



Key principles and operational practices for improved nanotechnology environmental exposure assessment

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Nanotechnology is identified as a key enabling technology due to its potential to contribute to economic growth and societal well-being across industrial sectors. Sustainable nanotechnology requires a scientifically based and proportionate risk governance structure to support innovation, including a robust framework for environmental risk assessment (ERA) that ideally builds on methods established for conventional chemicals to ensure alignment and avoid duplication. Exposure assessment developed as a tiered approach is equally beneficial to nano-specific ERA as for other classes of chemicals. Here we present the developing knowledge, practical considerations and key principles need to support exposure assessment for engineered nanomaterials for regulatory and research applications.

Environmental risk assessment (ERA) for any chemical relies on characterizing both exposure—the predicted environmental concentrations (PECs) of a substance that relevant receptors (human or species populations) encounter—and the hazard threshold—the predicted no-effect concentrations (PNEC) above which an effect on a relevant biological endpoint in those receptors is anticipated. An unacceptable level of risk is deemed to occur where exposure is predicted to exceed the hazard threshold. Within existing ERA frameworks for conventional chemicals, for example, for pesticides in the EU¹, a tiered approach to both exposure and hazard assessment is commonly used. Evaluations start using simple and conservative approaches for PEC and PNEC derivation and only advance to more complex (often more costly) and realistic approaches, which refine the exposure and hazard predictions if earlier tiers identify potential risk. For engineered nanomaterials (ENMs), it is accepted that this conventional ERA paradigm can be applied, albeit with adaptations to account for nano-specific considerations².

For the hazard characterization of pristine ENMs, it is generally accepted that the effect endpoints used for conventional chemicals, for example, survival and reproduction, are broadly applicable³. Hence, PNEC derivation for ERA can draw on existing hazard testing approaches. However, that said, some additional, ENM-specific considerations are needed. The outcomes of hazard testing for ENMs should be linked to the known possible range of ‘forms’ and ‘states’ in the environment as closely as possible^{4,5}. Thus, ENM

hazard assessments should include studies with environmentally aged forms, including non-nanomaterial forms such as dissolution products. Changes in form during the test should also be quantified, for example by monitoring dissolution, speciation chemistry and surface transformations. The overall goal should be to allow the derived hazard endpoints to be linked to forms measured or modelled in the environment to create a link between realistic environmental exposure assessment and hazard potential.

Environmental fate assessment remains a critical aspect of studies to understand how ENMs behave in the environment, and hence the nature and concentrations of the materials to which human and environmental species may be exposed. Any fate assessments for ENMs must address the diverse nature of ENM forms, for example, size, shape, organic coating and states, for example, free versus matrix-embedded, monodispersed versus agglomerated (see Box 1 for the fate terminology definitions used in this Review). At the same time the fate assessment must also take into account ENM behaviour, that is, the dynamic transformations affecting form and state that ENMs can undergo prior to and after entering the environment. These together determine the functional fate pathway that an ENM will follow after its release; following that pathway to create a robust exposure assessment for ERA is the challenge we examine in this Review.

In a screening tier nano-specific ERA exposure assessment, information on detailed ENM fate processes may not be important, because at this level, the aim is simply to predict average form and

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Box 1 | Terminology relevant for fate and exposure assessment in ERA

Reactors: a compartment, for example, waste management infrastructure, air, soil, water, sediment or biota, providing conditions in which ENM transformation can occur. Similar transformations may arise in different reactors (for example, dissolution in freshwater, soil pore water or biota gut) and multiple transformations may occur in a single reactor.

Form: ENM structure and composition at the individual particle level, including homogenous or core-shell chemistry, morphology (size, shape) and the presence of a manufactured or environmentally derived ('ecocorona') coating. (Please note that 'form' has been used previously to describe ENMs associated with other product components, which we here term 'state').

State: How ENMs exist in the environment, for example as free particles, matrix-embedded, agglomerated with each other (homoagglomeration) or with suspended particulate matter (heteroagglomeration), or bound to a solid matrix, for example in a soil.

Transformation: any reaction that changes the chemical form or state of ENMs including both chemical, physical and biological processes.

