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Nanomaterials in food packaging: An overview of regulatory frameworks and migration assessment

Mohammed Dilsad Izrayeel Ansari [a], Laura Principato [b], Luigi De Nardo [a,*], Carlo Punta [a,**]

[a] Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133, Milan, Italy

[b] Innovhub Stazioni Sperimentali per l'Industria S.r.l, Via G. Colombo, 83 20133, Milano, Italy

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ABSTRACT

Nanotechnologies hold significant promise for supporting the design of advanced food packaging materials with tunable properties. However, this potential is limited by an important knowledge gap about the migration of nanoparticles from the packaging material into food. So far, accurately measuring specific migration remains a major challenge. Current analytical methods mainly focus on inorganic systems such as metal and metal oxide nanomaterials. In contrast, the migration of organic nanomaterials is usually assessed through broad, non-specific overall migration measurements, which do not provide key data on the transfer of the nano-objects themselves. This review critically addresses this gap by: (1) systematically examining the migration behavior of inorganic, organic, and hybrid nanomaterials in food packaging; (2) evaluating the strengths and limitations of current analytical techniques for their detection and measurement; and (3) analyzing regulatory frameworks. The findings of this work highlight the existing analytical techniques as insufficient for tracking the specific migration of nanoscale organic materials from food contact materials (FCM). It also emphasizes the urgent need for unified analytical methods, reliable predictive models, and adaptable regulatory oversight to connect innovation with safety in nanotechnology-based food packaging materials.

List of Abbreviations

ADI	Acceptable Daily Intake
AF4	Asymmetric Flow Field Flow Fractionation
AAS	Atomic Absorption Spectrometry
BNC	Bacterial Nanocellulose
CFR	Code of Federal Regulations
CDs	Carbon Dots
CEF	Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids
CNC	Cellulose Nanocrystals
CNF	Cellulose Nanofibers
Di	Diffusion Coefficient
Ki	Packaging Layer
DLS	Dynamic Light Scattering
EC	European Commission
ECHA	European Chemical Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
EUON	European Union Observatory for Nanomaterials
FCM	Food Contact Materials
FDA	Food and Drug Administration
FE-SEM	Field Emission Scanning Electron Microscopy
GC-MS	Gas Chromatography-Mass Spectrometry
GO	Graphene Oxide
GRAS	Generally Recognized as Safe
HNTs	Halloysite Nanotubes
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ISO	International Organization for Standardization
LDPE	Low-Density Polyethylene
MALLS	Multi-Angle Laser Light Scattering
MSNS	Mesoporous Silica Nanoparticles
MWCNTs	Multi-Walled Carbon Nanotubes
NLCs	Nanostructured Lipid Carriers
NOAEL	No Observed Adverse Effect Level
PEO	Polyethylene Oxide
PHB	Polyhydroxybutyrate
PHBV	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)
PLA	Polylactic Acid
PP	Polypropylene
PS	Polystyrene

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* Corresponding author.
** Corresponding author.
E-mail addresses: mohammeddilsad.ansari@polimi.it (M.D.I. Ansari), laura.principato92@libero.it (L. Principato), luigi.denardo@polimi.it (L. De Nardo), carlo.punta@polimi.it (C. Punta).

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PS-b-PEO	Polystyrene-b-Polyethylene Oxide
PVC	Polyvinyl Chloride
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
ROS	Reactive Oxygen Species
s-CNC	Surfactant-Modified Cellulose Nanocrystals
SCF	Scientific Committee on Food
SLNs	Solid Lipid Nanoparticles
SML	Specific Migration Limit
SP-ICP-MS	Single Particle Inductively Coupled Plasma Mass Spectrometry
SWCNTs	Single-Walled Carbon Nanotubes
TEM	Transmission Electron Microscopy
TiO_2	Titanium Dioxide
UL	Upper Level
ZnO NPs	Zinc oxide Nanoparticles

1. Introduction

1.1. The role of nanomaterials in food packaging

Materials are crucial in food packaging design to maintain quality, increase shelf life, and ensure safety. In response to rising consumer expectations and stricter standards, research has increasingly focused on advanced materials, with nanotechnology emerging as a strategic option to support the development of innovative materials (Ashfaq et al., 2022). The unique properties of nanostructured materials, stemming from their characteristic size and high surface-to-volume ratios, offer superior performance over conventional materials.

The literature provides comprehensive evidence regarding improved food packaging material properties enabled by nanotechnologies. Nanomaterials can significantly improve moisture and gas barrier properties by creating a tortuous path for permeating molecules (Huang et al., 2025)s. For instance, the incorporation of nanomaterials such as nanoclays (Tornuk et al., 2018), carbon nanotubes (Yu et al., 2014), and nanocellulose (Park et al., 2019) significantly improves the mechanical properties of packaging materials, while various nanoparticles can be engineered for customized optical features (Olawore et al., 2024). Furthermore, the incorporation of antimicrobial agents, such as nanoparticles of silver (Carbone et al., 2016), zinc oxide (Espitia et al., 2016; Zhang & Rhim, 2022), and TiO_2 (Serov et al., 2024) has demonstrated efficacy against a range of foodborne pathogens, offering a direct route to enhanced food safety (Sohail et al., 2018). Nanosilver, which supports the detection of H_2S in meat packaging and volatile compounds in fish, paves the way for developing intelligent packaging that can detect, communicate, and monitor packaging conditions, quality, and authenticity in real time (Zhai et al., 2019).

While many reviews have examined the benefits of nanotechnology in this sector, such as the synergistic relationship between nanomaterials and biopolymers for sustainable packaging (Ghosh et al., 2025), important safety concerns persist. A pivotal review by Ashfaq et al. (Ashfaq et al., 2022) highlights the dual nature of nanomaterials, posing their outstanding functional capabilities with the associated risks of migration and toxicity, thereby underscoring the necessity of rigorous safety assessments. Indeed, some functional nanomaterials have exhibited cytotoxic or genotoxic effects in laboratory studies. For example, silver nanoparticles can release ions that impair mitochondrial activity (Chen & Schluesener, 2008uated cytotoxicity, genotoxicity, and oxidative effects on primary mouse embryo cells to determine the significantly greater cytotoxic effects of ZnO compared to non-metal nanomaterials (Yang et al., 2009). Sharma et al. measured reactive oxygen species (ROS) to evaluate the genotoxic effects of ZnO (Sharma et al., 2011). The results showed an increase in ROS and DNA damage. Toxicity studies on nanocellulose also show safety concerns when in contact with food (Silva-Carvalho et al., 2019hlight the importance of conducting thorough safety assessments on nanomaterials.

Despite extensive research on the applications and overall toxicity of nanomaterials, a systematic analysis of nanoparticle migration—the crucial link between packaging materials and potential consumer exposure—remains a gap in the literature, especially when dealing with organic nanostructures. This review aims to fill that gap by systematically examining recent studies on nanoparticle migration from food contact materials within the context of current regulatory frameworks. The review begins by outlining key applications and the regulatory status of common nanomaterials. It then provides an overview of the legal frameworks in the European Union and the United States before offering a comprehensive, material-by-material analysis of migration studies. Finally, the review concludes by discussing the main challenges and outlook for the field. An overview of the structure of this review is illustrated in Fig. 1.

1.2. Methodology: literature survey

1.2.1. Search strategy and data collection

The search involved accessing the online databases Scopus, Wiley Online Library, Google Scholar, and Science Direct. The primary search terms used were “Nanomaterials”, “Nanocomposites”, “Food packaging”, and “Food contact materials” to ensure broad initial coverage. This was supplemented by additional keywords, including “Migration assessment” and “Food simulant contact”. The literature search included articles published between the years 2000 and 2025. Specific inclusion and exclusion criteria were established to refine the selection of articles for detailed evaluation, ensuring the inclusion of the most relevant papers. The inclusion criteria were as follows: (i) Peer reviewed articles focusing on nanomaterial migration in food packaging/real food/food simulants quantitatively; (ii) Only those nanomaterials that have capability to improve performance of food packaging materials and enough published literature to undertake critical comparison, were included; (iii) Papers covering regulatory aspects were included; and (iv) Latest revisions of EU and US FDA regulations.

The exclusion criteria for literature were: (i) Articles not related to FCMs; (ii) Studies dealing exclusively with bulk transfer/release/diffusion and not specific diffusion; (iii) Articles focusing only on qualitative detection of nanomaterials; (iv) Non-English language articles; (v) Editorials/non-peer reviewed commentaries/National conferences abstracts.

1.2.2. Study selection and categorization

A multi-stage screening process was implemented to identify studies meeting the predefined criteria among the initial large pool that was the output of the initial search. First, titles and abstracts of the retrieved articles were screened for relevance to exclude those not meeting the inclusion criteria. Subsequently, the full texts of the potentially relevant articles were thoroughly assessed against the following specific eligibility criteria: (i) Articles providing experimental evidence of nanomaterial migration, (ii) Articles discussing compliance of nanomaterials under EU and US FDA Regulations. (iii) Articles containing critical information for data analysis (like migration techniques used, testing conditions, initial nanomaterial concentration). Following this rigorous selection process, 73 primary articles were identified for in-depth analysis and were categorized on a material-by-material basis, i.e., ZnO, Ag, Montmorillonite, TiO_2, and Nanocellulose. Other relevant articles identified during the literature search, which did not meet all criteria for detailed inclusion but provided valuable context, were utilized as supporting references.

2. Nanomaterials for food packaging

2.1. The frameworks of definitions of nanomaterials and nanotechnology

As per the technical specification ISO/TS 80004–1:2010, “nanomaterial is a material with any external dimension in the nanoscale or

