

EFSA Panel on Food Contact Materials, E. and P. A. (CEP), Lambré, C., Barat Baviera, J. M., Bolognesi, C., Chesson, A., Cocconcelli, P. S., Crebelli, R., Gott, D. M., Grob, K., Mengelers, M., Mortensen, A., Rivière, G., Steffensen, I.-L., Tlustos, C., Van Loveren, H., Vernis, L., Zorn, H., Dudler, V., Milana, M. R., … Lampi, E. (2024). Scientific Guidance on the criteria for the evaluation and on the preparation of applications for the safety assessment of post-consumer mechanical PET recycling processes intended to be used for manufacture of materials and articles in contact with food. *EFSA Journal, 22*(7), Article e8879. https://doi.org/10.2903/j.efsa.2024.8879

Marin-Kuan, M., Pagnotti, V., Patin, A., Moulin, J., Latado, H., Varela, J., Hammel, Y.-A., Gude, T., Moor, H., Billinton, N., Tate, M., Behnisch, P. A., Besselink, H., Burleigh-Flayer, H., Koster, S., & Szabo, D. T. (2023). Interlaboratory study to evaluate a testing protocol for the safety of food packaging coatings. *Toxics, 11*(2), 156. https://doi.org/10.3390/toxics11020156

Marsh, K., & Bugusu, B. (2007). Food packaging—roles, materials, and environmental issues. *Journal of Food Science, 72*(3), R39–R55. https://doi.org/10.1111/j.1750-3841.2007.00301.x

Martínez-Bueno, M. J., Gómez Ramos, M. J., Bauer, A., & Fernández-Alba, A. R. (2019). An overview of non-targeted screening strategies based on high resolution accurate mass spectrometry for the identification of migrants coming from plastic food packaging materials. *TrAC, Trends in Analytical Chemistry, 110*, 191–203. https://doi.org/10.1016/j.trac.2018.10.035

Ministry of Public Health. (2022). *Notification of Ministry of public health (No. 435) B.E. 2565 (2022) issued under the food Act, B.E. 2522*.

More, S. J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T. I., , … Wallace, H. M., & EFSA Scientific Committee. (2019). Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. *EFSA Journal, 17*(6), Article e05708. https://doi.org/10.2903/j.efsa.2019.5708

More, S. J., Benford, D., Hougaard Bennekou, S., Bampidis, V., Bragard, C., Halldorsson, T. I., Hernández-Jerez, A. F., Koutsoumanis, K., Lambré, C., Machera, K., Mullins, E., Nielsen, S. S., Schlatter, J., Schrenk, D., Turck, D., Naska, A., Poulsen, M., Ranta, J., Sand, S., … Younes, M. (2024). Guidance on risk–benefit assessment of foods. *EFSA Journal, 22*(7). https://doi.org/10.2903/j.efsa.2024.8875

National Health Surveillance Agency (ANVISA). (2012). *Resolution RDC No. 56 of 16 november 2012*.

National Standard of the People's Republic of China. (2015). *National foods safety standard general rules for migration test of food contact materials and articles*.

Nerín, C., Bourdoux, S., Faust, B., Gude, T., Lesueur, C., Simat, T., Stoermer, A., Van Hoek, E., & Oldring, P. (2022). Guidance in selecting analytical techniques for identification and quantification of non-intentionally added substances (NIAS) in food contact materials (FCMS). *Food Additives & Contaminants: Part A, 39*(3), 620–643. https://doi.org/10.1080/19440049.2021.2012599

Nishimura, A. (2022). *General food safety regulations in Thailand,Asia newsletter, september 21, 2022" and "FoodAct(B.E.2522)., Thailand, FAOLEX database*. Food and Agriculture Organisation of the United Nations. Record updated on 2020-08-02" This is a reference to Line 173 for Thailand Food Act BE,2522.

Official Gazette of the Republic of Argentina. (2013). *Resolución Conjunta 168/2013 y 229/2013*.

Oldring, P., Castle, L., & Franz, R. (2009). Exposure to substances from food contact materials and an introduction to the FACET project. *Deutsche Lebensmittel-Rundschau, 105*.

Oldring, P., Dixon, J., Vints, M., Mehegan, J., Dequatre, C., & Castle, L. (2013). Development of a new modelling tool (FACET) to assess exposure to chemical migrants from food packaging. *Food Additives & Contaminants Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment, 31*. https://doi.org/10.1080/19440049.2013.862348

Oldring, P., Faust, B., Gude, T., Lesueur, C., Simat, T., Stoermer, A., Van Hoek, E., & Nerin, C. (2023). ILSI Europe report series an overview of approaches for analysing NIAS from different FCMs. http://www.ilsi.eu.

