# Release of Engineered Nanomaterials from Polymer Nanocomposites: Diffusion, Dissolution, and Desorption

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ABSTRACT: Polymer nanocomposites—polymer-based materials that incorporate filler elements possessing at least one dimension in the nanometer range—are increasingly being developed for commercial applications ranging from building infrastructure to food packaging to biomedical devices and implants. Despite a wide range of intended applications, it is also important to understand the potential for exposure to these nanofillers, which could be released during routine use or abuse of these materials, so it can be determined whether they pose a risk to human health or the environment. This article is the first in a series of two that review the state of the science regarding the release of engineered nanomaterials (ENMs) from polymer nanocomposites. Two ENM release paradigms are considered in this series: the release of ENMs via passive diffusion, desorption, and dissolution into external liquid media and release of ENMs assisted by matrix degradation. The present article focuses primarily on the first paradigm and includes (1) an overview of basic interactions between polymers and liquid environments and a brief summary of diffusion physics as they apply to polymeric materials; (2) a summary of both experimental and theoretical methods to assess contaminant release (including ENMs) from polymers by diffusion, dissolution, and desorption; and (3) a thorough, critical review of the associated body of peer-reviewed literature on ENM release by these mechanisms. A short outlook section on knowledge gaps and future research needs is also provided.

KEYWORDS: nanocomposites, release, migration, environmental health and safety, nanoparticles, diffusion, exposure
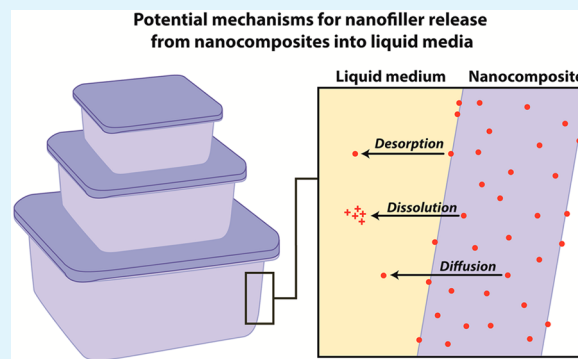
I. INTRODUCTION

Polymer nanocomposites (PNCs) are polymer-based materials that incorporate filler elements possessing at least one dimension in the nanometer range. Owing to the physical and chemical properties that can manifest in matter on this length scale, PNC materials can exhibit superior or unique properties compared with similar materials fabricated from polymers alone. Some of these potential benefits include impressive gains in mechanical strength;[1] elevated flame resistance;[2] attenuated mass transport kinetics (i.e., heightened gas barriers);[3] enhanced biodegradability;[4] and a range of customizable optical, electronic, or biocompatibility effects, such as changes in transparency,[5] fluorescence,[6] conductivity,[7] dielectric permittivity,[8] and biocidal activity.[3] Because of the potential for PNCs to improve upon existing structural and functional materials, they are being explored for use in a wide variety of commercial product applications, as described in Table 1. In some cases, PNC materials, or products fabricated from them, are already commercially available.

Although PNC materials may have beneficial properties, it is important to understand whether engineered nanomaterials (ENMs) incorporated within or on the surface of plastics could become released during routine use, storage, or disposal of these materials so that it can be determined if the released

ENMs could pose a risk to human health or the environment. ENM release is relevant for PNC materials to which humans will potentially be exposed through ingestion or absorption into human tissue, such as those intended for food packaging (e.g., beverage bottles, storage containers), potable water infrastructure (residential polyvinyl water pipes), or biomedical devices (e.g., surgical implants, catheters, wound dressings). A recently published article[9] on analytical methods to assess ENM release from food contact materials has organized potential release mechanisms into four broadly defined and interrelated categories: diffusion, dissolution, desorption, and matrix degradation, which is reproduced in Figure 1. The likelihood of ENM release from PNCs under various conditions, as well as the composition, morphology, and toxicological profile of released ENMs or residuals, is predicated on a sufficient understanding of these potential mechanisms. Because of the increasing interest in the potential applications of nanocomposites and, therefore, their safety to consumers, research related to ENM release has intensified in recent years, and thus,

Table 1. Some Commercial Sectors that May Benefit from PNC Materials and Example Applications[a]

category	potential applications	expected benefits	example ENMs
construction and infrastructure	exterior paints and coatings, air conditioning, water and sewage pipes, adhesives, sound proofing	hydrophobicity/self-cleaning, energy efficiency, strength and durability, reduced microbial growth	MONPs, SiO_2 NPs, graphite, AgNPs CNTs, CNFs
vehicles and aerospace	energetic materials, ablative materials, automotive parts and materials	heat shielding, light weight, high strength components, wear and abrasion resistance	metal NPs, MONPs nanoclays, CNTs, CNFs, graphite
biomedical	tissue engineering, biomolecular detection kits and monitors, antimicrobial materials, medical devices	biocompatibility, accelerated tissue growth, rapid detection of bioanalytes, reduced microbial growth	nanoclays, graphene hydroxyapatite, polysaccharides, AgNPs, MONPs
packaging materials	antimicrobial packaging, high barrier applications, ecofriendly packaging, contaminant detection and environmental monitoring, electromagnetic shielding	enhanced barrier to gases, increase in strength/stiffness, oxygen scavenging, reduced microbial growth, biodegradability	nanoclay, SiO_2 NPs, AgNPs, MONPs, CNTs, polysaccharides
electronics	transistors, antistatic coatings, conductive materials, sensors, photovoltaics, energy/memory storage	high electrical and thermal conductivity, electromagnetic shielding, energy efficiency, flexible display materials	CNTs, graphene, semiconducting nanocrystals, metal nanowires
consumer goods	sports equipment, food storage containers, appliances, clothing and textiles	improved strength, toughness, stiffness, scratch resistance; reduced microbial growth; biodegradability; flame retardancy	nanoclay, CNTs, AgNPs, MONPs

[a]Abbreviations in this table: NPs, nanoparticles; MONPs, metal oxide nanoparticles; CNTs, carbon nanotubes; AgNPs, silver nanoparticles; CNFs, carbon nanofibers.

the accumulated knowledge about these mechanisms has grown substantially.

This article is the first in a series of two that provide a collective overview of the state of the science of the potential release of ENMs from PNC materials, including an accounting of potential release mechanisms. We have organized this material by dividing the discussion into two separate ENM release paradigms: (1) release of ENMs via passive diffusion, desorption, and dissolution into external liquid media, and (2) release of ENMs assisted by matrix degradation. Release via passive diffusion, desorption, or dissolution generally involves short-term or prolonged exposure of the PNC material to a liquid environment (either a pure liquid; simple suspension; or a complex, liquid-based product, such as a soup), during which ENMs or their dissolved residuals spontaneously relocate from an area of high concentration (the PNC) to an area of low concentration (the external environment). An example of this scenario would be the release of ENMs from a PNC food packaging material into a liquid-based food item or beverage. Release due to matrix degradation includes release following either destructive mechanical or chemical changes to the host material, such as abrasion or photooxidation; such pathways would typically be most relevant to PNC applications such as construction or infrastructural materials, vehicles, and consumer products expected to be subjected to prolonged wear or UV-exposure. The present article focuses on the first release paradigm, whereas the second article[10] will focus on the effects of matrix degradation on ENM release.

II. PRINCIPLES OF DIFFUSION IN POLYMERS

In the context of ENM release from PNCs, and as depicted in Figure 1, the *diffusion* release mechanism is one in which whole ENMs relocate from the interior of a PNC to the external medium. This is contrasted with the *dissolution* mechanism, in which internally embedded or surface-bound ENMs dissolve into constituent atoms/ions, which may diffuse into the external medium, and the *desorption* mechanism, in which ENMs adsorbed at the polymer-liquid interface spontaneously partition into the liquid. In diffusion and desorption, released ENMs remain in nanoparticulate form, although their morphology, composition, or surface characteristics may alter during or after the release process. In dissolution, the ENMs are no longer particulate in nature after the release process, but subsequent reformation of nanoscale particles from the dissolved residuals is possible if there are favorable conditions. Note that the term "desorption" is frequently used to describe the inverse of "sorption": that is, both bulk and surface removal of a chemical species. However, in this article, we use "desorption" only to refer to "de-adsorption"; the complementary "de-absorption" process is embodied in the diffusion release mechanism. A recent review by Noonan et al. on analytical methods to detect ENMs released from food contact materials describes these mechanisms in more detail.[9]

We have chosen to frame this review around the diffusion mechanism because it is the primary way, short of destruction of the matrix (discussed in a subsequent article), that ENMs located in the interior of a polymer may become released intact, with possible changes to morphology, composition, or surface characteristics, into the external medium. Understanding the propensity of whole ENMs to become released is desirable because the unique chemical and physical properties associated with the nanoscale may lead to toxicological or environmental end points that could be significantly different from those of
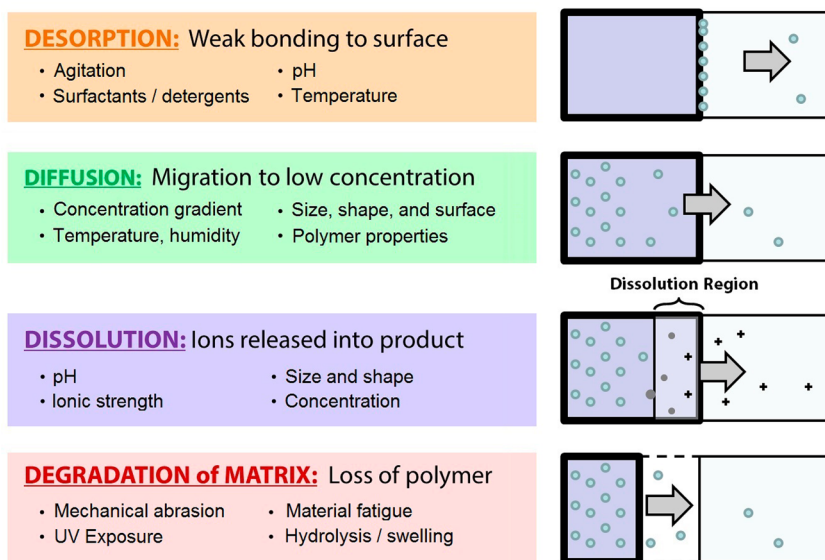
Figure 1. Four potential mechanisms for ENM release from PNC materials proposed by Noonan et al.[9] and some factors that may impact their relevance to a release scenario. *Desorption* is the spontaneous release of ENMs bound at the polymer-environment interface. *Diffusion* is the entropically driven mass movement of ENMs located within the interior of a PNC to the external environment or other low concentration regions. *Dissolution* is the gradual transformation of whole ENMs located within the interior of a PNC, or on its surface, into ionic residuals, which then diffuse into the external medium. Release of ENMs via *degradation of the matrix* would occur following any process that either destroys or sufficiently alters the host matrix such that ENMs are no longer rigidly fixed to the interior of the matrix. Note that release of an ENM in any scenario may occur by multiple mechanisms simultaneously. Adapted with permission from Noonan et al. *Comp. Rev. Food Sci. Food Saf.* **2014**, *13*, 679−692. Copyright 2014, John Wiley and Sons.
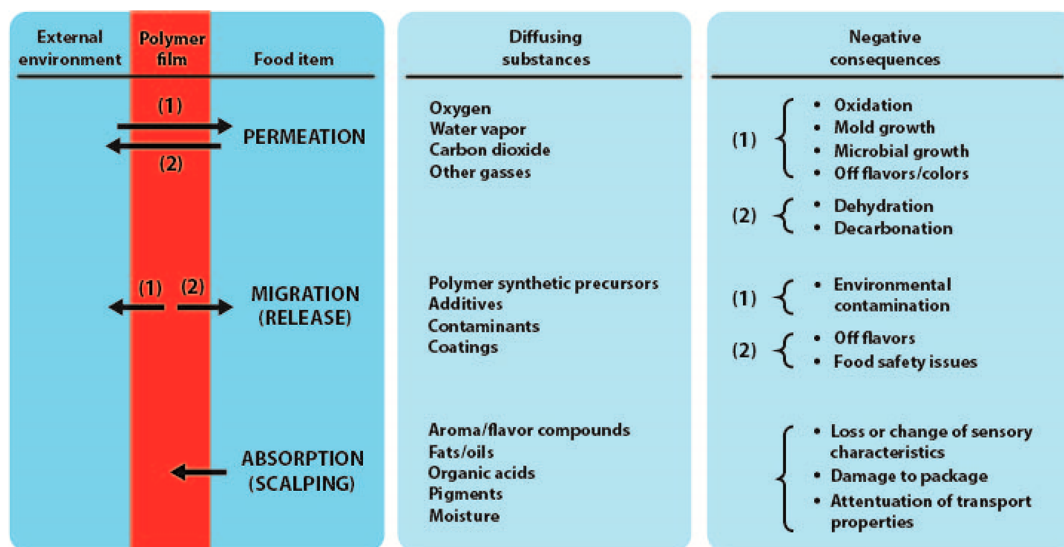

Figure 2. Depiction of some of the potential interactions between a food contact polymer film and both the contained food and the external environment. These processes can be generalized to nonfood environments, as well. Adapted from Brody, A. *Food Technol.* **2007**, *61*, 82−84.[12]

macroscale or dissolved materials with the same elemental composition. Nevertheless, desorption and dissolution likely also play significant, if not dominant, roles in the ability of ENMs or their residuals to become passively released into the surrounding environment. Practically speaking, it may be difficult to experimentally distinguish between these mechanisms using current analytical techniques. A discussion of experimental release studies at the end of this section presents some of these challenges as well as recent attempts to solve them.