Functional fate pathway: chain of transformations forming a linked sequence through which an ENM passes during release and transfer through waste and environmental reactors; ultimately determines the ENM form and state to which biota are exposed.

Functional fate group: set of ENMs that follow a similar functional fate pathway, such that they may be categorized together for assessment based on comparable form and state.

state independent concentrations over extended emission times or spatial scales. However, where greater realism of ENM fate prediction is demanded (that is, as we move to higher tiers of assessment), greater consideration is given to form and state to ensure the correct quantification of key reaction and transport processes governing exposure. The significance of these nano-specific considerations for exposure assessment may also differ depending on the regulatory regimes under which an ERA is conducted. For example, where exposure is a key consideration (as in, for example, a United States regulatory approach), transformation of ENMs to a chemically modified or non-nano form that reduces the PEC of the ENM itself, will be interpreted as a reduction in the level of risk since it is less likely that the nano-specific PNEC is exceeded. Whereas under a regime such as that in the EU, which more clearly enshrines the precautionary principle into risk assessment, the potential for physicochemical transformations affecting form and state need to be considered more holistically, including not only how they affect the environmental fate, but also their impact on ENM hazards (such as increasing effects through dissolution). Recognising that the accurate prediction of exposure is likely to be the most challenging aspect of nano-specific ERA, we present here the developing knowledge and key principles that can support ENM exposure assessments for research and regulatory applications.

Contemporary ENM fate prediction for ERA

Applications of nanotechnology cover many general product and process uses, including packaging, paints and coatings, cosmetics, electronics and consumer products, as well as those necessitating specific ERA considerations, such as medicines, plant protection products, biocides, food and food packaging materials^{6–8}. Exposure assessment tools for use in nanotechnology ERA must, therefore, be flexible to allow use across a range of nano-enabled products

(NEPs) at their different life cycle stages, but also complete enough to allow PEC estimation in the different environments into which ENMs may be released. A tiered approach, allowing screening-level ERA for whole production chains at large regional scales, as well as for product-specific and local scale assessments can provide such flexibility.

Both measurement and modelling can be useful for exposure assessment. Whenever possible, ENM measurements should assess not just total concentrations, but also form and state, for example, ENMs heteroagglomerated with suspended sediment versus non-heteroagglomerated. Progress in environmental analysis is now making such multifaceted analyses possible^{9–13}. However, routine and robust ENM detection and characterization in environmental settings, for example, natural waters, soils, effluents, sludges or biota, remain challenging due to high background concentrations and the presence of naturally occurring nanoscale particles. Consequently, information on form and state is frequently unavailable and even total concentrations may be uncertain or even unknown⁵. Environmental fate modelling is, therefore, an essential aspect of exposure estimation, providing (1) rapid predictions of PECs in different environmental compartments at different levels of complexity; (2) prospective assessment of new ENMs; and (3) large scale and temporal multimedia assessments where the costs of measurement may be prohibitive.

A tiered ERA framework for ENMs needs exposure models that span a range of complexities, from minimalist, conservative approaches to advanced tools commensurate with the most up-to-date scientific knowledge of processes affecting functional fate pathways and transport. The conceptualization of form and state transformation is already considered within some existing fate and exposure models (although these may employ different terms). Models that use only equilibrium partitioning approaches have been shown to be unsuitable for ENMs, for which transformations are predominantly under kinetic control and in many cases irreversible¹⁴. Fate models for organic compounds (such as pesticides) may include both kinetic transformation processes, expressed as 'half-lives'¹⁵ or first-order rate constants¹⁶ and equilibrium partitioning^{16,17} to describe key state and form transitions. Such parallels suggest that these models may be suitable for use in ENM fate and exposure assessment. However, this is unlikely to be the case, largely because key ENM transformations such as heteroaggregation^{18,19}, dissolution²⁰ and sulphidation²¹ are dependent on ENM size and so require a model conceptualization that depicts a particle size distribution (or at a minimum, an explicit size). Further, key concepts for organic chemicals, such as partitioning according to K_{ow}, are widely accepted not to be relevant for ENMs²². Thus, while ENM fate and exposure modelling can build on aspects of existing chemical fate and exposure models, a bespoke approach to fate model development is needed.