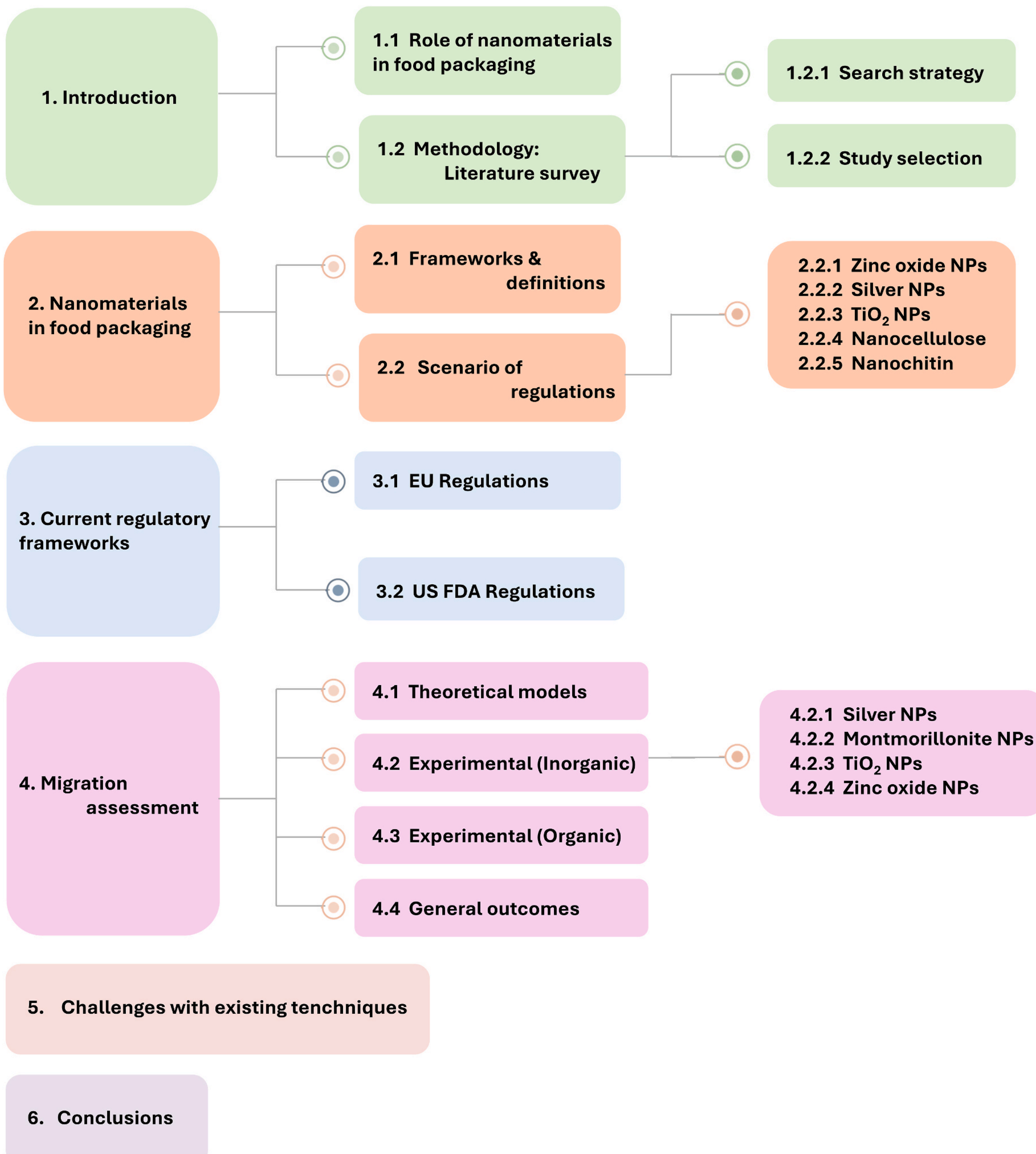


Fig. 1. Schematic overview of the structure of the review article.

having internal structure or surface structure in the nanoscale (where nanoscale is approximately 1–100 nm)" (International Organization for Standardization, 2023). The recommendation document of European Commission, 2022/C 229/01 defines 'Nanomaterial' as "a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of the particles in number-based size distribution must follow either of three points. (i) One or more external dimensions of the particle are in the size range 1 nm–100 nm. (ii) The particle has an elongated shape, such as a rod, fiber, or tube, where two external dimensions are smaller than 1 nm and the other is larger than 100 nm. (iii) The particle has a plate-like shape, where one external dimension is smaller than 1 nm, and the other is larger than 100 nm''(EEA Relevance (2022/C 229/01), 2022). The 2022 update (EU commission, 2022) offers a precise definition of nanomaterials, including details for elongated and plate-like particles and criteria for size and shape (Rauscher et al., 2023). The particles larger than 100 μm in any of the two dimensions were excluded. The new update also added an additional limit: a material should not be considered a nanomaterial if surface area per unit volume is less than 6 m^2/cm^3 (Rauscher et al., 2023).

It is crucial to note that the term 'particle size' was not used in the definition of European commission. Instead, the phrase 'external dimension' was used. This is because the techniques used to measure particle size do not measure the real particle size, but rather other properties indirectly correlated with the particle size. So, the 'particle size' term refers to the dimension of a fictional circle that inscribes the particle and creates a similar signal response as might have been created by the actual particle. Also, for non-spherical nanomaterials, the term 'particle size' demands further details of all three dimensions to determine if the material is on the nanoscale. Using the term 'external dimension' eliminates these complications, as it is clear to visualize and requires a single minimum dimension of a nanoparticle to determine if it falls on the nanoscale.

The *Feret diameter,* that is the distance between two parallel lines that can contain a nanoparticle along its length, can be used as an 'external dimension'(Rauscher et al., 2023), The guidance document ISSN 1831–9424 (Rauscher et al., 2023) also suggests using the maximum inscribed circle diameter to determine the external dimension. In most cases, the maximum inscribed circle diameter equals the *Feret* diameter. Still, a significant difference arises for stars or rods, as depicted in Fig. 2.

A widely accepted classification is based on the size of the particles in three-dimensional (3D) Cartesian space. The structures and shapes are 0D, 1D, 2D, and 3D. For 0D, no dimensions exist outside 100 nm. For 1D, only one dimension is in the 1–100 nm range. For 2D, nanomaterials have two dimensions out of the nano range. For 3D, materials aren't restricted to the nanoscale in any way (Paras et al., 2022).

However, this classification does not provide a clear definition for the classes of 0D, 1D, 2D, and 3D nanostructures, and it can have more than one interpretation (Herrera-Basurto & Simonet, 2000). Thus, The Nanoscience and Nanotechnologies Report has categorized nanostructures into three classes based on size (Royal Society & & Royal Academy of Engineering, 2004): (i) Nanosized in one-dimension (Surfaces, films, layers, etc.); (ii) Nanosized in two dimensions (Nanorods, nanotubes, nanowires, nanofibers); (iii) Nanosized in three dimensions (Quantum dots, nanoparticles, fullerenes, etc.)

The categories (i), (ii), and (iii) align with the ISO definition of "nanostructures" and should be preferred despite the more common interpretation in the literature based on the "number of dimensions."

2.2. *Scenario of regulatory implications on nanomaterials for FCMs*

Regulatory authorities in Europe and the United States have established guidelines and regulations for the risk assessment of nanomaterials. However, the advancement of these frameworks appears to lag the rapid pace of scientific research, a discrepancy that is clearly illustrated in Fig. 3. To illustrate the discrepancy between the pace of scientific publications and the speed of regulatory updates, data were gathered on the number of research articles related to nanomaterials in food packaging. This data was sourced from Scopus Elsevier, known for its extensive coverage of peer-reviewed literature and rigorous indexing capabilities. An advanced search strategy with search string "nanomaterials" and "food packaging/food contact materials" was employed, filtering out review articles and conference papers to include only original research articles. Additionally, a search of the Federal Register was conducted, encompassing all document categories from the US FDA, including Notices, Presidential Documents, Proposed Rules, and Rules. A total of 22 results were identified in the Federal Register that corresponded to the terms "nanomaterials" and "food packaging."

Table 1 mentions the most researched nanomaterials in food contact applications. Based on their structure and composition, nanomaterials can be categorized as metal and metal oxides, carbon-based, silicate-based, biopolymer-based, or lipid-based. Table 1 summarizes various classes of nanomaterials used in packaging, their morphologies, specific applications, and size range. For the classification of requirements for Nanoforms of material as per last amendment of EC No. 1907/2006 refer to Table S2 of attached supporting information.

A study conducted by university consortium commissioned by ECHA (European Chemical Agency) and EUON (European Union Observatory for Nanomaterials) has systematically reviewed nanomaterials release from consumer products, including FCMs (Estévez et al., 2024): one of the main findings of this work is that the release of nanomaterials is inevitable from all consumer goods at some point in their life cycle. The most common release form was observed in metallic nanoparticles, where transformation into cations under acidic conditions was detected. (Estévez et al., 2024). Surface phenomena are integral to understanding corrosion and ion release in nanomaterials utilized in food packaging, as these processes significantly influence migration into food products (Herting et al., 2008). Research has demonstrated that surface characteristics - such as oxidation state, surface charge, and adsorption of

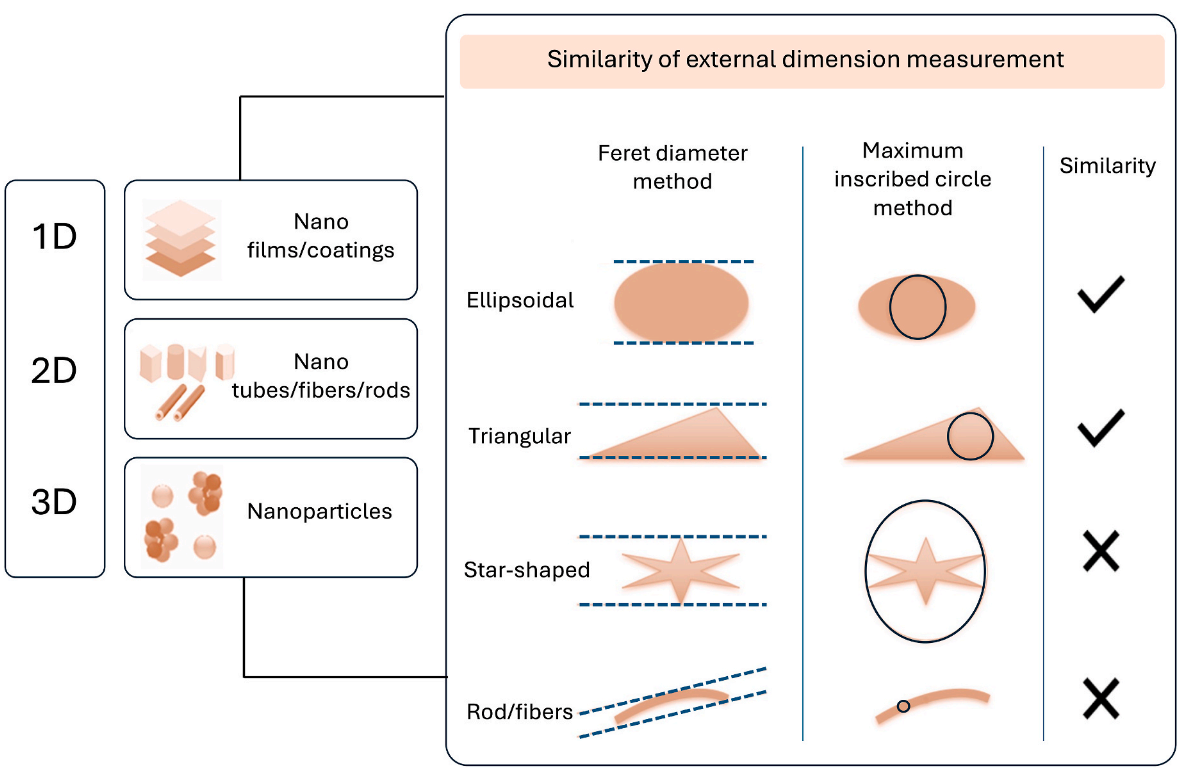


Fig. 2. Classification of nanomaterials based on dimensions and Comparison of external dimension determination by Feret diameter and Maximum inscribed circle diameter.

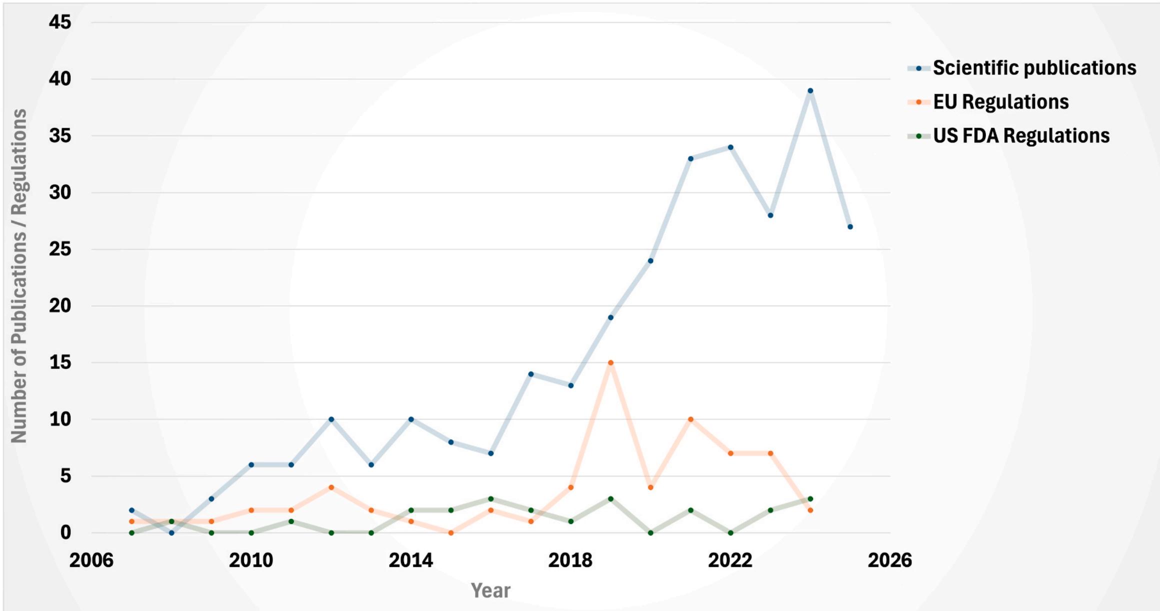


Fig. 3. Growth of Scientific Literature and Regulation documents on Nanomaterials (EU and US FDA).