The diffusion of an ENM through a polymer matrix and its subsequent release to the environment together constitute a process known as *migration*. For a conventional molecular scale migrant, migration is a thermodynamically favored, but usually a kinetically slow, process that is dependent on a number of interrelated factors. These factors may include those specific to the migrant (molecular weight, polarity), the host polymer (molecular weight, crystallinity, density, degradation state), or the environment (polarity, temperature, humidity). Migration of ENMs should be governed by many of the same principles that determine the mass transfer of molecular-scale migrants, although complicating factors may be at play that give rise to additional uncertainties. For instance, ENMs have size polydispersity that may introduce statistical complexity into

diffusion kinetics, and they also have surfaces coated with surfactants that could greatly impact their rate of motion through the host polymer. They may also have complex interactions with the host matrix such that conventional (i.e., Fickian) diffusion models may not apply. (Note that some of the potential ENM release mechanisms shown in Figure 1 may not be properly categorized as "migration", which typically includes diffusion and partitioning components. In this article, the term "migration" will be used primarily when discussing the general phenomenon of contaminant release from a polymer.[11] When specifically referring to release of ENMs by one or more of the mechanisms depicted in Figure 1, more generic terminology will be used.)

In the interest of disentangling some of these issues and to provide background for readers new to the area of contaminant release from polymer materials, this section will begin with a review of molecular diffusion physics in polymers, paying special attention to how they may relate to nanoscale migrants. This will be supported by an overview of basic interactions of polymers with liquid media.

Interactions between Polymers and Liquid Media. Consider a thin polymer film intended for a food packaging application in which the film separates the (predominantly liquid) food from the external environment (Figure 2). A primary function of the film in this scenario is to prevent substances in the external environment from contaminating the food and to prevent substances in the food from escaping to the external environment. In general, any solid barrier film is sufficiently impermeable to offer complete protection against the mass movement of macroscale particles such as dust and dirt. On the other hand, when a substance is on the molecular scale (e.g., aroma molecules, gases, solvents, etc.), thin film materials will not always provide a suitable barrier: compared with materials such as metal or glass, organic polymers have a comparatively large number of free volume spaces, sometimes even large enough to accommodate large molecules, and so permeability of polymers in food contact applications presents a constant challenge from both an engineering and safety standpoint.

The inherent free volume of polymers can enable several types of deleterious interactions with environmental matrixes, including permeation, migration, and absorption, as shown in Figure 2. This figure also lists example chemicals and potential negative consequences related to our food packaging material example that could be associated with these three general classifications. (These consequences are presented in a food context, but they can be generalized to other applications, as well.) In permeation, undesired substances from the external environment pass entirely through the film into the packaging interior, or vice versa. Migration is characterized by the bulk movement of a substance from the interior of the film to the interface between the polymer and either the external environment or (in this case) the liquid food matrix, whereupon it is released into the respective medium. Absorption is the reverse process, in which a substance localized in either the food matrix or external environment penetrates some distance into the polymeric interior, but typically not far enough that it can make it through to the opposite side. Although permeation is typically most relevant to gases, migration and absorption are the main processes considered when the diffusing substance is a larger molecule. This is the case because the diffusion rates of large molecules are too small to facilitate complete translocation across the

entire width of the polymer layer on relevant time scales. Note that although permeation is most relevant to thin, freestanding polymer films, migration and absorption, which do not require transit across the entire width of the material, are relevant to a broader range of polymeric material forms.

Molecular Principles of Diffusion in Polymers. A PNC material may feature ENMs either as filler elements (distributed throughout the interior of the material) or as coatings (adhered to the surface of the material), and the location of the ENMs will likely play a role in the mechanism (and, hence, kinetics) of release. ENMs located at the interface between the PNC and the external liquid environment could become released directly by simple desorption or dissolution. Conversely, ENMs distributed throughout the interior of a PNC would have to first diffuse from their starting positions (whole or as dissolved ions) to the interfacial boundary before they could become released, which is a significantly more complex process. Prior to presenting literature studies that have explored these possibilities, it is worth reviewing the basic physics of diffusion in polymeric matrixes because this will be a starting point for understanding experimental data.

The diffusion of any substance through an amorphous polymer matrix is, as a first approximation, treated no differently from diffusion through a fluid. Because diffusion is fundamentally an entropically driven process, statistical considerations demand that diffusing molecules move, on average, from an area of high concentration to an area of low concentration, and the rate at which the diffusing substance moves through an area element per unit time (the diffusion flux) is assumed, under the simplest, Fickian model, to be proportional to the concentration gradient at that point and directed perpendicular to the gradient plane. The proportionality constant, called the diffusion constant, is dependent on factors such as the size and shape of the diffusing molecules, the viscosity of the transmission medium, and the temperature. In a polymer, the diffusion constant is usually interpreted as being related to the ability of diffusing molecules to hop between transient free volume holes formed as a result of random chain movement. Therefore, the polymer molecular structure, crystallinity, degree of cross-linking, and so forth will all play a role in the diffusion rate.

In principle, the rate of diffusion in a polymer is also limited by the maximum solubility of the diffusing substance in the polymer (i.e., transition medium) under the conditions tested. Solubility is a thermodynamic factor determined in large part by the energy of interaction between diffusing molecules and the transmission medium. When the transmission medium is homogeneous, solubility may be less important because presumably, the substances are already dispersed at concentrations below the solubility threshold, even in regions where the concentrations are the highest. However, if diffusion occurs in biphasic or heterogeneous systems, through regions in which the solubility of the migrating substance is far less than its predicted concentration, then this solubility parameter can become a rate-limiting factor. This is particularly important when determining the permeation rates of oxygen or water vapor through polymer films (or neutral substances across a biological membrane), where the concentration of the substance outside the film is likely to be much higher than the maximum concentration of the substance that the interior of the film can tolerate. In these cases, a partition coefficient is typically defined that describes the (solubility-limited) concen-

tration of the diffusing molecule at the interfacial boundary between the polymer and the external environment.

Given these considerations, the overall diffusion rate of a substance through an amorphous polymer is based on a host of factors, including attributes of the diffusing substance (size/weight, polarity, charge, concentration, solubility), attributes of the diffusion medium (crystallinity, viscosity, density, molecular weight, polarity, tacticity, the presence of copolymers or other additives), and extrinsic factors such as temperature and pressure. Temperature, in particular, can influence the diffusion rate not only by affecting thermodynamic interactions between the diffusing substance and the transmission medium but also by altering the structure and properties of the medium itself; this is especially the case in polymers, which can have very different transport properties, depending on whether the temperature is above or below the polymer's glass transition temperature. In addition, the external environment can play a role in mass transport properties, as humidity or the presence of other migrating substances can cause swelling or plasticization of some polymer types, which in turn can impact the solubility of the diffusing substance as well as the polarity, viscosity, or density of the diffusion medium.

The diffusion of ENMs in polymers generally involves additional complexities. When it comes to determining whether ENMs embedded in a polymer may be able to diffuse on time scales relevant to consumer safety, the factor of greatest importance is likely the size of the particles. In general, larger-sized molecules would be expected to have slower diffusion rates. This is because the collisional cross section area increases with a molecule's size, which means there is an inverse relationship between size and the mean distance a molecule can travel before undergoing a collision that slows it down or alters its trajectory. In a semirigid condensed phase such as in a polymer, there also will be fewer free volume holes generated by random chain movement able to accommodate diffusants of larger size. Solubility factors related to ENMs are likely also size-dependent, as the amount of surface area available to interact with the external medium will create thermodynamic driving forces (minimization of surface free energy) that can either favor or inhibit mass movement. It is also worth noting that surface energy considerations and, hence, particle size may impact the fate of any released particles by influencing postrelease processes such as aggregation, dissolution, sedimentation/flocculation, or Ostwald ripening.

It has been suggested that a molar mass of ~2500 g/mol is the upper size limit where the diffusion rate of "small molecules" in polymers is large enough to be practically relevant.[13] ENMs do not have molecular weights, per se, but taking the case of a spherical silver nanoparticle, as an example, with an assumed density identical to that of conventionally manufactured silver (~10.5 g/cm^3), a particle diameter of ~1.33 nm is equivalent to this 2500 g/mol limit. This would suggest that diffusion rates of all but the smallest ENMs can be considered effectively zero when dispersed within polymers. However, it is unclear whether this molecular weight limit is applicable to ENMs or whether the diffusion is governed by a different set of physical rules. In addition, the inherent size polydispersity of ENMs means that even if the mean particle size is above any critical limit for a safety-relevant diffusion rate determined experimentally or theoretically, there could be a significant portion of ENMs with diameters below this limit in the tailing regions of the size distribution. Furthermore, efficient desorption of ions, atomic clusters, or nanoscale

fragments from the surfaces of "effectively stationary" nano-fillers could have higher diffusion rates than the parent particles, as issue that is not present for molecular additives and fillers. These are examples of unique issues related to nanoscale PNC additives, and methods which can be used to investigate such processes will be a key element of assessing exposure to ENMs from commercial PNC materials.

III. METHODS TO ASSESS ENM RELEASE

Experimental Methods. When a contaminant diffuses from the interior of a polymeric host material to the interface between the material and the external environment (in this case, a liquid medium), and then partitions into the environment, this process is called migration. While it may be acceptable to assume "100% migration" as an upper-limit estimate of exposure (i.e., all of the potential contaminant in the material is released), acquiring empirical migration data will ultimately provide more insight into the mechanisms that control the migration process, as well as provide a far more realistic quantitative picture of mass transfer. This section describes some commonly used methods to experimentally assess or theoretically predict contaminant release from polymers into liquid media, paying specific attention to strengths and weaknesses of applying these techniques to ENMs.

One experimental approach for the assessment of migration from thin polymer films is to submerge sections of test films containing the potential contaminant in a fluid into which the release characteristics need to be known; when the test film is a potential food contact material, this fluid is usually one that simulates the chemical or physical properties of a food class (e.g., dilute acetic acid to represent an acidic food), but other biological or environmental media may be used to assess potential migration for plastics intended for other applications. Samples are stored under specific conditions (e.g., time, temperature) and then the fluid is assayed for the presence of the migrant by a suitable analytical method. This experimental approach has the advantage of being straightforward and requiring minimal sample preparation, although the amount of exposed film surface area needed to obtain a high enough measurable released analyte concentration to be quantifiable, as well as practical details such as the melting point of the host polymer, will be important considerations in the experimental design. The submersion method also requires prefabrication or procurement of polymer composites containing the contaminant of interest in precisely known concentrations, which poses a problem for laboratories that do not have the proper mixing and extrusion equipment to do this. As a result, the submersion method is perhaps more commonly relevant to safety assessments of commercial materials that are already on the market than to basic research to understand potential migration rates of specific test compounds. Detailed descriptions of the submersion method, including testing conditions and parameters, experimental setups, and food simulating media recommended for migration testing of a food contact material by the US Food and Drug Administration and by the European Commission, are provided in the cited references.[14,15]

For research on ENM release via a diffusion mechanism, the submersion method is an attractive option, but here again, obtaining test materials can be problematic. If fabricating materials (either the ENM additives or the composites) in-house is not an option, they may be obtained from commercial or third party sources, but characterization data may be
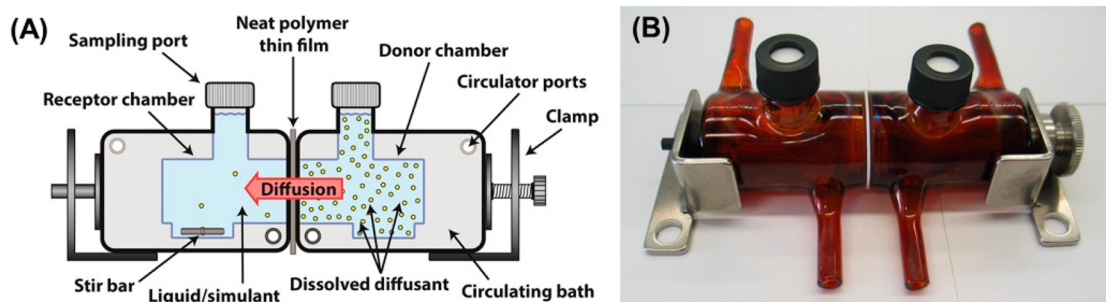
Figure 3. Schematic (A) and photograph (B) of a liquid diffusion cell, which may be used to assess the rate of diffusion of a dissolved substance across a thin polymer film. The diffusion cell depicted in panel B has a total liquid volume per side of 3.4 mL. Cells with larger volumes are commonly encountered, but small volumes may be attractive for ENM diffusion experiments due to the expense of acquiring good quality ENMs.

incomplete or unavailable for these materials, which introduces considerable uncertainty into analysis of results. The need for polymer composite materials also places a practical limitation on the number of experimental conditions that can be tested, as obtaining ENM-incorporated materials in sufficient quantities to do multiple tests can be time-consuming and expensive. An additional practical disadvantage when it comes to studying release mechanisms is the possibility of incidental ENMs located on the PNC surface; such surface-bound particles may become released into the liquid medium immediately after initialization of the release experiment and thus obscure diffusion-assisted release kinetics of ENMs. Sectioning PNC films for testing may also result in mechanical release of particles from cut edges into the liquid test medium, which could likewise interfere with measurability of diffusion-based release kinetics.