Release forms and state

A common starting point for fate assessment at any level of complexity is the identification of ENM release pathways throughout NEP value chains²³. Such analysis can help to identify major material flow pathways and point or diffuse sources, form and state on release, and the subsequent flows into and through waste streams and the environment²⁴ (Fig. 1). By understanding the different life cycle stages of NEPs, it is possible to identify any relevant temporal and spatial patterns in the nature and scale of releases. This quantitative assessment can be used as the input to exposure models at any tier. The value of information on form, state and spatiotemporal distribution is, however, greatest for the more complex, higher-tier models.

Numerous studies have collated data on concentrations released at different stages of ENM value chains, including for textiles^{25,26}, paints^{27,28} and polymeric composite NEPs^{29–32}. From such studies and the analysis of wearing and weathering processes, a set of

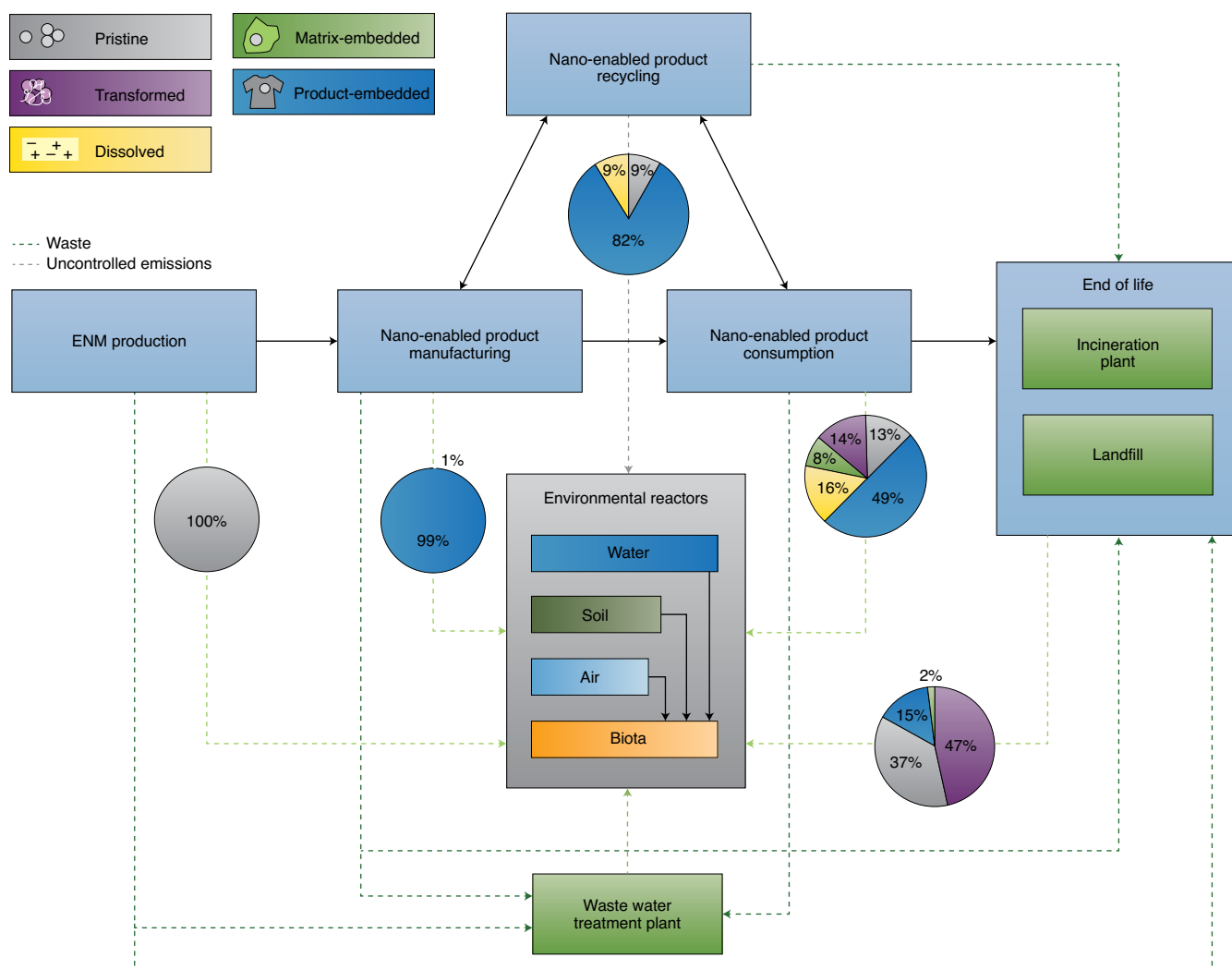


Fig. 1 | Overview of release pathways of engineered nanomaterials (ENMs) along their life cycle, showing entries to environmental reactors. Dark green dashed lines represent managed emissions, light green dashed lines are uncontrolled emissions. Pie charts show proportions of different ENM release forms entering the environment, exemplified using release data for Ag ENMs from nano-enabled products as reported in ref. ³⁸.

five different generic release states has been proposed as representative of ENM inputs into waste and the environment: (1) matrix-embedded ENMs, (2) ENMs heteroagglomerated with matrix components, (3) ENM homoagglomerates, (4) free ENMs and (5) 'disintegrated' ENMs (chemically, ions; physically shorter fibres or smaller particles)³³. For matrix-embedded and heteroagglomerated ENMs released from NEPs, the properties of the released materials will be determined primarily by those of the associated material (similarly hazard can also be modified by matrix association^{34–37}). Thus, the fate pathways followed by ENMs in an embedded state may differ from those for the same ENMs in a free or agglomerated state. These effects of the matrix need to be considered in higher tier fate assessment, especially as such associated states can represent up to 50% of the mass of total releases for some ENMs³⁸. For both agglomerated and free ENMs, nano-specific transformation and transport processes are important. This may not be the case for disintegrated ENMs. In particular, if transformed into non-nano forms, for example, ions. Indeed, if transformation into non-nano forms is irreversible, then this signals the end of the need for ENM-specific exposure assessment, although, for a complete ENM exposure assessment, their continued consideration is prudent.