Table 1
Review of nanomaterials used in Food packaging.

Category	Nanomaterial type	Size range	Morphology	Applications in Food packaging
Metal/Metal Oxides	TiO_2 NPs	10–50 nm	Spherical, rod-like	UV-Shielding (Kunz et al., 2017)
	Silver (AgNPs)	1–100 nm	Spherical, triangular, rod-like	Antimicrobial activity (Kaiser et al., 2023)
	Zinc oxide (ZnO NPs)	20–200 nm	Spherical, flower shaped	UV-Shielding (Kunz et al., 2017)
	Copper/Copper oxide (Cu/CuO NPs)	10–80 nm	Cubic and spherical	Antimicrobial activity (Kaiser et al., 2023)
	Gold (AuNPs)	5–50 nm	Spherical, Rod-like	Active packaging (Ahari et al., 2022)
Silicate and clay based	Kaolinite	Aspect ratio: 10–40, 1 nm thickness	Layered intercalated platelets	Barrier and mechanical (Wu et al., 2022) reinforcement (Rubentheren et al., 2015)
	Montmorillonite (MMT)	Aspect ratio: 50–1000, 1 nm thickness	Layered plates	Barrier and Mechanical reinforcement (Bangar et al., 2023)
	Halloysite nanotubes (HNTs)	Diameter: 30–70 nm, length: few microns	Tubular	Ethylene scavenging (Tas et al., 2017)
	Mesoporous silica (MSNs)	50–250 nm, pore sizes: 2–60 nm	Ordered pores in spherical particles	Stability of controlled release of active agents (Grini et al., 2025)
Carbon-based	Graphene/Graphene oxide (GO)	Thickness 0.34–1 nm	Sheet like	Thermal stability (Rossa et al., 2022)
	Single-walled carbon nanotubes (SWCNTs)	Length: 0.1–10 μm, Diameter: 0.8–2 nm	Cylindrical	Thermal conductivity and superior barrier (Bangar et al., 2025)
	Multi-walled carbon nanotubes (MWCNTs)	Diameter: 5–50 nm Length: 0.1–10 μm	Cylindrical	Thermal conductivity and superior barrier (Bangar et al., 2025)
	Carbon dots (CDs)	2–10 nm	Quasi-spherical	Anti-bacterial and Antioxidant (Deepika et al., 2023)
Biopolymer-based	Cellulose nanofibers (CNFs)	Length: Several μm, Width: 5–60 nm	Fibrillated	Mechanical reinforcement (Jonoobi et al., 2010), Oxygen barrier (Guivier et al., 2023)
	Cellulose nanocrystals (CNCs)	Length 100–200 nm, width 5–20 nm	Rod-like	Transparency (Chen et al., 2022), Nanofillers (Dhar et al., 2014)
	Chitosan nanoparticles	50–200 nm	Spherical	Edible packaging material (Kong et al., 2024)
	Protein nanoparticles	50–300 nm	Spherical	Active packaging (Bhavya & Raman, 2025)
	Starch nanoparticles	30–100 nm	Platelets/Spherical	Anti-bacterials (Topuz & Uyar, 2020), Drug delivery (Xiao et al., 2012)
Lipid based	Nanostructured lipid carriers (NLCs)	50–1000 nm	Spherical With imperfect matrix	Controlled release (Seyyedi-Mansour et al., 2025)
	Solid lipid nanoparticles (SLNs)	50–100 nm	Spherical	Edible films and coatings (Katiyar & Ghosh, 2021)
	Nanoemulsions	20–200 nm	Spherical droplets	Nutraceutical delivery (Ahari et al., 2021)

biomolecules - affect stability and dissolution behavior of nanomaterials (Kaymaz et al., 2023), which impact the capacity to release ions into food matrices. Furthermore, studies indicate that surrounding parameters, like pH, temperature, and food composition, can expedite surface reactions (Guzman et al., 2006), promoting the degradation of nanoparticles and increasing migration rates. The report by ECHA/2022/513 discusses all consumer products containing nanomaterials and potential release (Estévez et al., 2024). As per this report, only wood and FCMs have standard techniques in place to assess nanomaterial release. But for nanomaterials, it is complicated. And thus, EFSA (European Food Saftey Authority) 2021 guidance suggests that nanomaterials may be different structurally once incorporated into FCMs compared to their pristine form. Due to this, it recommends characterization of original nanomaterial used for manufacturing, nanomaterial present in FCM, and most importantly, nanomaterial released from FCM (S. More et al., 2021a).

2.2.1. Zinc oxide nanoparticles

ZnO Nanoparticles (ZnO-NPs) show excellent antimicrobial properties. Under EU Regulation No. 10/2011, zinc oxide (ZnO) is authorized for bulk and nanoform plastic food contact materials (FCMs), each governed by specific restrictions. Bulk ZnO is permitted as a general additive (FCM No. 402) with a Specific Migration Limit (SML) of 25 mg/kg of food. In nano form, authorizations are more targeted: coated ZnO nanoparticles (FCM No. 1046) are approved as a UV stabilizer, while uncoated ZnO nanoparticles (FCM No. 1050) are permitted only in polyethylene terephthalate (PET) materials up to 2.5 % w/w, provided the same SML of 25 mg/kg is met ((EU) No 10/2011, 2025).

A central finding in the safety assessment of these materials is the nature of the migrating species. The EFSA has concluded that migration from ZnO-based nanocomposites primarily consists of soluble ionic zinc, not nanoparticles (Claudia et al., 2016)((EU) No 10/2011, 2025)For example, in a study testing a ZnO/Low-Density Polyethylene (LDPE) nanocomposite at 2 % loading for migration at 60 °C for 10 days (Bolognesi et al., 2016), the migration data for ionic zinc from LDPE met the current SML. A key concern highlighted by EFSA is that while migration from an individual FCM may comply with the SML, this contribution could lead to an exceedance of the overall Tolerable Upper Intake Level (UL) when added to a person's baseline dietary intake.

EFSA CEF (Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids) panel confirmed that migration of ZnO was not in nanoform, and safety assessment should consider the soluble ionic zinc as the primary migrant (Bolognesi et al., 2016) The Scientific committee on food established a No-Observed-Adverse-Effect-Level (NOAEL) of 50 mg/person per day, and EFSA also validated this result in 2006 and 2014 (EC, 2003; EFSA Scientific Committee and NDA Panel, 2006; EFSA NDA Panel, 2014). Despite the limited number of participants and short duration of studies, a factor of 2 for uncertainty was deemed appropriate due to tightly controlled experimental conditions for metabolism used in studies (EFSA Scientific Committee and NDA Panel, 2006). A maximum of 25 mg/person daily was advised (from all the sources, including dietary sources, Zn ions, and Zn nanoparticles).

2.2.2. Silver nanoparticles

Silver nanoparticles are known for preventing microbial activity in FCMs. Silver in nanoform is more effective than its macro scale counterpart as it can penetrate microbial cells and interfere with important cellular functions such as DNA replication and protein synthesis (More et al., 2023).

Scientific assessments have established that migration does not occur via the direct diffusion of nanoparticles. Instead, it follows a two-step mechanism: the nanosilver first undergoes oxidation and dissolution on the polymer surface, forming soluble silver ions (Ag^+). These ions are released from the polymer and migrate into the food medium. This distinction is critical, as the toxicological and regulatory assessments focus on exposure to ionic silver.

Kaur et al., for instance, synthesized silver nanoparticles from *Lycium Shawii,* which resulted in impressive antimicrobial properties (Kaur et al., 2024). Concentrations of 1 mg/ml to 15 mg/ml represent the minimum inhibitory concentration against various microorganisms. Within these concentrations, migration up to 6 μg/kg of silver in soluble ionic form was reported. The European Food Safety Authority (EFSA) Panel evaluated the safety of this substance based on this ionic migration. Migration levels are typically low and fall well below the guidance value of 50 μg of silver per kg of food, as suggested by the former AFC Panel. Furthermore, the estimated consumer exposure from these FCMs is significantly lower than the strict Acceptable Daily Intake (ADI) of 0.9 μg of silver ions per kg of body weight per day established by ECHA. Consequently, the EFSA Panel concluded that nanosilver is safe for consumer use when employed as an additive up to 0.025 % w/w in polyolefins, which limit water uptake and subsequent ion migration (Lambré et al., 2021).

2.2.3. TiO_2 nanoparticles

TiO_2 nanoparticles in food packaging are mainly used for their UV-blocking abilities, which reduce light-induced food degradation (Hashhimoto & Sakamoto, 2011; Mohr et al., 2019). Moreover, their use can enhance the mechanical resistance of packaging materials (Kadam et al., 2017).

According to FDA regulations 21 CFR (Code of Federal Regulations) 73.575, TiO_2 can be added to foods as a color additive in quantities less than 1 % of the food. On the other hand, the EMA (European Medicines Agency) recommends suspending TiO_2 (E 171) use in food products due to its potential genotoxic traits and ability to induce oxidative stress and inflammation (Gupta et al., 2024). Therefore, TiO_2 (E 171) use in food products has been restricted.

2.2.4. Nanocellulose

Nanocellulose is a sustainable option for food packaging because of its biodegradability, mechanical properties, and barrier properties to gases (Ahankari et al., 2021). A review study on toxicity of nanocellulose showed that often there are conflicts in the results when tested in *in vivo* and *in vitro* (Stoudmann et al., 2020). Nanocellulose can cause oxidative stress and inflammation in human lung cells, indicating negative impacts (Vartiainen et al., 2011). CNFs, both non-oxidized and oxidized, were tested for *in vivo* toxicity with marine mussels *Mytilus galloprovincialis* (Rusconi et al., 2024). The findings showed that both types affected the P-gp efflux activity, hemocyte lysosomal stability, and cholinergic function. No significant effects were observed when the *in vitro* genotoxicity and cytotoxicity of CNFs and CNCs were assessed by cytokinesis-block micronucleus assay (Pinto et al., 2022). This contradicts the prior *in vivo* studies on aquatic mussels. Thus, a clear picture of the toxicity of nanocellulose remains unanswered. These results emphasized the need to conduct risk assessments for nanocellulose with a definitive conclusion.

The approval of nanocellulose as a food additive by the US FDA is pending because of a lack of information about its interaction with the human gastrointestinal tract (Cañas et al., 2024). EU laws control the registration of chemical substances, but there is no EU law/regulation/directive specifically governing nanocellulose and its safe usage with a minimum safe concentration value. Therefore, the overall law of Regulation (EC) No 1907/2006 of the EU and of the Council of December 18, 2006 is currently used.