An alternate experimental method that could be used to assess diffusion-assisted release of ENM from plastic films into liquid media is a liquid diffusion cell. In this experiment, a neat film composed only of the polymeric host material is inserted between two chambers filled with the liquid test medium, where one of the chambers is also charged with the potential migrant (Figure 3). Kinetics of migrant transit across the polymer film are then assessed by removing aliquots of the liquid medium from the opposite chamber at regular time intervals.

The liquid diffusion cell method has several advantages and disadvantages compared with the submersion method discussed above. One advantage of this technique is that films containing the migrant do not need to be fabricated or acquired, and therefore, numerous test conditions (temperatures, times, etc.) can be readily assessed. This could be useful for ENMs because the influence of parameters such as ENM size and shape could be studied without the need to generate PNCs containing ENMs with each variation. Moreover, because the diffusion cell method utilizes neat films and ENMs in pristine condition, identifying relationships between ENM structural parameters and release rate may be a simpler task than in the submersion experiment, in which the impact of polymer processing on the ENM properties may be a complicating factor. For example, a fundamental evaluation of the impact of ENM size on the release rate may be difficult with the submersion method because the high temperatures and pressures needed to create the PNC films may give rise to ENM aggregates or other particle-based structural changes within the polymer matrix that alter the diffusion kinetics compared with well-dispersed (individual) particles. Whether the diffusion cell method offers

a solution to this dilemma is not clear, but it seems to be worth investigating.

One of the most notable disadvantages of the diffusion cell method is that experiments will likely take longer than those based on extraction methods because potential migrants have to cross a larger distance of polymer from their starting point (Figure 3A, donor chamber) to become released into the assayed test medium (Figure 3A, receptor chamber). This may render the diffusion cell method useless for ENM release measurements because ENM diffusion is expected to be extraordinarily slow for all but the smallest particles (vide infra), and therefore, ENMs may not be able to pass through the full thickness of a thin film in sufficient quantities to be measured on any practical time scale. The problem of low concentration of detectable analyte is exacerbated by the fact that the diffusion cell method offers only a small amount of film surface area from which ENM release can occur, at least compared with the submersion method, in which numerous film sections can be added to a single test vessel simultaneously. Another potential disadvantage of the diffusion cell method for PNCs is that it may neglect the full impact of film processing parameters on the observed ENM release rate. Although this was highlighted as a potential advantage in the preceding paragraph, it may also be a disadvantage because diffusion of pristine particles across a neat film may not be a realistic model of ENM dispersion in and release from a commercially relevant PNC material. Along those lines, the kinetics of ENM release determined using the diffusion cell method will not include contributions due to surface desorption of ENMs incidentally located on the PNC surface, since the pristine polymer film used in this experiment obviously has no surface-bound ENMs. Finally, the need to use surfactants or stabilizers to disperse pristine ENMs in the liquid test medium or the polymer matrix (in the case of the submersion method) may also impact partitioning or diffusion rates. The dispersion of free ENMs in the donor chamber will itself be a remarkably complex process, and how the stability of ENMs in the donor chamber impacts their uptake by and transmission through the polymer film needs to be researched. Until the impact of all of these parameters on the type and magnitude of polymer-ENM interactions is better understood, it remains uncertain which experimental method is the best to assess release of ENMs from PNC materials. To our knowledge no published studies on ENM release from polymers have utilized a diffusion cell approach.

Theoretical Approaches. Conventional migration experiments are time-consuming, expensive, and prone to error due to the complexity of the experimental design and the low levels

of migrant typically being measured, particularly when the diffusion rate is anticipated to be slow. An alternative method of determining release from plastics is theoretical modeling based on physicochemical properties of the host material and basic diffusion physics. Theoretical modeling of mass transport within solids is complex but has received significant research attention both for food[16] and electronics[17] packaging.

The conceptual starting point for most first-principles theoretical treatments (i.e., those based on fundamental laws of physics) is that amorphous organic polymers behave in some ways like viscous fluids. As such, diffusion of small molecules in polymers follows, to a good approximation, Fick's Laws of Diffusion. In principle, if one had a method to predict the diffusion constant of a potential migrating substance as well as the likelihood that the migrating substance can partition from the host matrix into the surrounding liquid environment (represented by the "partition coefficient"), then the concentration of the migrant anywhere and at any time could be precisely determined. From this, the extent of release into the external liquid medium under a particular use condition could be predicted without any need for experiment. Unfortunately, because of the complex nature of migrant-polymer interactions (vide supra), predicting the diffusion constant and solubility parameters of a particular substance in a particular polymer is very challenging, particularly when the diffusant is a large or complex molecule, and so in practice, exclusively first-principles models of diffusion or migration are not widely used.

Semiempirical models are often preferred to model release of a substance from a polymer because they require only superficial knowledge of physics and rely on simple parameters and equations that can be applied to a diverse variety of polymer/migrant systems. A semiempirical model often begins with first-principles ideas but is fundamentally built around experimental data collected for real systems and then applied generally. The primary weakness of semiempirical modeling approaches is that predicted results may have poor precision, particularly when a target metric is outside the empirical parameters used to construct the model. This is not necessarily concerning in a regulatory context, in which ensuring that release remains below a certain, specified safety threshold is often more important than determining the exact quantity of released material. In such cases, one needs only to design a conservative model that ensures that any deviation of experimental diffusion or migration values from the predicted value always, to within an acceptable degree of tolerance, remains below the identified safety threshold.

There are numerous semiempirical models that can be used to estimate diffusion of a substance into a liquid medium from polymers. Currently, the most widely used, at least for food contact applications, is the Piringer Model, originally developed by Otto Piringer and co-workers at the Fraunhofer Institute for the diffusion of n-alkanes in polyethylene.[18] This model relates the "upper bound" (95% confidence limit) predicted diffusion constant, D, to a single molecular parameter, the migrant's molecular weight, M, which is a surrogate for the molecular size, as well as a polymer-specific parameter, A_p, and temperature, T, as shown in the following equation:

$$D_p^* = 10^4 \exp\left(A_p - 0.1351 M_r^{2/3} + 0.003 M_r - \frac{10454}{T}\right)$$
(1)

Using experimentally determined A_p values,[19] this model provides conservative estimates of diffusion constants, which

together with estimates for partition coefficients can be used to predict migration rates into the surrounding media. The coefficients in eq 1, as well as the published A_p values, are based on migration data accumulated for small molecule migrants of many molecular weights, assessed at different temperatures in numerous different polymers. This body of migration data is continually being expanded so that these A_p values can be further refined. Further development and refinement of semiempirical models continues to be an active area of research.[20−23]

Although diffusion and migration models can be useful tools to help assess mobility of a substance in or release from a polymer, care must be taken to ensure the model being used is appropriate to the system being studied. Diffusion of substances through highly crystalline, glassy polymers, for example, may be extensively non-Fickian in nature, which could give rise to large errors for semiempirical models formulated from data acquired for amorphous polymers. Importantly, existing semiempirical models were not developed to explicitly handle ENMs. This incompatibility may simply be a practical issue, such as needing to reformulate expressions such as eq 1 to be based upon parameters that are relevant to nanomaterials (e.g., what meaning does molecular weight have for a nanoparticle?). Alternatively, new models may be needed if diffusion of nanoscale particles in polymers is non-Fickian. In either case, the extent to which migration models, particularly first-principles models, can be used to estimate release rates of nanosized filler elements from PNCs into liquid media remains uncertain and needs to be studied in more detail. Recent efforts to develop diffusion-based release models specifically designed for ENMs is the topic of the next section.

IV. REVIEW OF ENM RELEASE LITERATURE

Theoretical Estimation of ENM Release from PNCs into Liquid Media. One of the early attempts to model the diffusion rates of ENMs in polymers (and subsequent release) was presented by Šimon et al.,[24] who modeled the diffusion of nanoparticles in polymers such as low density polyethylene (LDPE), high density polyethylene (HDPE), polypropylene (PP), polyethylene terephthalate (PET), and polystyrene (PS). The model assumes Fickian diffusion and calculates the diffusion coefficient (D) on the basis of the Stokes−Einstein relation, which describes the mobility of a spherical particle in a fluid:

$$D = \frac{K_B T}{6\pi\eta\alpha}$$
(2)

where K_B is the Boltzmann constant, T is the absolute temperature, η is the dynamic viscosity of the amorphous phase of the polymer, and a is the particle radius. The authors reasoned that if the diffusion constant is known and the direction of diffusion of any single particle is random, a "radius of diffusion" (r) could be specified which describes the maximum distance in any direction a particle could possibly travel through the host polymer away from its starting position (Figure 4A) during a given time. On the basis of eq 2, r for a given elapsed time, t, can be expressed by

$$r = 2\left(\frac{Dt}{\pi}\right)^{1/2} = \left(\frac{2k_B T t}{3\pi^2 \eta\alpha}\right)^{1/2}$$
(3)

If ENMs are homogeneously distributed throughout the polymer matrix, some portion of these particles will be near
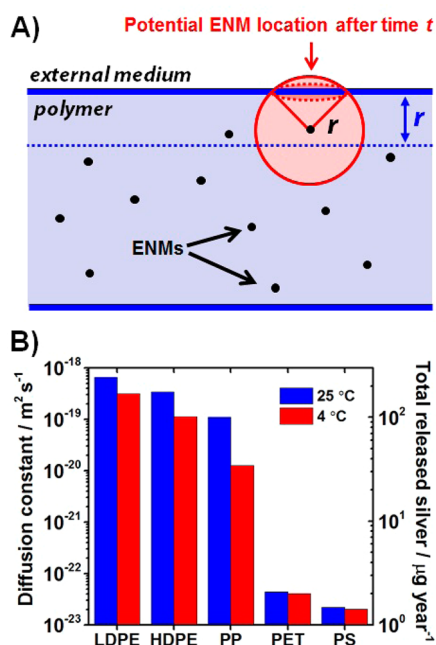
Figure 4. Illustration of concepts in a recent attempt[24] to theoretically model ENM diffusion and release from a polymer food packaging material. (A) On the basis of diffusion in a random direction, a nanoparticle embedded in a polymer matrix can travel anywhere in a sphere of radius r during a characteristic time. The magnitude of r depends on the diffusion rate of the particle in the polymer and the time. If the particle is within r distance of the surface of the material, there is a nonzero probability that the particle may be released into the external medium during time t, indicated by the red sphere. Therefore, using the estimated diffusion constant, D, which in the Stokes–Einstein model depends on the polymer viscosity and the temperature, plus the ENM concentration in the film and the total film surface area, the total number of released particles during t can be predicted (eq 4). (B) Some diffusion constants predicted using the Stokes–Einstein equation and associated release of hypothetical 5 nm (radius) AgNPs (on a mass basis) in various polymers at 25 °C over 1 year. To calculate the amount of released silver, an ENM concentration of 1 kg m^{-3} and total film surface area of 0.2 m^2 were assumed. Note that values for PET and PS represent maximum possible values, based on uncertainty in the dynamic viscosities for these polymers. See ref 24 for details.

enough to the polymer surface that there is a nonzero probability, based simply on random direction of motion, that the particle could move beyond the polymer-environment interface and become released into the exterior medium. This probability, for a randomly distributed particle within the distance r from the polymer surface, can be shown to equal 0.25 (for a full derivation, see Šimon et al., ref 24), which in turn can be used to predict the total expected number of particles, n, released into the liquid medium during time t:

$$n = \frac{Sc}{4}\left(\frac{2k_{\mathrm{B}}Tt}{3\pi\eta\alpha}\right)^{1/2} \tag{4}$$

where S is the total film surface area of the polymer, c is the initial concentration of nanoparticles in the polymer, and the other variables are defined above.

Using eq 4 and values for polymer dynamic viscosities at different temperatures determined from the empirical William-Landel-Ferry (WLF) model, Šimon and co-workers calculated a diffusion constant of 6.6×10^{-19} m^2/s for ENMs with 5 nm

radius dispersed in LDPE at 25 °C. The authors compared this calculated diffusion constant with an experimental diffusion constant of gaseous carbon dioxide, which has a value ∼8 orders of magnitude lower under the same conditions. To put this in perspective, the authors estimated that for a LDPE nanocomposite of 5 nm radius silver nanoparticles (AgNPs) dispersed at 1 kg/m^3 (∼0.11 wt %) with a surface area of 0.2 m^2, the total amount of released silver over a 1 year period of time at 25 °C would be ∼260 μg. Additional diffusion constants for 5 nm AgNPs predicted from the Stokes–Einstein equation in this study, and associated total amount of released silver at room temperature over 1 year, are plotted in Figure 4B, which reveal the expected dependence of ENM release on temperature and the polymer viscosity. Under these conditions, Šimon et al. estimated that chemical equilibrium for AgNP release would be reached only after about 1500 years.