Where ENMs are released from NEPs from product applications, abrasion, washing, weathering or general wear from use, their form and state can be further significantly transformed by passage through waste stream reactors before entering the environment. Processing facilities such as wastewater systems, anaerobic digesters, municipal waste incinerators, landfill and recycling facilities represent key gateway points for releases. During transit through waste reactors, ENMs may transform chemically, for example, sulphidization^{39–43}, redox reactions^{44,45} and physically, for example, homo- and heteroagglomeration^{46,47}. These waste reactor transformations are predictable from thermodynamic and chemical principles in most cases, except for a few instances for which size-dependent reactivity is sufficiently important that ENMs of different dimensions follow different functional fate pathways, for example, for CeO₂⁴⁵. The extent of transformation in waste reactors results from the interplay of reaction rates and residence time. For certain transformations, transit time will be long enough that complete transformation can take place, but this may not always be the case. For predictions, reactor transit periods will often be known, while reaction rates have to be derived from experimental studies. Combining this information ultimately dictates the nature (forms and states) of releases to subsequent environmental reactors.

Principles for ENM exposure assessment

The use of a tiered approach for exposure assessment in ERA by definition will necessitate a series of model applications operating at different levels of precision and realism. At the lowest tier of fate assessment, the emphasis is on estimating exposure in a simple way that reduces data requirements to a minimum. This typically results in the computation of temporally and spatially averaged PECs without consideration of chemical forms and/or states. Knowledge of the general properties of the substances, for example, whether a given ENM is susceptible to dissolution, might be used to shape the assumptions made, but would most likely not be used quantitatively. Assumptions on the rate of release into the environment are simplified and likely to be conservative (for example, full release, no removal through waste management). As the assessment process moves through the tiers, the degree of realism and complexity of predictions increases. Aspects of fate prediction such as temporal and spatial variability in environment properties (for example, river flow over time), transport of the substance between environmental compartments, and transformations of form and state, may all find use in higher tier assessment.