2.2.5. Nanochitin

Nanochitin is a reinforcing agent for biopolymer films (Liao et al., 2023). Cellulose films reinforced with chitin nanofibers have improved tensile strength and elongation values (Kadokawa et al., 2015). The US FDA has a series of task force reports about regulating nanoparticles, but specific requirements for nanochitin are missing. Nanochitin is recognized as a food additive in 21 CFR parts 170 and 174. Meanwhile, from the EU's point of view, Regulation 1906/2007 also does not specifically highlight the requirements of nanochitin. According to the current regulations nanochitin, must undergo risk evaluation by EFSA. This procedure assesses the substance's safety, regardless of whether it is specifically mentioned in the regulation. Its use can be regulated through multiple EU regulations depending on its usage. If used as part of food then it will be regulated by Novel foods regulation (EU 2015/2283) and if as an additive or a constituent of packaging material, then as per FCM regulation (EU 1935/2004) and Plastic FCM regulation (EU 10/2011). Active packaging films of nanochitin have shown broad ranges of antibacterial and antifungal activity (Hasanin et al., 2024), thus if it is used as an active agent in FCM then it must be complied by the active and intelligent packaging regulation (EC 450/2009).

3. Current regulatory frameworks

3.1. EU regulatory frameworks for FCMs

Several EU regulations and directives have been implemented to ensure the safety of FCMs. The objective is to safeguard consumer health while supporting the introduction of innovative solutions. The article 3 of Regulation EC (European commission) No. 1935/2004 provides a general requirement for the articles and materials intended for food contact: "*Materials and articles, including active and intelligent materials and articles, shall be manufactured in compliance with good manufacturing practice so that, under normal or foreseeable conditions of use, they do not transfer their constituents to food in quantities which could: (a) Endanger human health, or (b) Bring about an unacceptable change in the composition of the food, or (c) Bring about a deterioration in the organoleptic characteristics thereof*" (European Parliament & EC No. 1935/2004, 2021).

Although this article specifies a solid foundation for FCMs, there can be few ambiguities like: (i) The use of the terms "*Materials and articles, including active and intelligent materials and articles*" does not mention nanomaterials, thus the inclusion of nanomaterials is open to interpretation; (ii) It strongly relies on the good manufacturing practices (GMP), but there can be variations in the GMP across the EU member states, which poses a challenge for uniformity.

EC No. 1935/2004 uses a risk-based approach to determine the safety of FCMs. The list of articles and materials covered are present in Annex 1 of EC No. 1935/2004 (EC No 1935/2004, 2021). These materials should be harmonized across the EU, which means they should have a set of uniform regulations and standards followed across all EU member states. But, of all materials present in Annex 1, only a few have been harmonized. The EU permits member countries to implement national regulations for FCMs that are not standardized at the EU level. Accumulation of the Regulations/directives/legislations used for the materials to be used in food contact across the major EU member states are mentioned in the attached supporting information (Table S1).

The role of the EFSA is crucial alongside the harmonized regulations. It evaluates substances for FCMs and offers scientific opinions that serve as a foundation for legislative actions. The engineered nanomaterials are defined in regulation EU 2015/2283 (European Parliament & Council of the European Union, 2021), as any intentionally produced material that has one or more dimensions in the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions in the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale. Most of the nanomaterials in literature belong to engineered nanomaterials because they are synthesized and characterized for a targeted application or property. However, for the nanomaterials that fail to qualify the definition of engineered nanomaterial, there is a guidance document from EFSA (More et al., 2021), which discusses the criteria to assess a small fraction of nano-scale materials. This guidance document is only applicable if the material is (i) meant to be used in food and feed product applications like novel food additives, FCMs, pesticides, etc, (ii) requires risk assessment at the nano-scale, and (iii) does not qualify as an engineered nanomaterial. The guidance evaluates whether a material's conventional risk assessment can be complemented with nano-specific considerations or not. In 2021, EFSA introduced a major revision to one of its guidance documents about risk assessment of nanomaterials for food and feed chains, including FCMs (More et al., 2021). It suggested additional nanospecific considerations, such as dissolution or degradation behavior in gastrointestinal tracts, particle size distribution, and potential for nanoparticle migration from packaging matrices. Materials can be exempted from nano-specific risk assessment if their dissolution rate in $<$10 min is greater than or equal to 88 % dissolution. If the nanomaterial does not undergo dissolution and it stays as a particulate in physiological conditions, then *in vitro* toxicity and possibly *in vivo* studies are required. These requirements are also applied to materials that are not legally defined as nanomaterials but contain small proportions.

Additionally, REACH aims to protect human health from chemical risks. The first EU REACH regulation was Regulation EC No. 1907/2006 (European Parliament & EC No. 1907/2006, 2025), which was published on December 18, 2006. The original document was revised to newer versions to include the updated scientific and technical knowledge and to increase the scope of inclusion of new chemical risks. The latest revision (2018, EU 2018/1881) (European Commission, 2018) includes nanomaterials: this revision considers the toxicological profiles of nanoforms for the first time. The regulation does not assume nanomaterials to be safe by default, even if their bulk counterparts are GRAS (Generally Recognized as Safe). The specific requirements about nanoform of materials as per EU 2018/1881 can be categorized into four types, which are (i) regulatory clarifications, (ii) risk management, (iii) data requirement and documentation, and (iv) implementation and compliance.

The target goals and requirements stated by the regulation EU No. 2018/1881 (European Commission, 2018) challenge the existing analytical techniques. Currently, there is a lack of standard techniques for tracking and quantifying specific nanoform substances in food matrices (Franz et al., 2020). Thus, addressing such issues might pose the following questions: do the existing regulations and analytical techniques consider such transformative behavior of materials? What measures can be taken to improve uniform safety standards for nanomaterials in food packaging? What additional scientific evidence is required to completely comprehend the long-term effects of nanomaterials on health and the environment in food contact applications?

The Joint Research Centre of European Commission has developed a general framework for safe and sustainable by design criteria for all the chemicals and materials (Caldeira et al., 2022). This framework emphasizes the materials and chemicals to be designed safe and sustainable from its initial phase through to the disposal phase. So instead of facing the implications after the development of materials, the focus should be to develop materials that are safe by design from the initial stage. These issues highlight the continuous requirement for regulatory monitoring to protect consumer health and support innovation at the same time.

3.2. US FDA regulations for use of nanomaterials in FCMs

The CFR (Code of Federal Regulations) is a compilation of the regulations issued by the Executive branches and agencies of US Government. The CFR is divided into 50 titles which cover all the commercial markets in US. Title 21 covers the rules and regulations for food and drugs. As per US FDA's Nanomaterial guidance for Industries (U.S. Food and Drug Administration, 2024), there is no regulatory definition for "nanomaterial". The term "nanomaterial" is commonly used to describe materials within the nanoscale range and materials with dimension-dependent properties or phenomena. This means that if the final engineered product showcases a property like a nanomaterial, it will also be considered a nanomaterial regardless of its dimension, up to the maximum limit of 1 μm (1000 nm). Thus, unlike EU's take, US FDA definition is based on final product properties rather than dimensions. The FDA does not automatically classify products containing nanomaterials or involving nanotechnology as inherently safe or dangerous. Instead, it evaluates the quality of the final product (FDA, 2014). The recommendation documents approved by FDA are to be followed by the products that are categorized for FDA's premarket review. Products not in this category are suggested to consult independent scientific bodies to safeguard their products.

In FDA, regulatory instruction about nanotechnology is presented in form of Guidance documents for Industries. As shown in Fig. 4, there are a total of 6 guidance documents covering several aspects.

The initial guidance for nanomaterials from the FDA suggested that manufacturers quantify potential migration in food packaging based on their size because migration of materials can vary with dimensions

(Paidari et al., 2021). This size-dependent assessment of migration posed few scientific complexities. The critical setback for the guidance document was its dependability in the conventional diffusion model of Fick's law. Fick's law was originally derived for molecular migration. Therefore, if applied to nano particles, will not undertake important factors like particle-particle interactions, dynamics of aggregation, and interface phenomena at food-packaging boundaries (Gavriil et al., 2018).

In 2020, testing protocols for nanomaterial enabled food packaging were elaborated by FDA to introduce dual chemical-physical assessment protocols. They considered the possibility of chemical transformations of nanomaterials while undergoing migration. In 2024, a dedicated webpage was launched by FDA describing micro-and nano-plastics in food. This FDA webpage discussed the presence of micro plastics and nano plastics in food, primarily coming through environmental contamination. It emphasized the mere presence of micro or nano plastics in foods cannot violate regulation or pose a risk unless evidence based toxic concerns are observed.

U.S. FDA regulations and EU regulations for nanomaterials differ in approaches. In dealing with nanomaterials, the FDA uses existing regulatory processes and considers specific characteristics on an individual basis. Nevertheless, unlike in the EU, the FDA does not mandate its own set of regulations specifically for nanomaterials; instead, it modifies existing rules to account for nanoscale substances. For more information of US FDA's take on nanomaterials, refer section 2 of attached supporting information.

4. Migration assessment of nanomaterials in food packaging and safety analysis

The physicochemical interactions between the food matrix and nanomaterials are essential in migration assessment. Unlike traditional materials, nanomaterials can not only migrate from the polymer matrix but also adsorb onto food surfaces, form agglomerates, or undergo structural transformations during interactions with food. To understand this phenomenon, both experimental and theoretical approaches have been employed.

4.1. Theoretical models for determining migration

The models used for calculating nanomaterial migration from packaging into food are summarized in Fig. 5. Fick's law assumes the packaging material to be consistent throughout with no porosity, density, or molecular arrangement variability. It assumes the migration path is simple, along the direction of the thickness of the packaging material, and unhindered by any obstacles. The expression of Fick's model, as shown in Fig. 5, is a simplified form after assuming that the diffusion coefficient is independent of concentration (Titze et al., 2015). Using this equation, migration behavior of nano-selenium particles and relation between diffusion and distribution coefficient in different food simulants (4 % acetic acid solution, distilled water, 10 % ethanol solution, and *n*-hexane) at different temperatures (20 °C, 30 °C, 40 °C, and 50 °C) were analysed (Xiao et al., 2018). The diffusion coefficient was calculated based on the variation in the content of nano-selenium particles in food simulants. For all 4 simulants, the diffusion coefficient increased, and migration rates were higher with an increase in temperature. At the same time, with an increase in temperature, the solubility of nano-selenium particles increased, reducing the distribution coefficient. Thus, findings were in alignment with Fick's model. Still, there are often debates about whether nanomaterial migration follows diffusion-based mass transfer from the bulk of the polymer or oxidative dissolution on the surface. Cushen et al. proved experimentally that it follows surface-based oxidation (Cushen et al., 2013).

Nanosilver at two different sizes, 10 nm and 50 nm, were added in a film of PVC and first 1 % migration in chicken was found similar, regardless of different initial dimensions. It suggests superficial dissolution of particles rather than diffusion-based mass transfer. More studies have confirmed this behavior. For example, Su et al. investigated silver migration from nanosilver/polyethylene composites with and without antioxidants in food simulants, 50 % ethanol and 3 % acetic acid (Su et al., 2015). The results showed higher nanosilver release in the composites without stabilizers at 70 °C, thus supporting oxidative dissolution at the interface over a simple diffusion-based transfer. Another example (Song et al., 2011) where silver migration from nanosilver polyethylene films in 95 % ethanol and 3 % acetic acid was observed and migration in 3 % acetic acid increased more with temperature while negligible migration was observed in 95 % ethanol suggesting that acid-driven interface reactions govern nanoparticle release more than the diffusion-based bulk transfer.