Šimon et al. concluded from their work that ENM release from polymers into liquid media will be realistically detectable only for particles with very small radii (∼1 nm or less), from polymers of low dynamic viscosities (e.g., LDPE, PP), and from polymers that do not chemically interact with the dispersed ENMs. Although this might provide for an optimistic outlook on the exposure of ENMs from PNCs, this approach was based on a number of assumptions. First, the approach assumes Fickian diffusion kinetics, but the dispersion of particles in a PNC is not dissimilar from the dispersion of microcrystalline regions with glassy polymers, the latter of which are known to often exhibit non-Fickian behavior.[25] It is also unclear how well the Stokes–Einstein equation can estimate diffusion constants in polymers, which though often treated as "fluids" are actually complex, multiphase systems that contain crystals and other solid or other semisolid regions, even before ENMs are added. For instance, estimation of the diffusion constant of molecular CO_2 (radius ∼116 pm) in LDPE using this same Stokes–Einstein approach yields a value of ∼2.8×10^{-17} m^2/s, 6 orders of magnitude *lower* than the experimental value for molecular CO_2 provided by the authors as a reference value (3.71×10^{-11} m^2/s). A more expansive comparison of diffusion constants predicted by the Stokes–Einstein equation (eq 2) to experimental diffusion data for organic molecules, plotted as a function of estimated molecular size, is provided in Figure 5, along with similar predictions made using the semiempirical Piringer model (eq 1). It is immediately evident from this figure that the Stokes–Einstein approach is inadequate to predict diffusion constants in polymers: for organic molecules in LDPE, the approach appears to underestimate the diffusion constant by several orders of magnitude, and for nanoparticles, the rate of diffusion may be significantly overestimated on the basis of extrapolation. This analysis agrees with recent research that suggests that great care must be taken when using Stokes–Einstein to describe diffusivity in viscous materials[26,27] and suggests that relying on this model could lead to erroneous predictions about the likelihood of ENM from PNCs. From a more practical standpoint, the theoretical treatment put forward by Šimon et al. also neglects chemical properties of the liquid environment when estimating ENM release from the calculated diffusion constant and also assumes the viscosities of PNCs at different temperatures are the same as those of neat polymers.

All this is not to denigrate theoretical approaches to understand ENM diffusion or release. Investigations such as the Šimon study give valuable insight into the likelihood of ENM release and represent an excellent starting point toward fundamentally understanding a complex phenomenon. Never-
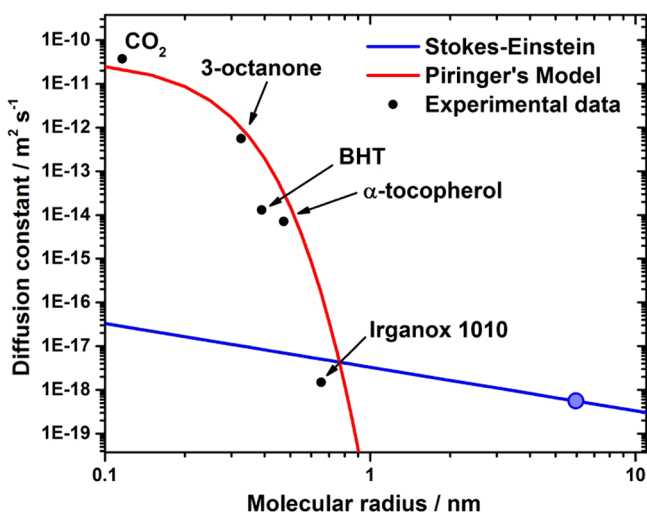
Figure 5. Comparison of experimental diffusion constants (black squares) for some selected organic molecules with diffusion constants predicted by the Stokes−Einstein (eq 2, blue line) and Piringer's semiempirical models (eq 1, red line) in LDPE at 25 °C, as a function of molecular radius. The diffusion constant of a hypothetical 5 nm ENM calculated by the Stokes−Einstein equation is shown as a blue circle. For the Stokes−Einstein model, a value of 6.6×10^4 PaS was used for the dynamic viscosity of LDPE at 25 °C.[24] With the exception of CO_2, for which the C=O bond length of 116 pm was used, molecular radii were determined by assuming spherical molecules and using the relationship $V = 1.13$ MW, where MW is the molecular weight in grams per mol and V is the molecular volume in angstroms cubed.[22] Using this formula, molecular radii for 3-octanone (MW = 128 g mol^{-1}), BHT (butylated hydroxytoluene, MW = 220 g mol^{-1}), α-tocopherol (MW = 430 g mol^{-1}), and Irganox 1010 (MW = 1176 g mol^{-1}) were determined to be 0.33, 0.39, 0.47, and 0.65 nm, respectively. Experimental diffusion constants for CO_2 ($D = 3.7 \times 10^{-11}$ m^2 s^{-1}),[24] 3-octanone ($D = 5.6 \times 10^{-13}$ m^2 s^{-1}),[28] BHT ($D = 1.3 \times 10^{-14}$ m^2 s^{-1}),[29] α-tocopherol ($D = 7.1 \times 10^{-15}$ m^2 s^{-1}),[30] and Irganox 1010 ($D = 3.7 \times 10^{-11}$ m^2 s^{-1})[29] were recorded at 25, 25, 21, 20, and 21 °C, respectively. Note that the Piriginer semiempirical equation is specifically designed to offer conservative estimates of (i.e., slightly overestimate) diffusion constants, and this is reflected in the plot.

theless, to better gauge the appropriateness of such models and understand potential shortcomings, theoretical studies must be supported with experimental data. Along these lines, one study has attempted to compare experimental release values (in this case, of ~10 nm silver or copper nanoparticles from polyethylene into raw chicken meat) with values predicted by a modified version of the model proposed by Šimon et al.[31] The results showed that a Stokes−Einstein approach performs quite well under some conditions (AgNPs, short exposure times), but not as well in others (CuNPs, longer exposure times). Another very recent hybrid theoretical and experimental study by Bott et al. on release of carbon black nanoparticles into food simulants from LDPE and PP nanocomposites concluded that the Stokes−Einstein approach significantly overestimates the diffusion constants of large particles, especially when the nanofillers are dispersed at high (percent range) concentrations in the host medium;[32] this study, as well as a companion study on titanium nitride nanoparticles,[33] also cross-evaluated some other potential theoretical models and discusses their various strengths and weaknesses in detail. Interestingly, although not related to ENM release, another recent experimental study on ENM diffusion reported that the

Stokes−Einstein approach actually *underestimated* the diffusion rate of ~5 nm quantum dots in polystyrene at high temperature (130−160 °C) by a factor of about 200.[34] Even in aqueous solution, experimental studies on ENM diffusion have cited significant deviations from the predictions of the Stokes−Einstein equation and have shown that ENM diffusion rates are highly sensitive to interactions between ENMs, including their bound ligands/surfactants, and other macromolecules in the diffusion medium.[35]

Together, these studies suggest that although the certain theoretical methods may be useful toward estimating nanoparticle diffusion rates in some circumstances, more experimental work is needed before they can be used broadly and with confidence. Although Figure 5 shows that semiempirical models do an excellent job of predicting diffusion constants (and migration into external media) for small molecules, it is important to underscore that their ability to model diffusion of nanoscale particulates in, or release from, polymers has not been systematically evaluated. In particular, we may anticipate failures of theoretical diffusion models to predict actual ENM release in certain cases because diffusion of whole particles from the interior of a polymer to the external environment may not be the only release mechanism involved for some materials. Other mechanisms such as dissolution or desorption of surface bound particles (Figure 1) likely will always contribute to the total measured metal ion content in an inductively coupled plasma−mass spectrometry (ICP-MS) assay.[9] Predicting total release of ENMs and their residuals into the external medium may therefore require a theoretical treatment not only of ENM diffusion, but also of desorption and dissolution kinetics or ion transport within the polymer medium. The latter process has been studied extensively in polymer/solid electrolytes and conducting polymers,[36,37] even conducting PNCs,[38] but applying these principles to ion diffusion within nonconducting polymers may not be straightforward. Even if it is possible to model these various processes independently, a larger issue is how we combine essentially decoupled theoretical treatments of potentially codependent ENM release mechanisms to obtain an accurate overall theoretical picture of total ENM release. In some instances, efficient release modeling may not even be practical at all, as in the case of materials, such as textiles, that have irregular or complex surfaces. For these reasons, although we should continue to evaluate the utility of theoretical models in ENM release prediction, these models will likely never fully replace experimental studies when it comes to fundamentally understanding release mechanisms.

Experimental Assessment of ENM Release from PNCs into Liquid Media. A preponderance of studies related to the release of ENMs from PNCs into liquid media have focused on AgNPs because of the ubiquity of AgNP-enabled composites intended for antimicrobial applications[3,39] and the relative ease of silver detection by ICP-MS. Some of these studies investigated release of silver from commercially available consumer products. For example, assessments have been reported for release of silver: from washing machines into wash water;[40] from commercial AgNP-enabled textiles into an alkaline aqueous detergent solution during wash cycles;[41,42] into rainwater from building facades coated with AgNP-containing white paint based on an acrylic binder;[43] into liquid food simulants from commercial plastic food containers;[44,45] and out of household consumer products such as fabrics, toys, and cosmetics into purified water, municipal tap water, and an acidic liquid intended to simulate landfill leachate.[46,47] Release

of nanosilver from toys, fabrics, breast milk storage bags, sippy cups, cleaning products, and humidifiers into such liquids as water, orange juice, milk formula, synthetic saliva, sweat, urine, and dermal wipes has also been studied.[48] In most of these experiments, the external liquid medium was collected after it was exposed to the PNC test material and a total silver concentration was measured, similar to the submersion method presented above.

Each of these consumer product studies reported detecting elemental silver released into the environment, although the amount of silver varied depending on the test material and experimental conditions. For instance, Benn et al. observed total silver release into municipal tap water in quantities ranging from <0.2 μg Ag/g product for a nanosilver-containing stuffed animal to 46 μg Ag/g product for a medical cloth.[47] The authors also observed that the total amount of silver initially present in the material did not correlate to the fraction of silver released during the experiment, suggesting that the way in which the AgNPs are incorporated into the product plays a dominant role in determining the release behavior. A medical face mask, for example, that contained ∼27% silver by weight, released <0.01% of its silver into the wash water, but another fabric, which initially contained only 0.0044% silver by weight, released about 2% of its total silver under the same conditions.

By passing the liquid matrix through a series of filters prior to analysis, the authors also were able to estimate the fraction of the total silver content corresponding to a specific particle size regime, and again, these relative values varied from product to product. In the study by Lorentz et al., concentrations of released silver when commercially available textiles were exposed to detergent solutions at pH 10 ranged from <5 to 38.5 μg/mL.[42] Note that silver release in this case was reported as silver per unit volume of liquid rather than amount of silver per mass of material tested, although they did also report their release values as a percentage of total silver in the test material.

Lorentz et al. also attempted to do a particle size fractionation, but they separated particles into only two fractions: above and below 450 nm. As with the Benn et al. study, there was variation in the fraction of small (<450 nm) versus large (>450 nm) particles among the tested samples, and the conditions of the liquid medium (washing vs rinsing) also appeared to be an influential factor. Given the differences in the way these various studies chose to report data as well as the lack of any general consistency between the amount of nanosilver released and the amount initially in the material, the question arises as to what is the most appropriate metric to quantify ENM release from nanotechnology-enabled materials. Without a standardized approach to ENM release quantification, it is difficult to compare the results of one study with the results of another and make meaningful, broad conclusions about ENM release.

All the consumer product studies used ICP-MS (or similar techniques) as a primary method to quantify silver content. A fundamental limitation of traditional forms of ICP-MS for assessment of ENM release is that, without specialized analysis modes, it cannot distinguish between release of whole ENMs and dissolved ions; therefore, studies that rely on only conventional ICP-MS will not reveal the form of released silver, which limits their ability to provide general conclusions about release mechanisms. Studies that supplement ICP-MS results with other analysis techniques, such as transmission electron microscopy (TEM), provide a more holistic view of what is occurring at a microscopic level.[49] Thankfully, most

investigators use at least one elemental analysis technique and one imaging or compositional analysis technique to analyze ENM release. For example, the researchers that focused on leaching of AgNPs from outdoor acrylic paint into rainwater deposited runoff samples directly on carbon-Formvar-coated copper grids, centrifuged them to remove particulates larger than a few hundred nanometers, and then imaged them with TEM to reveal the presence of AgNPs with diameters <15 nm aggregated into composite colloids attached to organic binders in the paint.[43] This provides important evidence that whole AgNPs, not just dissolved silver, were responsible for positive silver signals detected by ICP-MS. Moreover, via the use of compositional analysis techniques such as energy dispersive X-ray spectroscopy (EDS), the authors confirmed that much of this silver was present in the form of low toxicity (poorly absorbed) Ag_2S, likely as a result of reaction of elemental silver with hydrogen sulfide in the atmosphere. Similar compositional analysis of released particles also yielded important information in other studies: investigation of AgNP release from textiles into alkaline detergent solutions[42] revealed that more textiles released nonmetal AgNPs (e.g., those composed of silver chloride) than purely metal AgNPs, suggesting that reaction of particles with the liquid medium can be a major factor when determining the composition and, one presumes, the downstream toxicological and ecological impact of released particles. Such information underscores the need to use a robust analytical toolset when quantifying and qualifying the release of ENMs from PNC materials into liquid media.[9]

Release of AgNPs into liquid media from PNC materials with less complex surfaces, such as films or sheets, has also been investigated. Most of these test materials have been intended for food contact (packaging) applications, and therefore, the test liquids utilized were chosen to simulate the chemical properties of foods. Food-simulating liquids and oils are used in place of real foods because the latter are often heterogeneous or contain substances that can interfere with sensitive chemical analysis.[9] For example, Song et al. tested a commercially available LDPE-based material containing 7 nm AgNPs and followed a protocol established by the European Commission for testing migration of contaminants from plastic materials.[50] In this case, 3% acetic acid and 95% ethanol were used as food simulants. The authors reported that 5.6% of the total silver in the film was released into the simulant at 70 °C when the simulant was 3% acetic acid; the analogous result for the 95% ethanol simulant was 0.22% migrated silver. Kinetics tests determined that steady state for AgNP release was reached after ∼6 h. The significantly higher release in acetic acid is likely attributed to the higher solubility of silver in the acidic medium. The authors did not characterize the distribution, size, or aggregation state of AgNPs in the test materials prior to their release experiments; neither did they ascertain whether migrated silver was in ionic form or nanoparticulate.