Within exposure assessment at all tiers, at least some understanding of the nature of the major processes determining ENM fate and behaviour is useful, and higher tier assessment requires the explicit inclusion of such knowledge. The development of theory and algorithms that adequately represent key transformation processes individually was an essential first step in improving ENM exposure assessment, coupled with the development of functional assays to generate the data needed to parameterize the resulting equations. Based on this knowledge and building on recent research to evaluate the application of these transformations and transport processes to describe aspects of environmental ENM fate, we here identify a set of ten emerging key principles that we believe offer a sound foundation for improving ENM-specific exposure modelling to support ERA. We identify how these principles may be applied in exposure modelling tools applicable at different ERA tiers for simple to complex assessments.

Principle 1—Technical source and reactor design strongly impact on release rate. The majority of ENM releases are predicted to come from managed facilities during ENM and NEP production, use and disposal. In production facilities in countries with strong occupational exposure management policies in place, specific infrastructure is often in place to limit releases, for example, filtration of factory air^{48,49}, which removes ENMs based on their high diffusivity⁵⁰. Where such infrastructure is missing, greater occupational exposure and local releases may happen. When released to wastewater, the prevailing reaction conditions and residence times in treatment systems can lead to heteroagglomeration with flocs and subsequent sedimentation that removes a high proportion of ENMs from effluent flows to surface waters (although potentially the ENMs may enter sludge from where they may reach soils through land spreading^{47,51}). Again, this is most relevant to locations with large-scale advanced technical systems, whereas in locations with simpler (or no) treatment, a different profile of releases may occur that may be characterized by a higher proportion of untransformed or marginally transformed ENMs. Although even under these circumstances, some transformation such as the loss of highly labile coating may occur. For ENMs that enter and survive incineration, advanced facilities will include emission scrubbing with known effectiveness to prevent particulate releases to air that may be absent from less advanced facilities. Within modelling frameworks, these mitigating steps, and their relative efficiencies, can be included at different levels of complexity, that is, by simply modifying release estimates by considering release only in a certain form or state; or by modelling ENM removal as partitioning in wastewater treatment in models suitable for intermediate tier assessment^{51,52}.

Principle 2—Transformation reactions of ENMs in different reactors can be derived from chemical and thermodynamic principles. The chemical and physical transformations of ENMs will follow relatively simple principles that are primarily dependent on the composition of the core material and of the environment into which they are released. When entering harsh waste treatment systems, for example high-temperature incinerators, transformation will be rapid and will represent a ‘dead end’ for most organic and inorganic ENMs, resulting in a complete transformation that unifies speciation, for example, for CuO to CuS and ZnO to ZnS⁵³, or in destruction, for example, combustion of intentional or incidental nanoplastics, or incorporation into incineration fly ash for CeO₂⁴⁵. Combustion at temperatures over 800°C will also destroy any organic coatings. Some more recalcitrant ENMs, for example, TiO₂, may survive high-temperature incineration. The likelihood of such behaviours can generally be predicted by the inclusion of physical parameters such as melting point and redox activity into models, with the proviso that the remaining fraction of unreacted ENMs may be overestimated due to the high surface reactivity of some ENMs. Parameter estimates are available for many widely used ENMs materials, for example, CeO₂⁵⁴, Al₂O₃⁵⁵, but will need to be established for others.

Under less harsh conditions, transformations will occur as a result of the interactions between an ENM surface and its surroundings. In the atmospheric reactor, ENMs will undergo oxidation, adsorption of surface organic compounds or physical transformations such as homo- and heteroagglomeration. These are governed by ENM composition, particle and gas concentrations, as well as on thermodynamic conditions, such as temperature, and UV exposure. Sulphidization is well known and predictable for ENMs containing chalcophile elements such as Ag, Zn and Cu in reducing environments, such as sewage treatment, landfill and anoxic sediment. Dissolution rates are governed partly by ENM characteristics, but are also potentially predictable from environmental conditions such as ambient temperature and environmental chemistry, including pH and organic matter concentration⁵⁶. Modelling of such dynamic changes under different prevailing conditions is feasible for processes in water, for example for dissolution⁵⁷, and air⁵⁸, for inclusion into higher tier exposure models.