However, there are a few limitations in Fick's model. It fails to address parameters for agglomeration kinetics which were included in Modified Fick's model. The limitation of Modified Fick's law is that it doesn't consider the selective binding of nanomaterials on food-packaging matrix. It also fails to include effects of surface adsorption of nanomaterials on packaging layer. Hence, there can be mismatch between values of theoretically calculated migration and experimental.

Commercial food packaging available currently is mostly multilayer, where nanomaterial is added in specific layer for functional purposes. Instead of just relying on a single layer characteristic, multi-layer model includes diffusion coefficient (Di) of each layer and partition coefficient of each contact surfaces between food and packaging layer (Ki). The principle of mass conversion is used assuming flux leaving from each layer is same as entering adjacent layer and partition coefficient provides ratio of concentration of nanomaterial at equilibrium. Despite its

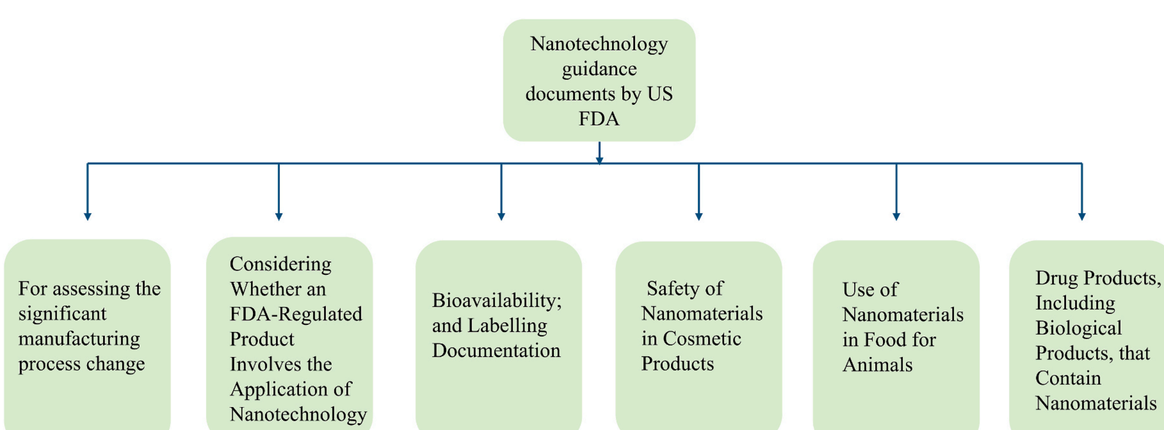


Fig. 4. Brief description of FDA guidance documents for nanomaterials (Eschenbach et al., 2024).

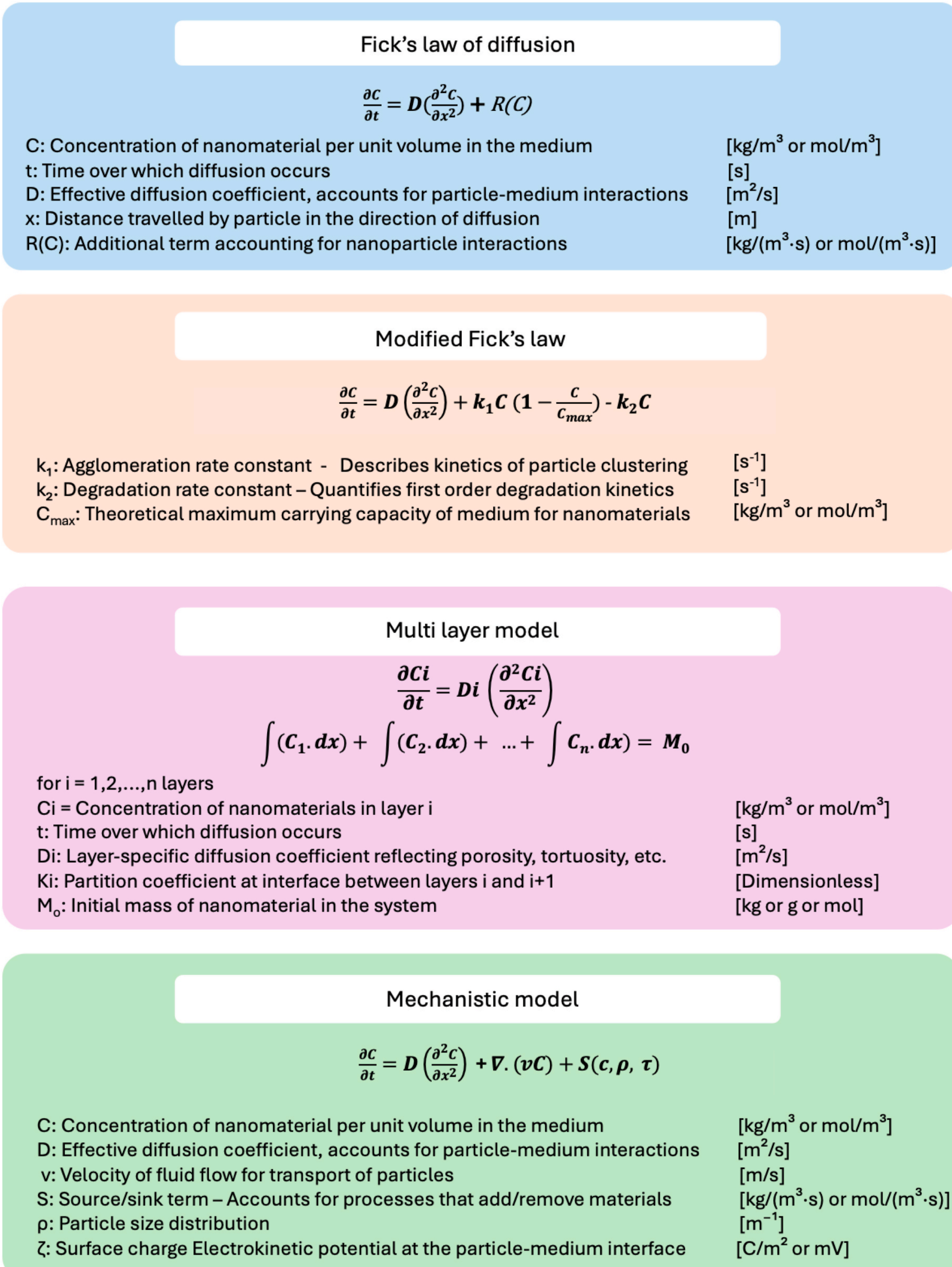


Fig. 5. Different theoretical models for diffusion of particles in a medium by Fickian, multi-layer and mechanistic approaches.

sophisticated approach, the model faces some challenges. It assumes perfect contact between food matrix and packaging surface, but in reality, contact might be uneven or not be there at all or is localized. It also assumes distribution of nanomaterial in packaging layer to be uniform; thus, this model works better for well dispersed inorganic nanoparticles like nano-silica and metal oxides such as TiO_2 and ZnO.

Previously mentioned models were mostly based on interface and diffusion of particles, but there is another model based on individual particle interaction behavior. It considers particle-particle interaction, surface charge distribution and dynamics of size distribution. Central equation of model comprises components for diffusive transport, convective transport, and source/sink terms considering particle transformations. Particle transformations can occur by agglomeration, fragmentation, or particle growth. These factors are considered by model through population balance equations. Apart from particle transformations, environmental conditions like pH, temperature, ionic strength are also featured. However, model's complexity is a downside, which requires numerous inputs which are challenging to determine accurately in real conditions. Another physicochemical model (Šimon et al., 2008) was proposed based on specific conditions like; for particles equivalent to 1 nm in size in low viscosity polymers where the interactions of nanoparticles with polymer matrix are negligible. This model suggests that packaging materials like PET or PS with nanoclays or silver does not pose high migration risk especially during the normal storage conditions of use. This model has some key limitations. It is strictly based on physico-chemical modeling without any experimental data. Secondly, it assumes there is no interaction between food interface and the polymer matrix. And it is targeted to only synthetic polymers like LDPE, HDPE, PP, PET, and PS, and does not consider any bio-based polymer matrix.

4.2. Experimental evaluation of inorganic nanomaterials' migration

Migration phenomena are governed by physicochemical parameters such as food composition, time and temperature of contact, contact area, size of nanomaterial, pH of food, storage temperature, nanomaterial concentration, etc (De Meulenaer, 2009; L. Castle, 2007; Vitrac, 2014). As shown in Fig. 6, migration phenomena can encompass both intentionally added substances and non-intentionally added substances. The prior includes monomers, oligomers, functional nanoparticles, pigments, and additives, while later consists of impurities, breakdown products, etc.

In case of nanomaterial migration, it's a critical question to understand if the migrants are still in nanoform post migration. It depends on the type, surface chemistry, the morphology of nanomaterial used, and the analytical techniques used to monitor them. Thus, a material-by-material analysis is required to understand the migration mechanism and traceability of nano scale migrants, which are discussed hereon.

4.2.1. Silver nanoparticles

The EFSA Panel evaluated the study by Bott and Franz (2019) regarding risk assessment of silver nanoparticles in non-polar plastics, when in contact with food; LDPE film containing 250 mg silver/kg was examined by abrasion test with quartz sand and rigorous motion in orbital shaker for 30–60 min (Lambré et al., 2021). The abrasion test attempts to mimic real-life conditions of abrasion at food-packaging interface and potential release of constituents. AF4 (Asymmetric Flow Field Flow Fractionation) was used to separate the nanoparticulates with respect to their hydrodynamic size and diffusion properties. And MALLS (Multi Angle Laser Light Scattering) was used to determine the particle size distribution. To quantify the silver content, ICP-MS was employed, particularly to quantify the ionic silver fraction in the food simulant. These combinations of techniques allow quantitative and qualitative presence of nanoforms post-migration in food simulants. The maximum migration determined by techniques AF4-MALLS and ICP-MS was only limited to ionic silver with magnitude of 6 μg/kg food which was less than allowed limit of 60 mg/kg. The panel concluded that the additive is considered safe for concentrations up to 0.025 % w/w, with remark of overall silver intake from alternative dietary sources may not surpass acceptable daily intake.