Compared with real foods, food simulants are relatively simple substances, and so finding and characterizing released ENMs or their residuals is relatively straightforward. Thus, studies that use food simulants offer an especially valuable opportunity to learn something about release mechanisms, provided extra steps are taken to study the characteristics of ENMs both before and after release experiments. As an example, Huang et al. stored food simulants (distilled water, 4% aqueous acetic acid, 95% ethanol, and hexanes, respectively) in commercially available AgNP/LDPE bags for 15 days at different temperatures and analyzed aliquots at regular time

intervals by atomic absorption spectroscopy (AAS) for elemental silver content.[51] An analysis of the PNC materials prior to the release experiments by ashing at 600 °C followed by SEM/EDS of the ash revealed the presence of large (100–300 nm) AgNPs, with a total elemental silver concentration of 100 μg of Ag per gram of PNC determined by AAS. Using SEM with EDS, the authors reported observing AgNP nanoparticles with diameters up to 300 nm released whole into the liquid food simulants. Given the theoretical considerations described earlier, desorption of AgNPs at the PNC-simulant interface seems to be a more likely release mechanism than one that requires diffusion of particles through the polymer matrix. The amount of released silver increased as a function of storage time and temperature, although the authors did not report whether the size of released AgNPs changed as a function of these parameters.

A more thorough characterization of released AgNPs was presented by Von Goetz et al., who used a series of food simulating substances, including water, 10% aq ethanol, 3% acetic acid, and olive oil, to determine the likelihood of release of AgNPs into foods from commercial plastic food containers under various conditions.[44] In addition to conventional solution-aspirated ICP-MS, they also used laser-ablation ICP-MS to investigate the characteristics of ENMs embedded near or adsorbed onto the surface of test materials and single particle ICP-MS (SP-ICP-MS) to study the properties of ENMs after they are released into the food simulant. SP-ICP-MS is a modified ICP-MS experiment in which the analyte peak intensity is plotted as a function of time, which allows researchers to distinguish between whole particles (which are recorded as spikes or bursts) and ions (recorded as a constant background), provided the particles are sufficiently dilute; in principle, the size distribution of suspended particles can be estimated by the integrated peak area on the basis of assumptions about particle geometry, although the minimum size that can be detected is highly dependent on the background ion concentration.

SP-ICP-MS experiments performed by Van Goetz et al. revealed that AgNPs were contained in the bulk material, as opposed to simply coated on the surface, and the dispersion of particles was very inhomogeneous. The authors found that the total silver released (over 10 days at 20 °C) depended highly on the simulant used, with acetic acid giving rise to the highest amount of migrated silver and olive oil giving the lowest. ICP-MS in single particle mode revealed that up to 12% of the released silver content was in the form of ENMs, with diameters estimated in the range of 100–350 nm, although the authors stated that these may be aggregates of smaller particles. These results were confirmed by TEM and SEM/EDX. The authors also evaluated release under multiple use conditions and found that the release level dropped significantly after each subsequent use period, and they used atomic force microscopy to reveal that the roughness of the material surfaces provided an effectively large surface area for release. Taken as a whole, this study shows the power of using a host of complementary analytical methods to explore release mechanisms: the authors compared their results with the Einstein–Stokes model presented by Šimon et al.[24] and found that their diffusion flux exceeded the predicted amount by nearly 5 orders of magnitude, even after accounting for the material's high effective surface area. This suggests that either most release occurred via dissolution or desorption mechanisms or the Einstein–Stokes model for ENM diffusion is inaccurate.

Detection of ENMs released in actual foods and other complex biological matrixes can also be challenging because of the many natural nanostructures (micelles, emulsions, etc.), which could interfere with isolation and detection, particularly if the analyte is an organic ENM.[52] In addition, preparation of samples for chemical analysis, such as acid digestion to prepare a homogeneous matrix for ICP-MS, may involve harsh conditions that could destroy or otherwise alter the properties of released ENPs.[52] Despite these difficulties, analysis of food matrixes for released ENMs is desirable because it may offer a more realistic picture of how the complexities of a biological matrix influence release characteristics. Along these lines, Emamifar et al. analyzed release of silver and zinc into orange juice from nancomposite LDPE materials containing either 5% P105 power (micrometer-sized TiO_2 coated with 5% by weight 10 nm AgNPs) or 1% 70 nm zinc oxide nanoparticles, which were fabricated into 50-μm-thick films by melt-mixing in a twin-screw extruder.[53] They reported release of 0.15 ± 0.002 μg/L of silver and 0.54 ± 0.005 of zinc after 112 days of storage at 4 °C by ICP-MS, but the lack of any imaging method prevented this study from reporting on whether the released silver and zinc was nanoparticulate in form.

More recently, Cushen et al. dispersed 10 and 50 nm AgNPs into plasticized poly(vinyl carbonate) at 0.5% and 5% weight loading by solvent casting and analyzed release of silver from these materials into skinless, boneless chicken breast meat by ICP-MS.[54] For these experiments, meat samples were vacuum-packed in the nanocomposite and stored in the dark at temperatures of either 7 or 20–25 °C, for time periods ranging from 1 to 4 days. The authors reported a positive correlation between released silver concentration and both initial AgNP fill fraction and exposure time, a negative correlation between released silver concentration and temperature, and no correlation between released silver to AgNP particle size. The total AgNP release fraction (percent of initial AgNPs in the PNC that migrated) ranged from 0.15% to 1.42%, with total released silver concentration ranging from 0.03 to 8.4 mg/kg. Although the study did not distinguish between whole particles and dissolved ions, the authors used a risk analysis approach in which the entire detected silver concentration was assumed to be from undissolved AgNPs. The authors acknowledged that this assumption is probably not accurate but justified it as a way of estimating a worst-case scenario for AgNP consumer exposure. The assumed release of whole nanoparticles was used to explain some of the observed trends in total silver release concentrations. For example, the authors hypothesized that the negative correlation between released silver and increasing temperature could have been a result of cross-linking of AgNP to PVC polymer chains, and the lack of any observed correlation between released silver concentration and AgNP diameter was speculated to possibly be evidence of faster rates of AgNP release from materials possessing smaller particle diameters (i.e., due to the inverse relationship between AgNP size and silver content per AgNP, a sort of canceling-out effect). The degree to which these various interpretations of the release data are correct will likely be difficult to sort out without experiments specifically designed to test the diffusion behavior of nanoparticles in polymers, which itself is predicated on the development of suitable analytical methods. Cushen et al. published a similar study related to release of AgNPs (and copper nanoparticles) from LDPE materials into chicken breasts[31] as well as a study on release of AgNPs and Ag-zeolites from LDPE into food simulants.[55]
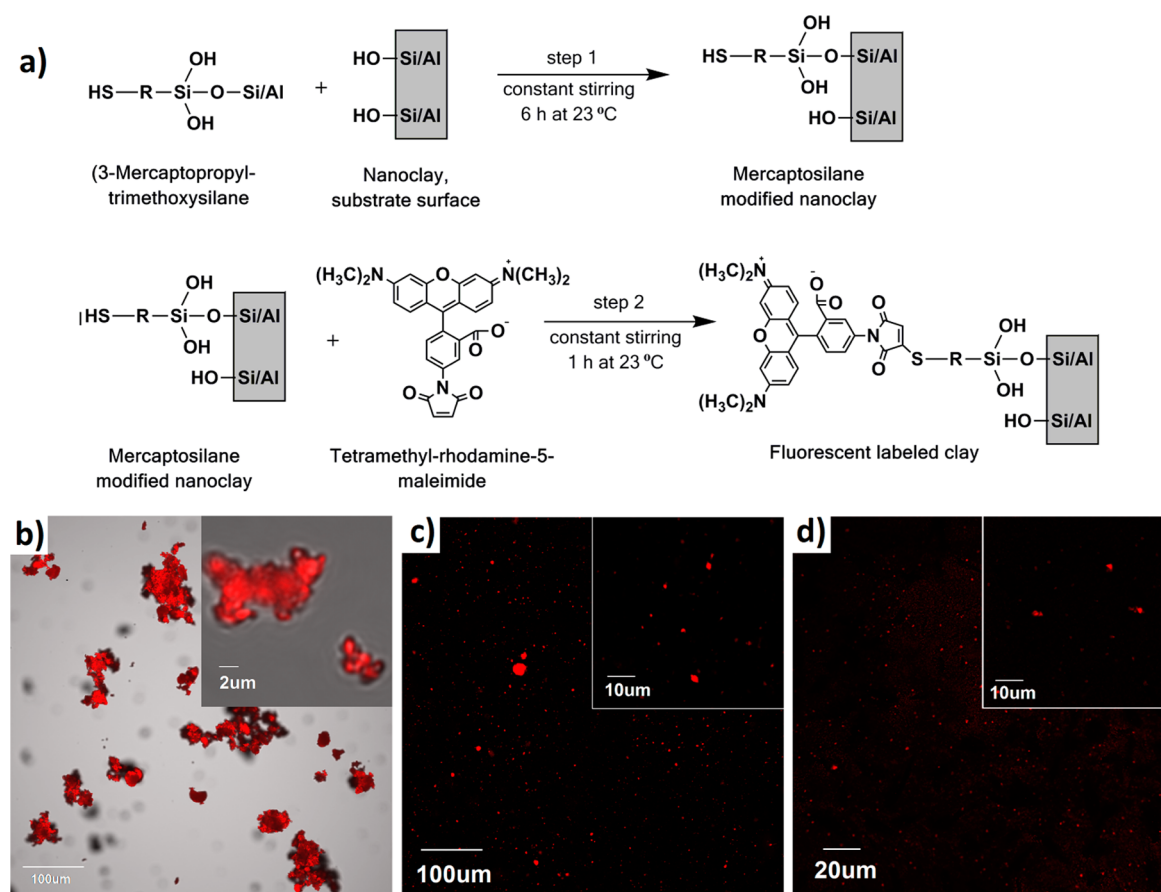
Figure 6. Depiction of fluorescent labeling strategy for assessment of nanoclay release from polymers: (a) synthetic scheme for covalent attachment of rhodamine fluorophore onto MMT clay; (b, c, d) CLSM images of fluorescent labeled nanoclays as prepared, fluorescent labeled nanoclays dispersed in poly(propylene) at 3 wt % and residual fluorescent labeled nanoclays after the test films were stored in ethanol 80 C for 4 h. Adapted from Diaz et al. Fluorescent labeling and tracking of nanoclay. *Nanoscale* **2013**, *5*, 164−168, with permission of The Royal Society of Chemistry.

Although AgNPs have been the most common subject of PNC release studies into liquid media, clay/polymer nanocomposites have also received some attention. Most nanoclays used in PNC applications are natural layered aluminosilicate materials that are often chemically modified to promote efficient exfoliation within the nonpolar polymer environment.[3] Unlike AgNPs, which usually are nanoscale in three dimensions, exfoliated nanoclays are high-aspect-ratio platelets; they can be as little as a nanometer thick but several thousand times larger in the two lateral dimensions. Although the large lateral size may make it unlikely that entire nanoclay platelets will migrate into an external liquid environment by diffusion, there still has been concern that ionic residuals or nanoscale platelet fragments generated in situ during the PNC manufacturing process may become released. Clay/polymer PNCs are currently being investigated for a number of packaging and textile applications because of their superior strength, flame retardancy and improved gas barrier properties compared with conventional polymer materials.[3]

One of the first release studies of nanoclays from a polymer examined spinach and lettuce stored in clay/starch biodegradable nanocomposite bags.[56] In this study, PNC films were fabricated from thermoplastic potato starch and sodium montmorillonite (MMT) by melt-processing, and the release tests were conducted at 40 °C and 50% relative humidity over a storage period of 10 days. After ashing of the vegetables, the residue was taken up in acid and analyzed by inductively coupled plasma−atomic emission spectroscopy (ICP−AES) for silicon, aluminum, and iron, three of the primary constituent elements of MMT. The authors found higher levels of silicon in vegetables stored in the PNCs versus those stored control films, but no elevation in aluminum or iron concentrations. The study did not explore the form (nanoparticulate, ionic, etc.) of the released silicon.