Omer, E., Cariou, R., Remaud, G., Guitton, Y., Germon, H., Hill, P., Dervilly-Pinel, G., & Le Bizec, B. (2018). Elucidation of non-intentionally added substances migrating from polyester-polyurethane lacquers using automated LC-HRMS data processing. *Analytical and Bioanalytical Chemistry, 410*(22), 5391–5403. https://doi.org/10.1007/s00216-018-0968-z

Peters, R. J. B., Groeneveld, I., Sanchez, P. L., Gebbink, W., Gersen, A., de Nijs, M., & van Leeuwen, S. P. J. (2019). Review of analytical approaches for the identification of non-intentionally added substances in paper and board food contact materials. *Trends in Food Science & Technology, 85*, 44–54. https://doi.org/10.1016/j.tifs.2018.12.010

Schwope, A. D., Goydan, R., & Reid, R. (1990). *Methodology for estimating the migration of additives and impurities from polymeric materials (EPA 560/5-85-015)*. U.S. Environmental Protection Agency.

Schymanski, E. L., & Williams, A. J. (2017). Open science for identifying "known unknown" chemicals. *Environmental Science and Technology, 51*(10), 5357–5359. https://doi.org/10.1021/acs.est.7b01908

Simoneau, C., Raffael, B., Garbin, S., Hoekstra, E., Mieth, A., Alberto Lopes, J., & Reina, V. (2016). *Non-harmonised food contact materials in the EU: Regulatory and market situation: Baseline study: Final report (issue LB-NA-28357-EN-N (online), LB-NA-28357-EN-E (ePub))*. Publications Office of the European Union. https://doi.org/10.2788/234276

Song, X.-C., Wrona, M., Nerin, C., Lin, Q.-B., & Zhong, H.-N. (2019). Volatile non-intentionally added substances (NIAS) identified in recycled expanded polystyrene containers and their migration into food simulants. *Food Packaging and Shelf Life, 20*, Article 100318. https://doi.org/10.1016/j.fpsl.2019.100318

Spiegelhalter, D. (2017). Risk and uncertainty communication. *Annual Review of Statistics and Its Application, 4*(1), 31–60. https://doi.org/10.1146/annurev-statistics-010814-020148

Su, Q.-Z., Vera, P., Van de Wiele, C., Nerín, C., Lin, Q.-B., & Zhong, H.-N. (2019). Non-target screening of (semi-)volatiles in food-grade polymers by comparison of atmospheric pressure gas chromatography quadrupole time-of-flight and electron ionization mass spectrometry. *Talanta, 202*, 285–296. https://doi.org/10.1016/j.talanta.2019.05.029

Tsochatzis, E. D., Gika, H., & Theodoridis, G. (2020). Development and validation of a fast gas chromatography mass spectrometry method for the quantification of selected non-intentionally added substances and polystyrene/polyurethane oligomers in liquid food simulants. *Analytica Chimica Acta, 1130*, 49–59. https://doi.org/10.1016/j.aca.2020.07.018

Ubeda, S., Aznar, M., & Nerín, C. (2018). Determination of oligomers in virgin and recycled polyethylene terephthalate (PET) samples by UPLC-MS-QTOF. *Analytical and Bioanalytical Chemistry, 410*(9), 2377–2384. https://doi.org/10.1007/s00216-018-0902-4

Use of the EFSA comprehensive European food consumption database in exposure assessment. *EFSA Journal, 9*(3), (2011). https://doi.org/10.2903/j.efsa.2011.2097

Vera, P., Canellas, E., Barknowitz, G., Goshawk, J., & Nerín, C. (2019). Ion-mobility quadrupole time-of-flight mass spectrometry: A novel technique applied to migration of nonintentionally added substances from polyethylene films intended for use as food packaging. *Analytical Chemistry, 91*(20), 12741–12751. https://doi.org/10.1021/acs.analchem.9b02238

Vera, P., Canellas, E., & Nerín, C. (2018). Identification of non volatile migrant compounds and NIAS in polypropylene films used as food packaging characterized by UPLC-MS/QTOF. *Talanta, 188*, 750–762. https://doi.org/10.1016/j.talanta.2018.06.022