Apart from friction and abrasion, the nature of food media plays a key role in influencing diffusion. Polyethylene bags with 0.07 mm thickness, containing nanosilver, were digested in microwave to quantify nanosilver present (Yanmin et al., 2011). The amount of nanosilver as per AAS (Atomic Absorption Spectrometry) was found 100 μg/g of polyethylene. The bags of size 15 cm * 15 cm were filled with 200 ml of food simulants (4 % acetic acid, pure hexane, and 95 % ethanol) and were stored at 40 °C in oven for 15 days. It was reported that acidic conditions (with migration between 1.5 and 7.9 μg/L) enhanced release of silver ions due to corrosive interaction between acid and nanosilver particles. A similar trend with higher migration values in acetic acid as compared to deionized and tap water was observed in another study

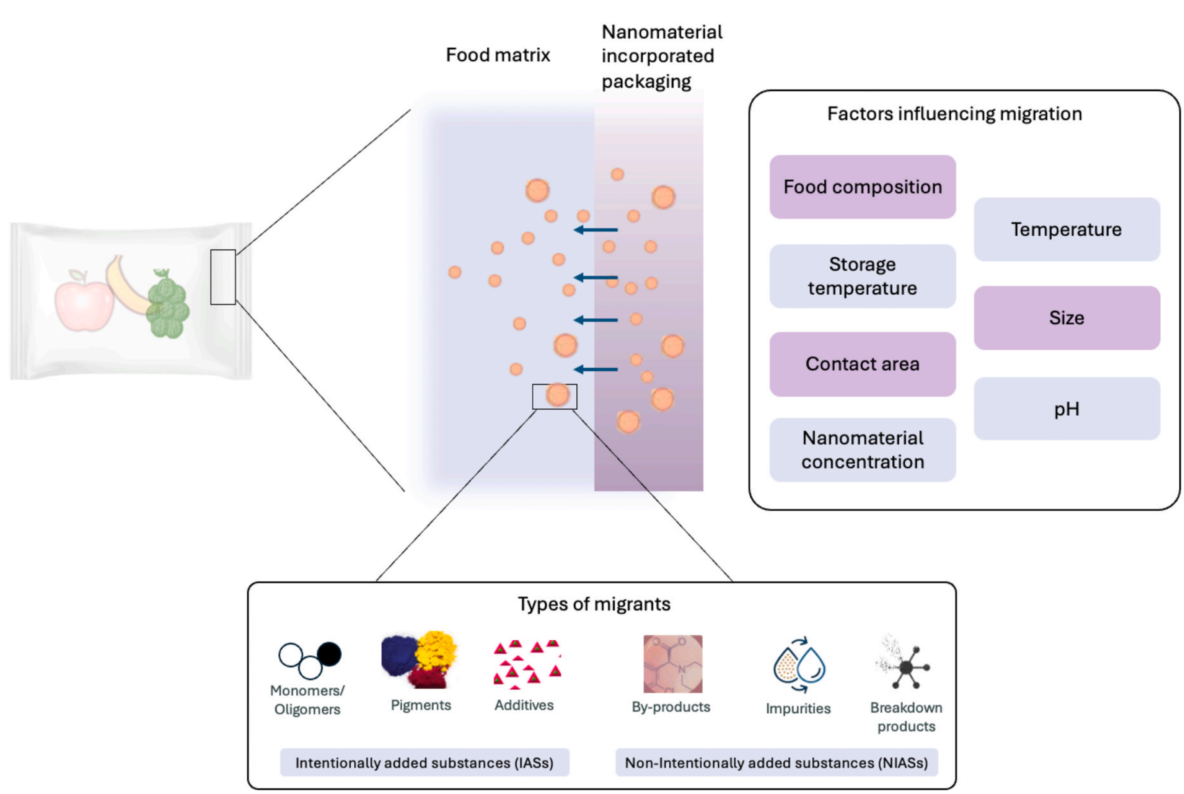


Fig. 6. Schematic representation of nanomaterial migration from food packaging: Influencing factors and types of migrants.

(Hauri & Niece, 2011). The reason reported was oxidative dissolution of silver nanoparticles. Thus, findings indicate influence of food simulant on migration behaviour, especially acidity of food simulants. A study (Yang et al., 2021) revealed that prior investigations on nanomaterial migration in food packaging predominantly utilized standard food simulants instead of actual food matrices, limiting their applicability; consequently, it examined the migration behavior of nanosilver in artificial sweeteners, uncovering a sevenfold increase in migration and the reformation of silver nanoparticles from dissolved ions during storage.

Safety concerns arise from nanosilver migration from FCMs. Despite a small magnitude, studies have shown oxidative stress effects (Valerio-García et al., 2017) and cellular damage (Guo et al., 2017). Despite the antimicrobial properties of nanosilver, the use of nanosilver in FCMs needs to be carefully evaluated, as well as ongoing research to fully understand the risks associated with chronic exposure.

4.2.2. *Montmorillonite nanoparticles*

Montmorillonite, a type of smectite clay has 2:1 layered silicate structure consists of two tetrahedral sheets of SiO_4 units and one octahedral sheet of $Al(OH)_6$ (or sometimes Mg^{2+}, $Fe^{2+/3+}$) in between. The schematic chemical structure is reported in Fig. 7.

Migration studies were conducted on montmorillonite in a commercial LDPE bag using various simulants and testing conditions (ethanol 10 % and acetic acid 3 % as food simulants, 40 °C for 10 days, and 70 °C for 2 h) to analyze aluminum migration in dissolved form and as nanoparticles via SP-ICP-MS (Echegoyen et al., 2016). Aluminum migration was noticed in both samples, reaching a peak migration value of 51.65 ng/cm^2. SP-ICP-MS showed spikes working individually, suggesting aluminum existed in nanoparticle form. The migration levels were lower than what is allowed by EU regulations. Nonetheless, some research suggests that nanoclays may have toxic effects when modified (Brandelli, 2018). This modification is usually quaternary ammonium salts functionalization, commonly used to improve dispersion of nanoclays in polymers and to enhance mechanical properties (Shah et al., 2016). Research conducted using an assay involving microsomes (Salmonella) revealed that organophilic nanoclays exhibited genotoxic effects because of presence of modified quaternary ammonium ions that caused separation between intercalated layers (Sharma et al., 2010). Cloisite 30B is one of the most popular derivatives of montmorillonite clay, mostly used for improved thermal stability and mechanical properties (Sharma et al., 2017). It can exfoliate uniformly in polymer matrix distributing mechanical stress uniformly. A study (Schmidt et al., 2009) to understand the migration of Cloisite 30B nanoclay was done by adding 5 % of Cloisite 30B in PLA. The food simulant 95 % ethanol was inspected by AF4-MALS and ICP-MS. The particle size distribution of food simulant obtained by MALS showed size ranges of particles in range 50–800 nm. No characteristic constituents of nanoclay were detected by ICP-MS in food simulant. The migrated substances were found to be oligomers of PLA. AF4-MALLS was also used for determining migration of carbon black. Two different kinds of carbon black were added to LDPE and PS at loadings of 2.5 % and 5.0 % (w/w) respectively, and subsequently underwent migration experiments (Bott et al., 2014), allowing exposure to food simulants according to standard European method October 2011. AF4-MALLS detector was utilized to segregate, define, and measure potential discharge of nanoparticles. The AF4 technique effectively distinguished carbon black from other components in migration solution, such as extracted polymer chains. No migration of carbon black was found under highly sensitive detection limit of 12 μg/kg in experimental setup. Nevertheless, there can be a drawback in measurement of size distribution by MALS. Because most algorithms used in scattering equipment are optimized for common shapes and geometries of nanoparticles and not for plate-shaped high aspect ratio particles like Cloisite 30B nanoclay.

4.2.3. *TiO_2 nanoparticles*

PP containers with TiO_2 sourced from dairy products were exposed to 50 % (v/v) ethanol and 3 % (w/v) acetic acid, serving as food simulating substances (Bastardo et al., 2024). The migration tests were conducted following standard packaging conditions recommended by Commission Regulation (EU) N° October 2011. Results indicated that TiO_2 particles of sizable dimensions (averaging 164 and 175 nm) were released from dairy product containers and spiked PP due to mechanical degradation, which occurs when the polymer structure is compromised. The dairy product containers had the highest levels of TiO_2 measured by single particle ICP-MS at 0.62 ng/cm^2 after 10 days in 50 % ethanol at 50 °C, while spiked PP had levels of 0.68 ng/cm^2 after 1 day under same conditions. Nevertheless, the amount of Ti released as particles was minimal in comparison to the overall Ti content in the packaging and significantly below the migration limits set by European laws.

4.2.4. *Zinc oxide nanoparticles*

In a recent study, the migration of ZnO nanoparticles was determined from nanocomposite of ZnO/PBAT-Starch by overall migration technique as per EU 1186-3 (Singh et al., 2024). The food simulant used was 10 % ethanol. It was noted that overall migration was reduced with the addition of ZnO especially at high temperatures. According to infrared spectroscopy, overall migration limit was found to be surpassed due to release of starch. Moreover, diffusion of PBAT oligomers from nanocomposite was also examined by GC-MS (Gas chromatography – Mass spectrometer). Results exceeded the minimum allowable safety threshold of 50 μg/kg, suggesting further toxicity evaluations. This study highlights that apart from migration of nanoparticles from the composites, release of oligomers should also be monitored under varying time-temperature conditions, for example, the release of starch and PBAT in this case. Addition of ZnO tends to reduce overall migration

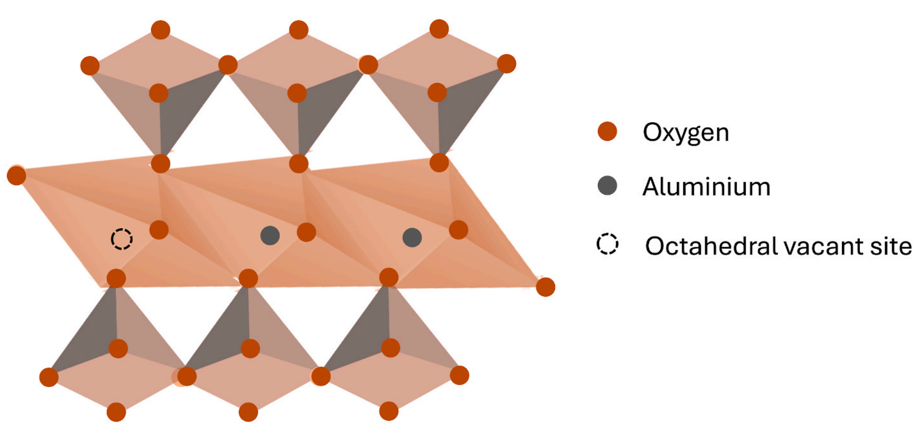


Fig. 7. The chemical structure of montmorillonite, Na^+MMT.

from a nanocomposite, but its effectiveness depends upon food-simulant in contact and also the polymer matrix. As per the current regulatory scenario, further toxicological evaluations are required to ensure ZnO's safety and its possible usage in commercial food packaging applications.

4.3. Experimental evaluation of organic nanomaterial migration

One of the most widely researched organic nanomaterials is nanocellulose. Generally, cellulose and its derivatives have been deemed safe and have already received authorization under the European Regulation (EC) No October 2011 for use in plastics intended for food packaging. These substances are permitted as polymer additives, production aids, and other starting materials. In context of food packaging, cellulose, cellulose acetate butyrate, different alkyl and hydroxyalkyl celluloses are authorized as additives and aids in polymer production. Nitrocellulose and lignocellulose are also authorized as monomers under the same regulation (Reg 10/2011). However, it is important to note that nanocellulose is not specifically listed and therefore does not currently have authorization for food contact applications (Silva et al., 2020).

A study (Bott et al., 2014) has theoretically determined the migration levels of nanocellulose to be less than allowed safety levels. Mathematical modelling as per Fick's Second Law of Diffusion was carried out using the guidelines as per Simoneau, 2010; Simoneau, 2010), for modelling migration from a monolayer material in contact with well-mixed liquids. The polymer specific coefficient (A'_P) for LDPE was 11.5 and the time delay was 0. The theoretical calculation of an apparent diffusion coefficient (D) of 1.1×10^{-35} cm^2 s^{-1} for nanocellulose particles with a diameter of 10 nm, embedded in a LDPE host matrix, suggests a negligible risk of unintentional migration. It is important to note that nanocellulose particles were considered as spheres, which is not the case in real nanocellulose particles, as CNC have either needle-like or rod-like structures, and CNF, while presenting diameters in the nanoscale, reach lengths in the order of μm.