In a study more specifically targeted toward evaluation of nanoclay release, Mauricio-Iglesias et al. incorporated 5% sodium MMT into refined wheat gluten with glycerol as a compatibilizer and formed this composite into thin films with a heated hydraulic press.[57] They then immersed these materials into one of four food simulating liquids (water, 15% ethanol, 3% acetic acid, and olive oil) for 10 days at 40 °C and analyzed the liquid for aluminum and silicon. Their results revealed elevated levels of aluminum only in 3% acetic acid, which they attributed to the higher degree of alumina solubility in acidified media; on the other hand, silicon exhibited elevated concentrations in 3% acetic acid, water, and olive oil. The authors reported even higher levels of released silicon in all four simulants (but not aluminum) when the PNC films were subjected to a high-pressure treatment (5 min at 800 mPa and 40 °C) prior to the release test; high-pressure treatment is an emerging technology being explored for food preservation. This report did not provide a full explanation of these observations, but it might be speculated that the higher release rate of silicon could indicate a dissolution mechanism due to the 2:1 layered

Table 2. Summary of Studies Related to the Release of Nanoparticles from Composite Materials into Liquid Media by Diffusion, Desorption, Or Dissolution.[a]

ENM composition	ENM size (diameter if not specified)	host material	test conditions[b]	external matrixes examined	max ENM loading	max release amount reported[b]	ref
theoretical nanoparticle	5 nm	LDPE, HDPE, PP, PET, PS	25 °C	n/a	1 kg/m^3	1.3 mg/m^2/year	24
Ag	10–500 nm	clothing	washing, 24 h	water	57.7 µg/g	1845 µg	46
Ag	*	fabric, toothpaste, shampoo, detergent	washing	tap water	23 wt %	46 µg/g	47
Ag	40–70 nm	polyester fabric	washing	0.5% Felosan RG-N	145 µg/g	69.6 µg/kg	62
Ag	<15 nm	paint	1 year of natural weathering	rain water	1.5 mg/m^2	0.5 mg/m^2	43
Ag	4.8 nm, 40–80 nm	glass microfiber paper	magnetic stirring, 300 rpm	acetate buffer (pH 5.6)	200 µg	2 mg/L	63
Ag	10 nm	washing machine surfaces	60 °C	water, detergent	*	11 µg/L	40
Ag	20–80 nm	poly(DL-lactide-co-glycolide) (PLGA)	37 °C, 100 days	water	7 wt %	~1.2 ppm[c]	64
Ag	100–300 nm	PE	50 °C, 15 days	water, 4% AA, 95% ethanol, hexanes	145 µg/g	~4.0 µg/dm^2 [c]	51
Ag	7 nm	PE	70 °C, 9 h	3% AA, 95% ethanol	234 mg/kg	5.6%	50
Ag	diam = 4–8 nm thick = 1.3–8.3 nm	PTFE	3 days	deionized water	surface coating	92.71%	65
Ag	30, 70 nm	polysulfone	37 °C, 24 h	0.9% NaCl	2 wt %	0.2 ppm	66
Ag	10, 50 nm	PVC	20 °C, 4 days	chicken meat	5 wt %	3.94 mg/kg	54
Ag	8.8 nm	PE	40 °C, 10 days	water and 3% AA	0.5 wt %	0.38 mg/L	55
Ag	generated in situ, 2–10 nm typically	plasma polymer-ized ethene, 100 nm coating	14 days, temperature unspecified	deionized water	*	~8 µg/cm^2 [c]	67
Ag	*	commercial plastic (LDPE, PP) food storage containers	40 °C, 10 days	50% aqueous ethanol, 3% AA	*	31.46 ng/cm^2	45
Ag	*	commercial plastic food storage containers	20 °C, 10 days	water, 10% ethanol, 3% AA, olive oil	*	30 ng/cm^2 of surface area	44
Ag	*	commercial textiles	40 °C, 30 min (wash cycle w/agitation)	wash cycles with detergent, pH ~ 10.6	1.5–2925 mg total Ag/kg	575 mg/kg	42
Ag	*	commercial textiles	40 °C, 30 min (wash cycle w/agitation)	pH = 10 buffer, peroxides, wash cycles with detergent	0.39–2.66 mg total Ag/g[d]	35% of total silver content	41
Ag	*	toys, fabrics, bags, and other consumer products	varied, depending on intended use	water, juice, milk formula, biological fluids, dermal wipes	varied	up to 38% of silver mass	48
Ag	*	commerial plastic (PP, HDPE) food storage containers and bags	70 °C, 2 h	water, 10% ethanol, 95% ethanol, and 3% AA	varied	17 ng/g (0.06% of total silver content)	68
Ag, Cu	1–20 nm	silicone	37 °C, 85 days	water	0.1 wt %	Cu = 1300 ng/cm^2, Ag=250 ng/cm^2	69
Ag, Cu	~10 nm	PE	3.1 days; 8.1 °C (Ag), 21.8 °C (Cu)	chicken meat	0.5 wt %	Cu = 0.382 mg/kg Ag = 0.042 mg/kg	31
Cu	50 nm	LDPE	37 °C, 120 days	dilute nitric acid	25 wt %	19.1 µg/day	70
Cu	36 ± 9 nm	PLA	24 h	plate count broth	1.5 wt %	~2000 ppb[c]	71
Zn, ZnO	Zn = 30 nm, ZnO = 50 nm × 200 nm rods	LDPE	3 °C, 200 days	simulated uterine solution	15 wt %	~1.2 × 10^{-4} g/day[c]	72
Ag-zeolites	zeolite diameter = 2.5 µm	PLA	20 °C, 72 h	3% AA, 10% and 90% ethanol	5 wt %	0.7 mg/kg	73
Ag-zeolites	zeolite =1–3 µm thick AgNP < 50 nm	macroporous alumina	48 h, gentle shaking	LB broth	*	20 ppm	74
Ag-zeolites	3–4 µm	PVC	37 °C, 20 days	human sterile urine	20 wt %	~0.9 mg/L[c]	75
Ag-zeolites	~3 µm	PE	40 °C, 10 days	water and 3% AA	2%	5.4 × 10^{-2} mg/L	55

Table 2. continued

ENM composition	ENM size (diameter if not specified)	host material	test conditions[b]	external matrixes examined	max ENM loading	max release amount reported[b]	ref
Mg/Al layered double hydroxide	diam ~ 200 nm thick. < 20 nm	PLA	40 °C, 10 days	95% ethanol	5.5 wt %	2.2 mg/dm²	76
Ag-based nanoclay	Ag diam ~ 20 nm	PLA	orbital shaking, 150 rpm, 8 days	2.0×10^{-3} M HNO$_3$	10 wt %	~6 mg/kg[c]	77
carbon black	16 nm	LDPE, PS	60 °C, 10 days; 40 °C, 24 h (for iso-octane)	3% AA, 95% ethanol, iso-octane	5.0 wt %	<12 μg/kg (none detected)	32
CdSe/ZnS	5 nm core	proprietary acrylate polymer coating (on glass)	30 days	1 mM H$_2$O$_2$, PBS, gastric acid, hard water and others	*	Cd = 1.2 mg/g polymer; no whole ENMs observed	78
clay	*	starch	40 °C, 10 days	vegetables	4%	1.9 mg/100g	56
clay	aspect ratio ~320	PLA	40 °C,10 days	95% ethanol	5 wt %	6.7 mg/dm²[e]	61
clay	*	wheat gluten	high-pressure treatment +10 days at 40 °C	water, 3% acetic acid, 15% ethanol, olive oil	5 wt %	Al = ~1 mg/kg food simulant[c] Si = ~4.5 mg/kg food simulant[c]	57
clay	*	PP	80 °C, 4 h	100% ethanol	3 wt %	*	60
clay	25–30 nm wide x 130–200 nm long	PET	45 °C, 90 days	3% acetic acid	3 wt %	Al = 0.34 mg/kg Si = 9.5 mg/kg	59
TiN	~20 nm	LDPE	60 °C, 10 days; 40 °C, 24 h (for iso-octane)	3% AA, 95% ethanol, iso-octane	1000 mg/kg	<0.09–0.11 μg/kg (none detected); <0.24 in 3% AA	33
TiO$_2$	~60 to ~3500 nm	commercial clothes/textiles	40 °C, 30 min (wash cycle w/agitation)	wash cycles with detergent, pH ~ 10.6	0.22–0.85 wt % (total Ag)	4.7 mg Ti/L	79

[a]An asterisk indicates that the information was not available or unspecified. Abbreviations used in this table: AA, acetic acid; PE/LDPE/HDPE, low density/high density/poly(ethylene); PET, poly(ethylene terephthalate); PLA, poly(lactic acid); PP, poly(propylene); PS, poly(styrene); PVC, poly(vinyl chloride). [b]The maximum release amount refers to the highest observed degree of release (typically in concentration in solution or total mass of analyte per surface area or mass of material) observed in the study. The conditions column refers to the conditions under which the maximum release was observed. Note that the release amount refers only to the mass of elemental residual released and does not necessarily mean undissolved particles migrated. [c]This value was estimated from data depicted in a figure. [d]This study also investigated a fabric with significantly higher total silver content (21.6 mg/g), but in this case, the silver was an electrolytically deposited silver layer several micrometers thick, so it has not been included in this table. [e]In this study, the authors observe 6.7 mg/dm² of particles by MALS, but were unable to confirm by ICP-MS that these particles were clay.

structure of MMT, in which each clay platelet consists of a single octahedral alumina layer sandwiched between two tetrahedral silica layers exposed to the external environment;[3] such structures may be anticipated to give rise to higher concentrations of dissolved silicon because the silica layers have greater accessibility to the liquid medium. The authors hypothesized that the higher release rates observed after high pressure processing were likely due to mechanical forces which changed the structure of MMT. This hypothesis was confirmed in a follow-up study in which the authors showed FTIR-based evidence for molecular structural changes of embedded MMT nanoplatelets during the high pressure processing of MMT/polymer nanocomposites.[58] The implication is that the processing conditions to which a PNC material is subjected, both during and after the material's fabrication, may have a significant impact on the ENM release characteristics.

A more recent investigation by Farhoodi et al. studied release of MMT clay residuals from poly(ethylene terephthalate) PNCs prepared by melt-blending, extrusion as pellets, and then blow-molding into bottles.[59] When 3% acetic acid was stored in these MMT/PET bottles at 24 and 45 °C for times ranging from 7 to 90 days, conditions intended to simulate use of these materials as carbonated beverage containers, trace metal analysis revealed released aluminum under the most extreme conditions (45 °C for 90 days) to be 0.34 mg/kg. As above, these authors also observed a significantly higher silicon content (9.5 mg/kg). The observed ratio of aluminum to silicon in the simulant after the release test at 45 °C was found to be significantly different from the analogous ratio observed in the solid PNC film prior to the release test (0.036 vs 0.37). Thus, although the authors make some arguments about the ability of clay platelets to diffuse throughout the polymer matrix and become released, it also seems possible that the release of clay residuals observed here may be primarily in the form of partial dissolution of embedded or surface-bound clays platelets. Such mechanistic details will be difficult to work out via trace-metal analysis results alone, and future experimental efforts related to nanoclay release may benefit from additional methods that can probe the form of released nanoclay residuals.

Because of some of the aforementioned difficulties of assessing ENM release via direct detection of metal residuals, some researchers have opted for less direct means to learn about ENM release mechanisms. For example, Diaz et al.[60] labeled commercially available MMT with fluorescent xanthene dyes and incorporated the tagged nanoclay at 3 wt % into a poly(propylene) (PP) matrix by melt-mixing (Figure 6a,b). The labeled-clay/PP resin was then processed into thin films by compression molding. Confocal laser scanning microscopy (CLSM) showed that these films had fluorescent clay particles distributed throughout the polymeric interior (Figure 6c). By tagging the clay particles with fluorescent dye molecules, the authors hoped to observe any release of clays by monitoring the liquid medium for fluorescence as a function of time and storage conditions. After storing cut sections of the fluorophore-labeled films at 80 °C for 4 h in neat ethanol, the authors evaporated the ethanol and observed fluorescence signals in the residue, which the authors put forward as evidence of the diffusion-based release of nanoclay particles from the PNC into the liquid medium (Figure 6d). Such a diffusion-mediated release mechanism would also be dependent on the solubility parameters of the external phase (liquid or food).

The approach devised by Diaz et al. is a clever method to explore ENM release from plastics into liquid media and deserves further study, particularly in light of some of the systematic limitations of ICP-MS-based methods. It is noteworthy that the authors did not quantify the amount of nanoclay released, so at present, their approach appears to be qualitative or semiquantitative. Additional work will be needed to determine if quantification of these results is possible. Other lingering questions that may be useful to explore are whether the presence of the dye impacts the release characteristics of the clay and whether a portion of the observed fluorescent clay particles in the simulant after storage could have originated from mechanical cutting, stamping or pressing of test films in accordance with the ASTM D4754 protocol used. The latter point raises the general question of whether established methods to measure release of contaminants from polymeric thin films are suitable to assess release of ENMs. This is an issue that needs more attention from the research community.