Principle 3—Heteroagglomeration is a key process in all reactors but does not always need to be modelled. ENMs in air^{50,59,60}, wastewater^{40,61–64}, surface waters^{65–67} and soils^{68,69} aggregate with naturally occurring particulate matter. Attachment efficiency (α), which describes the probability that an ENM–natural particle collision will result in sticking, is currently seen as the most useful and logical fate descriptor for this process⁷⁰. Use of α can explain differences in settling rate or loss of the free—but not soil- or floc-associated—ENMs, including the effects, if any, relating to different size or coating^{19,65–67,71,72}, indicating a benefit for the use of α in intermediate and higher tier ERA fate modelling, for example, for natural waters. However, while useful in some contexts, there are other cases where using specific values of α may introduce unneeded complexity into models. In air, the use of a single value for α has so far proven sufficient for modelling dispersion behaviour⁶⁰. Furthermore, wastewater treatment plants may also not warrant using α for detailed heteroagglomeration modelling, since (1) high ENM to biosolid collision frequencies and attachments make the precise α values less critical and (2) the high prevailing ionic strength effectively shields the electric double layer to increase α for all ENMs relative to values expected in freshwaters. Under these circumstances, simple modelling using partitioning coefficients can be used in such specific cases⁷³. In reality, stormwater overflows may even dominate ENM releases from wastewater systems to water bodies, independent of attachment processes⁷⁴.

Principle 4—Parameter α describes attachment, but its measurement is operationally defined. Despite limitations on potential use as identified above, measured hetroagglomeration rates still have some value as descriptors for fate processes for aspects of exposure modelling in ERA. Methods for measuring α are currently being developed to predict hetroagglomeration in natural waters⁷⁵ and also in soils and sediments⁷⁶. In soil studies, ENM specific α values are derived from column tests using colloid filtration theory, assuming that only attachment occurs. However, α obtained from such tests will be operationally defined⁷⁷, because other processes such as air–water interface interactions and straining occur⁶⁸ to an extent dependent on the structure of the media tested⁷⁸. In principle, α values derived from column testing are integrative over all deposition-relevant properties of the tested soil relating to its texture, porosity and chemistry. However, ranking soils for ENM mobility will only be possible if column tests, including the way α is calculated, are standardized, which has not been the case. Consequently, it has been argued that uncertainties in determining α in column tests do not support its use in landscape level modelling⁷⁹. Developing batch tests (similar to those developed for hetroagglomeration in surface waters) to provide structure-independent α values could alleviate the need for column testing and methods for this are emerging⁸⁰. However, even if an accurate α value can be measured, its use may ultimately be limited for soil transport modelling, because other processes, such as bioturbation and preferential flow, may play a more dominant role in natural systems⁸¹.

Principle 5—Coating and size of pristine ENM play relatively minor roles in fate processes. Bench-scale experiments conducted under controlled conditions in simplified media have shown size, core and coating dependent ENM fate processes, for example, dissolution^{20,56} and heteroaggregation^{10,82}. For matrix-embedded or matrix-associated ENM release states, any such differences may be masked by the dominant influence of the surrounding material that may negate the need for nano-specific ERA for some product applications. Furthermore, even for agglomerated and free ENM states, the dominant conditions in waste or environmental reactors, for example, organic material content and redox conditions, will tend to unify ENM properties and, thus, weaken process dependencies on size and coating. Exposed to bacterial action, ENMs may lose their polymer coatings (if it is sufficiently biodegradable) and become covered in a ‘corona’ of natural organic matter. Even if the original coating is recalcitrant, the polymerized surface can become similarly overcoated by organic matter. This environment driven ‘ecocorona’ will have a dominant and unifying effect on heteroagglomeration dynamics even for initially divergent ENMs⁸³. In soils, it has been shown that transport distances in unsaturated soils will be generally low, independent of particle characteristics⁸⁴ (and soil type⁸⁵), suggesting similar transport dynamics for physicochemically divergent ENMs. In air, meteorological conditions, rather than ENM form and state, predominantly govern dispersion^{86,87}. Thus, even though particles may initially have different characteristics, the key processes determining fate such as dissolution, heteroagglomeration, deposition and sedimentation in different environmental compartments will be mainly determined by environmental conditions rather than ENM characteristics.