Apart from theoretical approaches, experiments have been conducted to investigate the impact of nanocellulose in composites on migration of components from polymeric phase. Specifically, incorporation of CNC in various plastic films, particularly biopolymers like PHB, PHBV, and PLA, has been examined in relation to overall migration. To assess the effects, CNC-PHB films with different CNC loadings were subjected to migration tests using ethanol (10 % v/v) and pure isooctane as simulants (Dhar et al., 2015). The overall migration test was carried out as per Standard European Regulation No. October 2011. The tests were conducted at temperatures of 40 °C for 10 days and 20 °C for 2 days, respectively. Results indicated lower concentrations (1–2 %) of CNC dispersed in the PHB matrix, overall migration decreased compared to neat PHB for both simulants. However, when CNC loadings exceeded 3 %, higher overall migration values were observed. At lower concentration of CNCs, good adhesion between polymer matrix and CNCs could be the reason which restricted movement of polymer chains. But on contrary, at higher concentration of CNCs, adhesion between hydrophilic CNCs and hydrophobic PHB became poor, which lead to sudden increment in the levels of overall migration. Notably, migration significantly increased when PHB was loaded with 5 % CNC, resulting in an increase from 20 to 40 μg/kg in isooctane and from 90 to 180 μg/kg in ethanol (Dhar et al., 2015). In another study, nanocomposites of CNC with PLA were produced, and overall migration technique was used (Fortunati et al., 2012a). The nanocomposites PLA/5CNC (with 5 % by weight loading of CNC in PLA) was incubated at 20 °C for 2 days in iso-octane which resulted in the migration of 0.16 mg/kg of simulant while Pristine PLA and PLA with 1 % loading of CNC showed negligible migration. Overall migration was increased with higher concentrations of CNCs. The pristine CNCs were modified by surfactant to see the influence of a modified CNC and its barrier properties. Migration results showed surfactant-modified CNCs (s-CNC) reduced the overall migration from the composite. This was attributed due to enhanced interaction and adhesion between polymer matrix and nanocrystals. In relation to migration in ethanol 10 % (v/v), it is generally noted that higher levels of migration were observed when compared to isooctane. However, all values observed were significantly lower than what is established by the current legislation, Commission Directive 2002/72/EC, which is 60 mg/kg of simulant or 10 mg dm^{-2} in the case of thin films and membranes. It is important to highlight once again that most studies used the overall migration technique, which fails to provide insights into potential nanosized releases or details about constituents. This method only emphasizes the overall diffusion of substances from FCMs into food. The main issue is the lack of data on specific migration of targeted materials, leading to ambiguity in the results.

4.4. General overview and outcomes on nanomaterial migration studies

Table 2 summarizes representative migration studies for nanoparticles commonly used in food contact materials. It also includes information such as the technique used to measure migration, conditions of contact with food simulant, and concentration of nanoparticles initially present before food simulant contact. The data reveal that migration behavior is highly dependent on the specific chemistries of the nanoparticle, the food simulant, and the polymer matrix. For inorganic nanoparticles, a clear trend is the influence of simulant polarity. Zinc oxide (ZnO), for instance, consistently shows higher migration into ethanol-based simulants than acetic acid, which can be attributed to the favorable absorption of ethanol into many polymer matrices. Conversely, TiO_2 and silver (Ag) migrate more in acidic conditions, with silver migration often occurring via the release of silver ions. The polymer substrate also plays a critical role, as evidenced by the varying migration rates of TiO_2 from polypropylene (PP), polylactic acid (PLA), and low-density polyethylene (LDPE) matrices under similar test environments.

In contrast to inorganic materials, assessing the migration of organic nanomaterials like nanocellulose presents a distinct analytical challenge. Due to the lack of techniques to specifically track and quantify their migration, studies are limited to reporting overall migration, the total mass of all substances transferred to the food simulant. While these reported values often fall within regulatory limits, a crucial knowledge gap remains: the nanoscale structure and identity of the migrated species have not been investigated. This analytical limitation, coupled with the experimental variability seen across all studies, highlights the difficulty in directly comparing literature data and underscores the need for a more standardized method of analysis.

Table 2 summarizes the migration levels of nanomaterials reported in the literature. Table 3 contains the values of specific migration limits allowed as per EU and US FDA regulations along with respective conditions, restrictions and comments. Comparing the migration studies is inherently difficult: the literature reports significant variability in experimental conditions, such as the initial concentration of nanomaterials, the thickness of the nanocomposite films, and the contact area with food simulants. These differences can hinder meaningful cross-study analysis and make understanding material performance challenging. We developed and applied a normalization procedure to the data to overcome this issue. For each study, the absolute initial weight (μg) of nanoparticles was calculated based on the reported sample thickness, contact area, and material density. Migration values were then normalized to a standard contact surface area of 1 cm2. This process creates a consistent basis for comparison, and the full set of normalized results is shown in Table 4.

Analysis of the normalized data in Table 4 highlights that the physicochemical properties of the polymer matrix and the food simulant strongly influence migration. For instance, zinc oxide (ZnO) nanoparticles exhibited the highest migration from a hydrophilic gelatin matrix into bread, likely due to the porous nature of the food medium. In contrast, when embedded in a bacterial nanocellulose (BNC) matrix, ZnO migration was substantially lower (0.09 %–0.3 %), suggesting the BNC formed a more stable network that effectively retained the

Table 2
Summary of migration studies of nanomaterials in food contact/simulants along with techniques and conditions of measurement.

Nanomaterial	Size	Concentration	Substrate	Technique to Measure Migration	Contact media during migration		Contact time	Contact temperature (°C)	Migration values	References
					Standard food simulants as per EU October 2011	Non-standard food simulants				
ZnO	15–40 nm	NA	PBAT/Starch-based material	GC-MS ICP-OES	**10 % Ethanol**	**-**	**10 days**	**40**	**0.966 mg/kg**	Singh et al. (2024)
					3 % Acetic acid	**-**	**10 days**	**40**	**Below detectable limit**	
					Olive oil	**-**	**10 days**	**40**	**7.235**	
ZnO	15–25 nm	1.5 %	Gelatin matrix	**ICP-OES**	–	Bread	5 days	30	0.0208 mg/g of dry matter	Parida et al. (2022)
ZnO	100–300 nm	27 %	Bacterial nanocellulose (BNC)	AAS	**10 % Ethanol**	–	15 days	60	3.6 mg/L	(Silva et al., 2023)
					20 % Ethanol	-	15 days	60	2.2 mg/L	
					50 % Ethanol	–	15 days	60	1.1 mg/L	
Zn	100 nm	1 %	Low-Density Polyethylene (LDPE)	ICP-MS	–	Distilled water	2 h	70	4.1 mg/kg	Huang et al. (2017)
					95 % Ethanol	–	2 h	70	0.5 mg/kg	
					10 % Ethanol	–	2 h	70	1.8 mg/kg	
Ag	15	0–5 %	LDPE (Low Density Polyethylene)	Not mentioned, migration of ionic silver measured	3 % Acetic acid	**-**	**2 h**	**100**	**6 μg/kg**	Lambré et al. (2021)
					10 % Ethanol	–	2 h	60	0.7 μg/kg	
Ag	5–10 nm	0.6 %	**polystyrene-b-polyethylene oxide (PS-b-PEO) block copolymer**.	ICP-AES	3 % Acetic acid	–	2 h	100	0.46 mg/kg	Hannon et al. (2016)
Ag	40 nm	9.15 μg cm^{-2}	Polypropylene	AF4-ICP-MS	–	Ultrapure water	10 days	40	0.112 % of total Ag	(Corps Ricardo et al., 2021)
Ag	40 nm	0.1048 μg cm^{-2}	Food grade silicon-propylene	AF4-ICP-MS	3 % Acetic acid	–	2 h	70	16 % of total Ag	(Corps Ricardo et al., 2021)
TiO_2 nanoparticles	164–175 nm	10g/kg polypropylene	Polypropylene containers (from dairy products)	SP-ICP-MS	**50 % Ethanol**	–	10 days	50	0.62 ng/cm^2	(Bastardo et al., 2024)
					3 % Acetic acid	–	7 days	50	0.45 ng/cm^2	
TiO_2	30 nm	0.2 %	Polyethylene	ICP-MS, **field emission scanning electron microscopy (FE-SEM)**, and **laser particle size analysis (LPSA).**	**3 % Acetic acid**	–	8 h	100	12.1 μg/kg	Lin et al. (2014)
					50 % Ethanol.	–	8 h	100	2.1 μg/kg	
Ti	100 nm	1 %	Low-Density Polyethylene (LDPE)	ICP-MS	3 % Acetic acid	–	2 h	70	0.61 mg/kg	Huang et al. (2017)
TiO_2	<100 nm	20 %	Polylactic Acid (PLA)	ICP-AES	50 % Ethanol	–	45 days	40	0.54 mg/kg	Yang et al. (2019)
Copper nanoparticles	25–40 nm	0.6 %	**polystyrene-b-polyethylene oxide (PS-b-PEO) block -copolymer**.	ICP-AES	3 % Acetic acid	–	10 days	60	0.82 mg/kg	Hannon et al. (2016)
Carbon black	16 nm	0–5 %	LDPE and Polystyrene (PS)	AF4-MALS	**3 % Acetic acid**	–	10 days	60	Below detection limit (12–14 μg/kg)	Bott et al. (2014)
					–	**95 % Ethanol**	10 days	60	Below detection limit (12–14 μg/kg)	
					–	**Isooctane (often used as substitute to food**	10 days	60	Below detection limit (12–14 μg/kg)	

(*continued on next page*)

Table 2 (*continued*)

Nanomaterial	Size	Concentration	Substrate	Technique to Measure Migration	Contact media during migration		Contact time	Contact temperature (°C)	Migration values	References
					Standard food simulants as per EU October 2011	Non-standard food simulants				
						simulant D2 i.e., olive oil)				
Cellulose nanocrystals	15–20 nm width and 150–200 nm length	0–5 %	PHB	EU October 2011 Overall migration	**10 % Ethanol** –	– **Isooctane (often used as substitute to food simulant D2 i.e., olive oil)**	10 days 2 days	40 20	175 µg/kg 40 µg/kg	Dhar et al. (2015)
Cellulose nanocrystals	100–200 nm length, 5–10 nm width	5 %	PLA	EU October 2011 Overall migration	Ethanol 10 % –	– Isooctane (often used as substitute to food simulant D2 i.e., olive oil)	10 days 2 days	40 20	100 µg/kg 160 µg/kg	Fortunati et al. (2012b)
Silver-based nanoclay (Bactiblock™)	20 nm	1, 5 and 10 %	PLA	Stripping Voltammetry	3 % Acetic acid	–	10 days	40	0.1 mg/kg	Busolo et al. (2010)

nanoparticles. The polarity of the food simulant was also a key determinant. In the ZnO/BNC system, migration decreased as the ethanol concentration of the simulant increased from 10 % to 50 %, indicating a stronger affinity of ZnO for less polar environments. This polarity-dependent behavior was corroborated in other systems; for example, TiO_2 migration from low-density polyethylene (LDPE) was higher in polar acetic acid than in less polar ethanol.

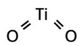
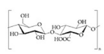
Furthermore, the choice of polymer had a profound impact. Under identical simulant conditions (50 % ethanol), TiO_2 migrated significantly more from a biodegradable polylactic acid (PLA) matrix than from a polyolefin like polypropylene (PP). This suggests that the inherent structure of some biodegradable polymers may facilitate nanoparticle diffusion more readily than conventional, non-polar plastics. Finally, film thickness showed a clear inverse relationship with migration. For example, a 0.6 mm thick TiO_2/PP composite showed no detectable migration, whereas a much thinner (0.05 mm) TiO_2/PE film allowed 0.38 % migration under similar conditions. A greater thickness creates a more complex and tortuous diffusion path for nanoparticles, enhancing the material's overall barrier performance.