V. CONCLUSIONS AND KNOWLEDGE GAPS

Table 2 summarizes experimental parameters for many relevant studies related to release of ENMs from polymers into liquid media. Critical review of the represented literature confirms that ENMs or their component elements can be released into liquid media from PNCs under some conditions, but the available information is not yet sufficient to inform detailed diffusion or release models or make detailed conclusions about factors that are most likely to influence specific release mechanisms such as those shown in Figure 1. Although many studies have established a positive correlation between temperature and ENM release as well as a positive correlation between storage time and ENM release, there are few studies available that specifically probe key structure–function relationships between particle- or polymer-specific structural attributes and release characteristics. It is also difficult at this time to say what types of applications (say, food packaging versus biomaterials) are likely to give higher rates of ENM release. Research efforts are needed that explore the quantitative dependence of release on various ENM characteristics (for example, size, shape, dispersion characteristics, and surfactant type) or host polymer attributes (for example, molecular weight, viscosity, molecular structure, and the presence of compatibilizers/additives); the impact of PNC processing conditions on release characteristics also needs to be rigorously studied, and storage conditions other than temperature may be worth investigating. The tendency of acidic media to lead to enhanced release of ENMs or their residuals has been well-established, but mechanistic details remain unclear, and the influence of the external liquid medium (e.g., polarity, viscosity, etc.) needs more attention. The influence of other contributing factors, such as the presence of UV light, may also be important, although the contribution of matrix effects will be presented in more detail in a subsequent paper.[10] Finally, the current body of literature has been predominantly focused on quantitating release of particles, and some studies have tried to determine whether the released material is still nanoparticulate in nature, but beyond this, there has been little work done to inform a broader understanding of postrelease processes. Even if it can be established that whole particles are being released, understanding whether these released particles dissolve, aggregate, or change composition or morphology is important from a health and environmental safety perspective because such factors likely impact the downstream rate of translocation

into various biological systems. Along those lines, relationships between the size, shape, or surface area polydispersity of embedded nanofillers and subsequent property distributions of released particles also need to be revealed.

One of the present barriers to obtaining detailed information about factors that influence ENM release and their postrelease behavior is the fact that many ENM release studies use poorly characterized test materials. Reliance on third party or commercial sources for PNCs to test for ENM release makes sense if the object is to evaluate the release characteristics of materials that are on the marketplace now or will likely be in the near future. However, because such sources may be reluctant to share proprietary information about the way their products are manufactured and because a limited selection of commercial materials is available, they may reveal little information on how the attributes of these composites or their synthetic starting materials impact release characteristics. Therefore, a pressing area of public need is more studies that use PNC test materials fabricated in-house from well-characterized ENMs and polymers that are chosen specifically to probe structure–function relationships. A wider selection of validated ENM reference materials would also be useful.

A second barrier that is currently hindering ENM release studies is the lack of a robust toolset capable of detecting and characterizing released ENMs in liquid media at low concentrations. A number of the studies in Table 2 failed to use an analytical method beyond ICP-MS or a similar technique to verify that the detected elemental residual in the liquid medium was in nanoparticulate form. Imaging methods such as TEM or SEM can provide valuable confirmation of whole ENM release, but these techniques may be difficult to use when ENMs are released at very low concentrations, especially when they are released into complex (heterogeneous) liquid media. Emerging technologies such as single-particle ICP-MS (SP-ICP-MS) may find utility here, but because they are not yet standardized methodologies and currently have some limitations (e.g., minimum detectable particle size), it may be some time before these techniques are widely adopted. Likewise, advanced characterization of released ENMs may be possible using hyphenated techniques that employ front-end separation methods, such as asymmetric field flow fractionation or hydrodymamic chromatography; the former method has already been utilized successfully to examine release of nanoclay platelets from a poly(lactic acid)-based PNC,[61] but here again, more work needs to be done to fully evaluate and validate such methods for routine measurement of ENM release. In addition to the difficulty surrounding instrumental analysis of released materials, the ENM release experiments themselves are for the most part identical to those that have been used for years to assess molecular migration (vide supra). Although these methods may be acceptable for ENM release measurements, proper validation experiments need to be conducted. For further details related to the state of measurement science in support of understanding ENM release from polymers (especially related to food contact applications), see the recent review by Noonan et al.[9]

In summary, there has been intensification in nanocomposite safety research in recent years, and the resulting progress in our understanding of ENM release mechanisms has certainly been impressive. What is needed now is more focused, systematic studies on specific relationships between characteristics of the host materials and the quantity and form of released particles. Such studies will lead to an even more robust understanding of

the risks these materials pose to consumers in a variety of applications and, thus, to a higher level of confidence in their safety as the technology matures.

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■ REFERENCES

(1) Podsiadlo, P.; Kaushik, A. K.; Arruda, E. M.; Waas, A. M.; Shim, B. S.; Xu, J. D.; Nandivada, H.; Pumplin, B. G.; Lahann, J.; Ramamoorthy, A.; Kotov, N. A. Ultrastrong and Stiff Layered Polymer Nanocomposites. *Science* **2007**, *318*, 80−83.

(2) Li, Y.-C.; Schulz, J.; Mannen, S.; Delhom, C.; Condon, B.; Chang, S.; Zammarano, M.; Grunlan, J. C. Flame Retardant Behavior of Polyelectrolyte−Clay Thin Film Assemblies on Cotton Fabric. *ACS Nano* **2010**, *4*, 3325−3337.

(3) Duncan, T. V. Applications of Nanotechnology in Food Packaging and Food Safety: Barrier Materials, Antimicrobials and Sensors. *J. Colloid Interface Sci.* **2011**, *363*, 1−24.

(4) Ray, S. S.; Yamada, K.; Okamoto, M.; Ueda, K. Polylactide-Layered Silicate Nanocomposite: A Novel Biodegradable Material. *Nano Lett.* **2002**, *2*, 1093−1096.

(5) Althues, H.; Henle, J.; Kaskel, S. Functional Inorganic Nanofillers for Transparent Polymers. *Chem. Soc. Rev.* **2007**, *36*, 1454−1465.

(6) Fang, Y.; Chen, L.; Wang, C.-F.; Chen, S. Facile Synthesis of Fluorescent Quantum Dot-Polymer Nanocomposites Via Frontal Polymerization. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 2170−2177.

(7) Grossiord, N.; Loos, J.; van Laake, L.; Maugey, M.; Zakri, C.; Koning, C. E.; Hart, A. J. High-Conductivity Polymer Nanocomposites Obtained by Tailoring the Characteristics of Carbon Nanotube Fillers. *Adv. Funct. Mater.* **2008**, *18*, 3226−3234.

(8) Wang, Q.; Zhu, L. Polymer Nanocomposites for Electrical Energy Storage. *J. Polym. Sci., Part A: Polym. Phys.* **2011**, *49*, 1421−1429.

(9) Noonan, G. O.; Whelton, A. J.; Carlander, D.; Duncan, T. V. Measurement Methods To Evaluate Engineered Nanomaterial Release from Food Contact Materials. *Comp. Rev. Food Sci. Food Saf.* **2014**, *13*, 679−692.

(10) Duncan, T. V. Release of Engineered Nanoparticles from Polymer Nanocomposite Materials: Effects of Matrix Degradation. *ACS Appl. Mater. Interface* **2014**, 10.1021/am5062757.

(11) In this article, "migration" is also generally understood to be distinct from other forms of mass transport, such as electrophoresis or sedimentation, that are also often called migration and are driven by external, physical forces.

(12) Brody, A. L. Flavor Scalping in Plastic Packaging. *Food Technol.* **2007**, *61*, 82−84.

(13) Mercea, P. Models for Diffusion in Polymers. In *Plastic Packaging*; Piringer, O., Baner, A. L., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008; pp 123−158.

(14) The US Food and Drug administration lays out recommended test conditions, analytical methods, and food simulants in a publicly available guidance document entitled "Preparation of premarket submissions for food contact substances: chemistry recommendations". This document is freely available online at the FDA's website, currently at http://www.fda.gov/Food/GuidanceRegulation/ G u i d a n c e D o c u m e n t s R e g u l a t o r y I n f o r m a t i o n / IngredientsAdditivesGRASPackaging/ucm081818.htm (Accessed 12/ 02/2014). Note that in the FDA document, "migration cell" is the name given to the experimental apparatus used to perform the submersion method discussed in this article.

(15) The guidelines and recommendations set forward by the European Commission for migration testing from food contact materials is available in the document "Union Guidelines on Regulation (EU) No. 10/2011 on Plastic Materials and Articles Intended to Come into Contact with Food", which can be accessed at http://ec.europa.eu/food/food/chemicalsafety/foodcontact/docs/10-2011_plastic_guidance_en.pdf (Accessed 12/02/2014).

(16) Poças, M. F.; Oliveira, J. C.; Oliveira, F. A. R.; Hogg, T. A Critical Survey of Predictive Mathematical Models for Migration from Packaging. *Crit. Rev. Food Sci.* 2008, 48, 913−928.

(17) Shirangi, M. H.; Michel, B. Mechanism of Moisture Diffusion, Hygroscopic Swelling, and Adhesion Degradation in Epoxy Molding Compounds. In *Moisture Sensitivity of Plastic Packages of IC Devices, Micro- and Opto-electronic Materials, Structures, and Systems*; Fan, X. J., Suhir, E., Eds.; Springer US: New York, 2010.

(18) Brandsch, J.; Mercea, P.; Rüter, M.; Tosa, V.; Piringer, O. Migration Modelling as a Tool for Quality Assurance of Food Packaging. *Food. Addit. Contam.* 2002, 19, Supplement, 29−41.

(19) Begley, T.; Castle, L.; Feigenbaum, A.; Franz, R.; Hinrichs, K.; Lickly, T.; Mercea, P.; Milana, M.; O'Brien, A.; Rebre, S.; Rijk, R.; Piringer, O. Evaluation of Migration Models That Might Be Used in Support of Regulations for Food-Contact Plastics. *Food. Addit. Contam.* 2005, 22, 73−90.

(20) Welle, F.; Franz, R. Migration of Antimony from PET Bottles into Beverages: Determination of the Activation Energy of Diffusion and Migration Modelling Compared with Literature Data. *Food. Addit. Contam., Part A* 2011, 28, 115−126.

(21) Welle, F.; Bayer, F.; Franz, R. Quantification of the Sorption Behavior of Polyethylene Terephthalate Polymer Versus PET/PA Polymer Blends Towards Organic Compounds. *Packag. Technol. Sci.* 2012, 25, 341−349.

(22) Welle, F. A New Method for the Prediction of Diffusion Coefficients in Poly(ethylene terephthalate). *J. Appl. Polym. Sci.* 2013, 129, 1845−1851.

(23) Fang, X. Y.; Domenek, S.; Ducruet, V.; Réfrégiers, M.; Vitrac, O. Diffusion of Aromatic Solutes in Aliphatic Polymers above Glass Transition Temperature. *Macromolecules* 2013, 46, 874−888.

(24) Šimon, P.; Chaudhry, Q.; Bakoš, D. Migration of Engineered Nanoparticles from Polymer Packaging to Food − A Physicochemical View. *J. Food Nutr. Res.* 2008, 47, 105−113.

(25) Frisch, H. L. Sorption and Transport in Glassy Polymers − Review. *Polym. Eng. Sci.* 1980, 20, 2−13.

(26) Brillo, J.; Pommrich, A. I.; Meyer, A. Relation between Self-Diffusion and Viscosity in Dense Liquids: New Experimental Results from Electrostatic Levitation. *Phys. Rev. Lett.* 2011, 107, 165902.

(27) Schober, H. R. Reining in Diffusion in Dense Liquids. *Physics* 2011, 4, 80.

(28) Finnigan, B. Barrier Polymers. In *The Wiley Encyclopedia of Packaging Technology*, 3rd ed.; Yam, K. L., Ed.; John Wiley & Sons: Hoboken, NJ, 2009; pp 103−109.

(29) Schwope, A. D.; Till, D. E.; Ehntholt, D. J.; Sidman, K. R.; Whelan, R. H.; Schwartz, P. S.; Reid, R. C. Migration of BHT and Irganox-1010 from Low-Density Polyethylene (LDPE) to Foods and Food-Simulating Liquids. *Food Chem. Toxicol.* 1987, 25, 317−326.

(30) Siró, I.; Fenyvesi, É.; Szente, L.; De Meulenaer, B.; Devlieghere, F.; Orgoványi, J.; Sényi, J.; Barta, J. Release of Alpha-Tocopherol from Antioxidative Low-Density Polyethylene Film into Fatty Food Simulant: Influence of Complexation in Beta-Cyclodextrin. *Food. Addit. Contam., Part A* 2006, 23, 845−853.

(31) Cushen, M.; Kerry, J.; Morris, M.; Cruz-Romero, M.; Cummins, E. Evaluation and Simulation of Silver and Copper Nanoparticle Migration from Polyethylene Nanocomposites to Food and an Associated Exposure Assessment. *J. Agric. Food Chem.* 2014, 62, 1403−1411.

(32) Bott, J.; Störmer, A.; Franz, R. Migration of Nanoparticles from Plastic Packaging Materials Containing Carbon Black into Foodstuffs. *Food. Addit. Contam., Part A* 2014, 31, 1769−1782.

(33) Bott, J.; Störmer, A.; Franz, R. A Model Study into the Migration Potential of Nanoparticles from Plastics Nanocomposites for Food Contact. *Food Packag. Shelf Life* 2014, 2, 73−80.

(34) Tuteja, A.; Mackay, M. E.; Narayanan, S.; Asokan, S.; Wong, M. S. Breakdown of the Continuum Stokes−Einstein Relation for Nanoparticle Diffusion. *Nano Lett.* 2007, 7, 1276−1281.

(35) Mun, E. A.; Hannell, C.; Rogers, S. E.; Hole, P.; Williams, A. C.; Khutoryanskiy, V. V. On the Role of Specific Interactions in the Diffusion of Nanoparticles in Aqueous Polymer Solutions. *Langmuir* 2014, 30, 308−317.

(36) Ratner, M. A.; Shriver, D. F. Ion-Transport in Solvent-Free Polymers. *Chem. Rev.* 1988, 88, 109−124.

(37) Gadjourova, Z.; Andreev, Y. G.; Tunstall, D. P.; Bruce, P. G. Ionic Conductivity in Crystalline Polymer Electrolytes. *Nature* 2001, 412, 520−523.

(38) Croce, F.; Appetecchi, G. B.; Persi, L.; Scrosati, B. Nano-composite Polymer Electrolytes for Lithium Batteries. *Nature* 1998, 394, 456−458.

(39) Maillard, J. Y.; Hartemann, P. Silver as an Antimicrobial: Facts and Gaps in Knowledge. *Crit. Rev. Microbiol.* 2013, 39, 373−383.

(40) Farkas, J.; Peter, H.; Christian, P.; Gallego Urrea, J. A.; Hassellöv, M.; Tuoriniemi, J.; Gustafsson, S.; Olsson, E.; Hylland, K.; Thomas, K. V. Characterization of the Effluent from a Nanosilver Producing Washing Machine. *Environ. Int.* 2011, 37, 1057−1062.

(41) Geranio, L.; Heuberger, M.; Nowack, B. The Behavior of Silver Nanotextiles During Washing. *Environ. Sci. Technol.* 2009, 43, 8113−8118.

(42) Lorenz, C.; Windler, L.; von Goetz, N.; Lehmann, R. P.; Schuppler, M.; Hungerbühler, K.; Heuberger, M.; Nowack, B. Characterization of Silver Release from Commercially Available Functional (Nano)Textiles. *Chemosphere* 2012, 89, 817−824.

(43) Kaegi, R.; Sinnet, B.; Zuleeg, S.; Hagendorfer, H.; Mueller, E.; Vonbank, R.; Boller, M.; Burkhardt, M. Release of Silver Nanoparticles from Outdoor Facades. *Environ. Pollut.* 2010, 158, 2900−2905.

(44) von Goetz, N.; Fabricius, L.; Glaus, R.; Weitbrecht, V.; Günther, D.; Hungerbühler, K. Migration of Silver from Commercial Plastic Food Containers and Implications for Consumer Exposure Assessment. *Food. Addit. Contam., Part A* 2013, 30, 612−620.

(45) Echegoyen, Y.; Nerín, C. Nanoparticle Release from Nano-Silver Antimicrobial Food Containers. *Food Chem. Toxicol.* 2013, 62, 16−22.

(46) Benn, T. M.; Westerhoff, P. Nanoparticle Silver Released into Water from Commercially Available Sock Fabrics. *Environ. Sci. Technol.* 2008, 42, 4133−4139.

(47) Benn, T.; Cavanagh, B.; Hristovski, K.; Posner, J. D.; Westerhoff, P. The Release of Nanosilver from Consumer Products Used in the Home. *J. Environ. Qual.* 2010, 39, 1875−1882.

(48) Quadros, M. E.; Pierson, R.; Tulve, N. S.; Willis, R.; Rogers, K.; Thomas, T. A.; Marr, L. C. Release of Silver from Nanotechnology-Based Consumer Products for Children. *Environ. Sci. Technol.* 2013, 47, 8894−8901.

(49) Szakal, C.; Tsytsikova, L.; Carlander, D.; Duncan, T. V. Measurement Methods for the Oral Uptake of Engineered Nanomaterials from Human Dietary Sources: Summary and Outlook. *Comp. Rev. Food Sci. Food Saf.* 2014, 13, 669−678.

(50) Song, H.; Li, B.; Lin, Q.-B.; Wu, H.-J.; Chen, Y. Migration of Silver from Nanosilver-Polyethylene Composite Packaging into Food Simulants. *Food. Addit. Contam., Part A* **2011**, *28*, 1758−1762.

(51) Huang, Y.; Chen, S.; Bing, X.; Gao, C.; Wang, T.; Yuan, B. Nanosilver Migrated into Food-Simulating Solutions from Commercially Available Food Fresh Containers. *Packag. Technol. Sci.* **2011**, *24*, 291−297.

(52) Singh, G.; Stephan, C.; Westerhoff, P.; Carlander, D.; Duncan, T. V. Measurement Methods to Detect, Characterize, and Quantify Engineered Nanomaterials in Foods. *Comp. Rev. Food Sci. Food Saf.* **2014**, *13*, 693−704.

(53) Emamifar, A.; Kadivar, M.; Shahedi, M.; Soleimanian-Zad, S. Effect of Nanocomposite Packaging Containing Ag and ZnO on Inactivation of *Lactobacillus plantarum* in Orange Juice. *Food Control* **2011**, *22*, 408−413.

(54) Cushen, M.; Kerry, J.; Morris, M.; Cruz-Romero, M.; Cummins, E. Migration and Exposure Assessment of Silver from a PVC Nanocomposite. *Food Chem.* **2013**, *139*, 389−397.

(55) Cushen, M.; Kerry, J.; Morris, M.; Cruz-Romero, M.; Cummins, E. Silver Migration from Nanosilver and a Commercially Available Zeolite Filler Polyethylene Composites to Food Simulants. *Food. Addit. Contam., Part A* **2014**, *31*, 1132−1140.

(56) Avella, M.; De Vlieger, J. J.; Errico, M. E.; Fischer, S.; Vacca, P.; Volpe, M. G. Biodegradable Starch/Clay Nanocomposite Films for Food Packaging Applications. *Food Chem.* **2005**, *93*, 467−474.

(57) Mauricio-Iglesias, M.; Peyron, S.; Guillard, V.; Gontard, N. Wheat Gluten Nanocomposite Films as Food-Contact Materials: Migration Tests and Impact of a Novel Food Stabilization Technology (High Pressure). *J. Appl. Polym. Sci.* **2010**, *116*, 2526−2535.

(58) Mauricio-Iglesias, M.; Gontard, N.; Gastaldi, E. Impact of High Pressure Treatment on the Structure of Montmorillonite. *Appl. Clay Sci.* **2011**, *51*, 174−176.

(59) Farhoodi, M.; Mousavi, S. M.; Sotudeh-Gharebagh, R.; Emam-Djomeh, Z.; Oromiehie, A. Migration of Aluminum and Silicon from PET/Clay Nanocomposite Bottles into Acidic Food Simulant. *Packag. Technol. Sci.* **2014**, *27*, 161−168.

(60) Diaz, C. A.; Xia, Y.; Rubino, M.; Auras, R.; Jayaraman, K.; Hotchkiss, J. Fluorescent Labeling and Tracking of Nanoclay. *Nanoscale* **2013**, *5*, 164−168.

(61) Schmidt, B.; Petersen, J. H.; Koch, C. B.; Plackett, D.; Johansen, N. R.; Katiyar, V.; Larsen, E. H. Combining Asymmetrical Flow Field-Flow Fractionation with Light-Scattering and Inductively Coupled Plasma Mass Spectrometric Detection for Characterization of Nanoclay Used in Biopolymer Nanocomposites. *Food. Addit. Contam., Part A* **2009**, *26*, 1619−1627.

(62) Ilić, V.; Šaponjić, Z.; Vodnik, V.; Lazović, S.; Dimitrijević, S.; Jovančić, P.; Nedeljković, J. M.; Radetić, M. Bactericidal Efficiency of Silver Nanoparticles Deposited onto Radio Frequency Plasma Pretreated Polyester Fabrics. *Ind. Eng. Chem. Res.* **2010**, *49*, 7287−7293.

(63) Liu, J.; Sonshine, D. A.; Shervani, S.; Hurt, R. H. Controlled Release of Biologically Active Silver from Nanosilver Surfaces. *ACS Nano* **2010**, *4*, 6903−6913.

(64) Fortunati, E.; Latterini, L.; Rinaldi, S.; Kenny, J. M.; Armentano, I. PLGA/Ag Nanocomposites: In Vitro Degradation Study and Silver Ion Release. *J. Mater. Sci.: Mater. Med.* **2011**, *22*, 2735−2744.

(65) Alissawi, N.; Zaporojtchenko, V.; Strunskus, T.; Hrkac, T.; Kocabas, I.; Erkartal, B.; Chakravadhanula, V. S. K.; Kienle, L.; Grundmeier, G.; Garbe-Schönberg, D.; Faupel, F. Tuning of the Ion Release Properties of Silver Nanoparticles Buried under a Hydrophobic Polymer Barrier. *J. Nanopart. Res.* **2012**, *14*, 928.

(66) Mollahosseini, A.; Rahimpour, A.; Jahamshahi, M.; Peyravi, M.; Khavarpour, M. The Effect of Silver Nanoparticle Size on Performance and Antibacteriality of Polysulfone Ultrafiltration Membrane. *Desalination* **2012**, *306*, 41−50.

(67) Körner, E.; Aguirre, M. H.; Fortunato, G.; Ritter, A.; Rühe, J.; Hegemann, D. Formation and Distribution of Silver Nanoparticles in a Functional Plasma Polymer Matrix and Related Ag$^+$ Release Properties. *Plasma Processes Polym.* **2010**, *7*, 619−625.

(68) Artiaga, G.; Ramos, K.; Ramos, L.; Cámara, C.; Gómez-Gómez, M. Migration and Characterisation of Nanosilver from Food Containers by AF^4-ICP-MS. *Food Chem.* **2015**, *166*, 76−85.

(69) Hahn, A.; Brandes, G.; Wagener, P.; Barcikowski, S. Metal Ion Release Kinetics from Nanoparticle Silicone Composites. *J. Controlled Release* **2011**, *154*, 164−170.

(70) Xia, X.; Tang, Y.; Xie, C.; Wang, Y.; Cai, S.; Zhu, C. An Approach To Give Prospective Life-Span of the Copper/Low-Density-Polyethylene Nanocomposite Intrauterine Device. *J. Mater. Sci.: Mater. Med.* **2011**, *22*, 1773−1781.

(71) Longano, D.; Ditaranto, N.; Cioffi, N.; Di Niso, F.; Sibillano, T.; Ancona, A.; Conte, A.; Del Nobile, M. A.; Sabbatini, L.; Torsi, L. Analytical Characterization of Laser-Generated Copper Nanoparticles for Antibacterial Composite Food Packaging. *Anal. Bioanal. Chem.* **2012**, *403*, 1179−1186.

(72) Yang, Z.; Xie, C.; Xia, X.; Cai, S. Zn^{2+} Release Behavior and Surface Characteristics of Zn/LDPE Nanocomposites and ZnO/LDPE Nanocomposites in Simulated Uterine Solution. *J. Mater. Sci.: Mater. Med.* **2008**, *19*, 3319−3326.

(73) Fernández, A.; Soriano, E.; Hernández-Muñoz, P.; Gavara, R. Migration of Antimicrobial Silver from Composites of Polylactide with Silver Zeolites. *J. Food Sci.* **2010**, *75*, E186−E193.

(74) Nagy, A.; Harrison, A.; Sabbani, S.; Munson, R. S.; Dutta, P. K.; Waldman, W. J. Silver Nanoparticles Embedded in Zeolite Membranes: Release of Silver Ions and Mechanism of Antibacterial Action. *Int. J. Nanomed.* **2011**, *6*, 1833−1852.

(75) Zampino, D.; Ferreri, T.; Puglisi, C.; Mancuso, M.; Zaccone, R.; Scaffaro, R.; Bennardo, D. PVC Silver Zeolite Composites with Antimicrobial Properties. *J. Mater. Sci.* **2011**, *46*, 6734−6743.

(76) Schmidt, B.; Katiyar, V.; Plackett, D.; Larsen, E. H.; Gerds, N.; Koch, C. B.; Petersen, J. H. Migration of Nanosized Layered Double Hydroxide Platelets from Polylactide Nanocomposite Films. *Food. Addit. Contam., Part A* **2011**, *28*, 956−966.

(77) Busolo, M. A.; Fernandez, P.; Ocio, M. J.; Lagaron, J. M. Novel Silver-Based Nanoclay As an Antimicrobial in Polylactic Acid Food Packaging Coatings. *Food. Addit. Contam., Part A* **2010**, *27*, 1617−1626.

(78) Liu, J.; Katahara, J.; Li, G.; Coe-Sullivan, S.; Hurt, R. H. Degradation Products from Consumer Nanocomposites: A Case Study on Quantum Dot Lighting. *Environ. Sci. Technol.* **2012**, *46*, 3220−3227.

(79) Windler, L.; Lorenz, C.; von Goetz, N.; Hungerbühler, K.; Amberg, M.; Heuberger, M.; Nowack, B. Release of Titanium Dioxide from Textiles During Washing. *Environ. Sci. Technol.* **2012**, *46*, 8181−8188.