5. Challenges with the existing techniques

Based on current literature, one of the major issues is to determine the form of nanomaterial migrants. Several techniques have been used to quantify size and number concentration of NPs. One such technique is SP-ICP-MS. The least size detection limit of SP-ICP-MS was tested and found to be between 22 nm and 32 nm which depends on dwell time and instrument sensitivity during measurement. In one of the works, detection limit of SP-ICP-MS in presence of background noise was tested (Goossens, 2018). Gold nanoparticles (AuNPs) were used as target nanomaterials and dissolved Au was added to mimic background noise. There was an overlap between signals of the background noise and the target AuNPs, which kept on decreasing as dwell time increased. Dwell times of 50 µs were initially utilized, however, it was discovered that they had to be combined into larger dwell times for accurate outcomes in detection algorithm. For 70 ppb of dissolved AuNPs in background, it was nearly impossible to separate target signals from high background noise. Thus, SP-ICP-MS is one of the most promising techniques, but it has shortcomings of low concentration limits and background interferences.

The NanoLyse project, featured in 2013(Newsome, 2014), highlighted an important challenge in the field of quantifying nanomaterials in food matrices after migration. Techniques like ICP-MS and electron microscopy were employed to characterize and detect nanosilver particles in the gastrointestinal fluid simulants. These methods were found essential for metallic nanoscale materials, but the challenge to quantify organic nanomaterials still persists. ICP-MS is a popular method for identifying and measuring small amounts of elements, including FCMs. However, to properly investigate NPs migration, it is important to know their form. With this technique, simulant media, nanoparticles, and other compounds are vaporized into constituent ions by high temperatures (approximately 6000 K or higher) in plasma (Noonan et al., 2014). This implies that data regarding physical conditions of nanoparticles (such as whether they were in individual form, grouped together, or chemically attached) is not retained. ICP-MS can only offer data on overall elemental levels of metals like silver, titanium, or zinc post vaporization. It shows no distinction between ionic forms and metallic nanoparticle forms. This poses major restriction in research concerning nanoparticles, as toxic characteristics can vary based on specific shape and dimensions. For this reason, regulatory authorities have pointed out that relying solely on measuring total elemental concentration (as done by ICP-MS) is not enough to assess potential hazards of nanoparticles. Size-specific methods like TEM or DLS (Dynamic light scattering) should be considered, as they allow to simultaneously obtain morphological and structural information on nanoparticles. Besides these standard techniques, Asymmetric Flow Field-Flow Fractionation (AF4) is a

Table 3
Regulatory migration limits for selected nanomaterials in food contact materials according to EU and US FDA guidelines.

Nanomaterial	Chemical structure	EU SML (Regulation October 2011 + updates)	Nano-specific conditions (EU)	US FDA Regulation	Nano-specific conditions (US FDA)	References
Zn/ZnO	Zn=O	5 mg/kg (as Zn)	No distinction between bulk and nano ZnO	No numeric SML; ZnO is GRAS. Must pass extractives (e.g., ≤0.5 mg/in^2)	Requires FCN or GRAS notification; evaluated case-by-case	(21 CFR 175.300, 2023; EU Reg. 10/2011, 2011; EU Reg. 2016/1416, 2016)
TiO_2		Authorized as additive (FCM 610). No specific SML default 60 mg/kg applies.	TiO_2 nanoparticles not specifically authorized in plastics	Approved as color additive in foods (≤1 % w/w; 21 CFR 73.575).	FDA does not distinguish nanoscale in TiO_2 approvals.	(21 CFR 73.575, 2023; EU Reg. 10/2011, 2011; Younes et al., 2021)
Ti	Ti	Not listed in Regulation October 2011; thus, default limit = 0.01 mg/kg for non-listed substances under precautionary principle	≤0.01 mg/kg applies if not intentionally added or approved	No explicit SML	Nano-Ti use must be notified via FCN and shown to have negligible migration	(21 CFR 177.2600, 2023; EU Reg. 10/2011, 2011)
CNCs		Not listed in EU October 2011. Therefore, default migration limit = 0.01 mg/kg	Nano-cellulose (including CNCs) is not explicitly addressed	No specific SML; if considered cellulose derivative, must comply with 21 CFR 177.1200 and extractives	Nanoform requires safety dossier or FCN; treated differently from bulk cellulose	(21 CFR 177.1200, 2023; EU Reg. 10/2011, 2011)
Ag	Ag	Not in EU positive list. If used, default limit = 0.01 mg/kg food. But EFSA set 0.05 mg/kg for silver zeolite (FCM 1073)	EFSA considers nano-Ag potentially more bioavailable; not currently approved. Default limit of 0.01 mg/kg applies	No specific SML; governed by extractives and indirect additive petitions	Nano-silver is not explicitly approved; FDA evaluates under FCNs. Must prove no significant migration	(21 CFR 174.5, 2023; EFSA Journal, 2020; EU Reg. 10/2011, 2011)

sophisticated method commonly employed to separate and analyze nanoparticles by size and molecular weight, providing a non-invasive method to characterize various types of nanoparticles in complex mixtures. The separation principle refers to relative mobility of constituents within the flow field created by liquid passing over the membrane and crossflow across channel. AF4 offers several advantages in comparison to traditional size-exclusion column chromatography. In addition to separating soluble components, AF4 can also separate colloidal components over a wide range of concentrations. Due to the lack of column material, AF4 exhibits little or no direct interaction that could influence elution. The ability to accurately separate nanoparticles without the use of harsh chemicals is particularly useful in research on the movement of nanoparticles from food-contact materials (Corps Ricardo et al., 2021). AF4 can be significantly affected by sample matrix composition, making it challenging to examine the movement of nanoparticles from food-contact materials. There is a potential for disruption in the fractionation process and the subsequent identification of nanoparticles when food matrixes contain emulsions, oils, and intricate mixtures. Consequently, it is difficult to distinguish and precisely quantify nanoparticles in practical food substitutes, which typically combine organic and inorganic ingredients (Ventouri et al., 2022). AF4's operational flexibility in terms of carrier solution composition and crossflow gradients allows for optimization of separation conditions, which enables to preserve native structural integrity of organic compounds. Thus, making it more advantageous than conventional separation techniques.

Although the EU October 2011 regulations include guidelines for both overall migration and specific migration, most scientific literature on organic nanomaterials focuses primarily on overall migration values. This trend is largely due to the challenges in finding analytical methods to measure specific migration accurately. None of the reviewed studies explore the assessment of structural and morphological features of the migrating organic nanoparticles; moreover, as already stated, the regulations lack of the values of specific migration limits for most of the organic nanomaterials. Suitable analytical techniques such as SP-ICP-MS (Echegoyen et al., 2016), AF4 (Lambré et al., 2021), and AAS (Huang et al., 2011), etc.) to measure the specific migration were considered for only metallic, metal oxides and few carbon based nanoparticles. A 2017 article by Jokar et al. (Jokar et al., 2017) highlighted six unresolved issues regarding nanomaterial migration from food packaging, pointing out the absence of standardized methodologies and the discrepancies in existing theoretical models, which primarily rely on diffusion mechanisms, while also noting conflicting results in the literature about migration levels and the lack of detection limits in many studies.

Additionally, the literature indicates that there are different methods for measuring migration, but the data available and the diversity in experimental methods makes the comparison of results more challenging. The EFSA and other regulatory agencies have proposed the necessity of standardized testing procedures to guarantee consistency in research. It is challenging to make definite conclusions about the safety and behavior of nanomaterials in food packaging due to inconsistent reporting on factors such as nanoparticle size, aggregation states, and matrix interactions.

6. Conclusions

Nanotechnology offers promising opportunities for food packaging applications. However, the integration of innovative technologies and materials necessitates risk assessment based on specific migration limits. This review underscores that, although significant advancements have been achieved in the development of analytical methodologies to quantify the migration of inorganic nanoparticles such as silver (Ag), TiO_2, and zinc oxide (ZnO), there remains a lack of similar methodologies for organic nanomaterials including nanocellulose, nanochitin, and polymeric nanoparticles. The challenge of detecting organic nanomaterials constitutes a critical gap in current literature and regulatory frameworks. This obstacle impedes risk assessment and the establishment of specific migration limits (SML) by regulatory authorities. Despite the considerable potential of these materials in food packaging, uncertainty in establishing comprehensive regulations—primarily due to limited information on their migration—serves as a significant barrier to commercialization. The disparity between the rapid pace of innovation in nanomaterial discovery and the slower development of relevant analytical techniques for measuring the migration of organic nanomaterials. Addressing this gap will enhance regulatory frameworks, highlighting the pressing need for innovative testing protocols. Furthermore, the development of standardized methodologies can foster collaboration among industry, academia, and policymakers, thereby advancing a comprehensive understanding of the safety profiles of organic nanomaterials.

Table 4
Normalized migration values for food simulant contact area of 1 cm^2 for various nanocomposites.

Nanocomposite	Thickness (mm)	Area of simulant contact (cm^2)	Contact time	Contact temperature (°C)	Aqueous Food Simulants		Initial mass of nanomaterial in composite before migration (μg)	Mass of migrated nanomaterials (μg)	Normalized initial mass of nanomaterials for 1 cm^2 contact area (μg)	Normalized migration values for 1 cm^2 contact area (μg)	Ref.
					Standard food simulants as per EU October 2011	Non-standard food simulants					
ZnO/BNC	9	0.635	15 days	60	10 % Ethanol	–	2840	8.4	4470	13.2	(Silva et al., 2023)
			15 days	60	20 % Ethanol	–		5.1	4470	8	(Silva et al., 2023)
			15 days	60	50 % Ethanol	–		2.5	4470	3.9	(Silva et al., 2023)
ZnO/Gelatin	-	50.24	5 days	30	–	Bread[a]	64	32	1.2	0.6	Parida et al. (2022)
Zn/LDPE	0.04	12.25	2 h	70	–	Distilled water	400	200	32.7	16.3	Huang et al. (2017)
			2 h	70	95 % Ethanol	–		20	32.6	1.6	Huang et al. (2017)
			2 h	70	10 % Ethanol	–		88	32.6	7.2	Huang et al. (2017)
Ag/PP	–	6	10 days	40	–	Ultrapure water	54.9	0.6	9.2	0.1	(Corps et al., 2021)
			2 h	70	3 % Acetic acid	–		0.3	9.2	0.1	(Corps et al., 2021)
TiO_2/PP	0.6	1	10 days	50	50 % Ethanol	–	540	0.0006	540	0.006	(Bastardo-Fernández et al., 2024)
TiO_2/PE	0.05	1	8 h	100	3 % Acetic acid	–	24	0.6000	24	0.6	Lin et al. (2014)
			8 h	100	50 % Ethanol	–		0.0900	24	0.09	Lin et al. (2014)
Ti/LDPE	0.04	12.25	2 h	70	–	Distilled water	450	12	36.7	0.9	Huang et al. (2017)
			2 h	70	3 % Acetic acid	–		22	36.7	1.7	Huang et al. (2017)
			2 h	70	–	95 % Ethanol		0.8	36.7	0.06	Huang et al. (2017)
TiO_2/PLA	–	16	45 days	40	50 % Ethanol	–	16	15	1	0.9	Yang et al. (2019)
CNC/PLA	0.04	10	10 days	40	10 % Ethanol	–	250	0.9	25	0.09	Fortunati et al. (2012b)
			2 days	20	–	Isooctane (often used as substitute to food simulant D2 i.e., olive oil)		1.1	25	0.1	Fortunati et al. (2012b)

[a] Refers to the real food and not an aqueous food simulant.

CRediT authorship contribution statement

Mohammed Dilsad Izrayeel Ansari: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Laura Principato:** Writing – review & editing, Validation, Methodology, Conceptualization. **Luigi De Nardo:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **Carlo Punta:** Writing – review & editing, Validation, Supervision, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodcont.2025.111707.

Data availability

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

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