Although we contend that under realistic environmental conditions, behaviour dependent on particle properties may be less prevalent than under more simplified laboratory conditions, there are still nonetheless cases where property-specific environmental fate has been found. However even when demonstrated, often such effects have had only a relatively minor effect on fate parameters, such as sedimentation rates, affecting partitioning and transport⁷³. Hence, although worthy of consideration, they may be of limited importance even within higher tier exposure assessments. The most likely exceptions to this principle may occur for more inert ENMs, such

as for CeO₂, for which size-specific effects have been more commonly observed in real-world environments. For example, Geitner et al. found a greater fraction of small CeO₂ ENMs remaining in the upper floc layers of sediment relative to larger particles and also higher bioavailability for plant, snail and insect species⁷¹. Also for CeO₂, Gogos et al.⁴⁵ found that larger ENMs were more resistant to reduction during anaerobic digestion and incineration than small particles and, thus, better survived through sewage sludge production and incineration.

Principle 6—Some ENM will follow similar fate pathways to form similar functional fate groups. Some initially different ENMs will follow the same functional fate pathways, that is, be subjected to the same transformation and transport processes upon passage through linked waste and environmental compartments. These ENMs may be associated as a functional fate group based on similarities in final form, state and transport behaviour. ENMs in the same functional fate group may potentially be combined with an acceptable level of accuracy as needed for specific tiered level modelling during PEC estimation. As transformation processes are largely predictable from chemistry, colloid theory and transport dynamics, it is possible to link algorithms for functional fate pathways with mechanistic fate models assessing, for example, speciation, soil or water transport, and so on. Furthermore, the application of the functional fate group concept can be used for grouping and read-across of exposure for different ENMs (for example, different sizes of coated ENMs with the same core chemistry), as transformed ENMs present as a single form for the exposure assessment. This concept is shown schematically in Fig. 2.

Principle 7—Chemical transformation and dissolution are key determinants of exposure. Dissolution is a key transformation reaction affecting potential exposure⁸⁸ and biouptake^{89,90}. During laboratory tests, the attachment efficiency of ENMs to organisms has been shown to be a good predictor of their uptake potential and subsequent toxicity⁹¹. However, this is only relevant should intact ENMs actually reach organisms, which may be limited by transformations⁹² or attachment to other surfaces in more realistic environments⁹³. Engineered nanomaterials in real environments and even in bioassays may often have limited mobility due to attachment to abiotic surfaces, whereas ions released by dissolution can diffuse more freely towards biological receptors and transfer across cellular boundaries. For exposure modelling, therefore, the ENM dissolution rate coefficient (k_{diss}) could be a more important fate descriptor than α . Indeed, to date, no data have emerged linking α as a single driving predictor of ENM exposure for organisms⁹³, whereas k_{diss} has been convincingly linked to exposure in waters^{94,95} and in relation to soil incubation times^{96,97}. This fate descriptor, thus, offers a potential approach for future modelling of ENM bioavailability based on media-specific dissolution behaviour at least for readily solubilized ENMs. These observations strongly indicate that form as arising from chemical speciation is extremely important in decisions on modelling ENM exposure, especially at higher tiers.

Principle 8—Interactions with biota can affect ENM form and state. Recent insights have established the roles of organisms as reactors within ENM functional fate pathways. Microbial activity in sewage treatment plants is the primary cause of the anoxic conditions in these systems that support chemical transformations, for example, sulphidization, and also the degradation of manufactured organic ENM coatings⁹⁸. Further, bacterial, plant and animal exudates may associate with the ENM surface^{99,100}, either displacing or overcoating the manufactured layer^{101,102}. A further biotic mechanism for ENM transport is through bioturbation by ecosystem engineers, for example, earthworms in soil or worms and amphipods in sediments. A simplified model for estimating the contribution of

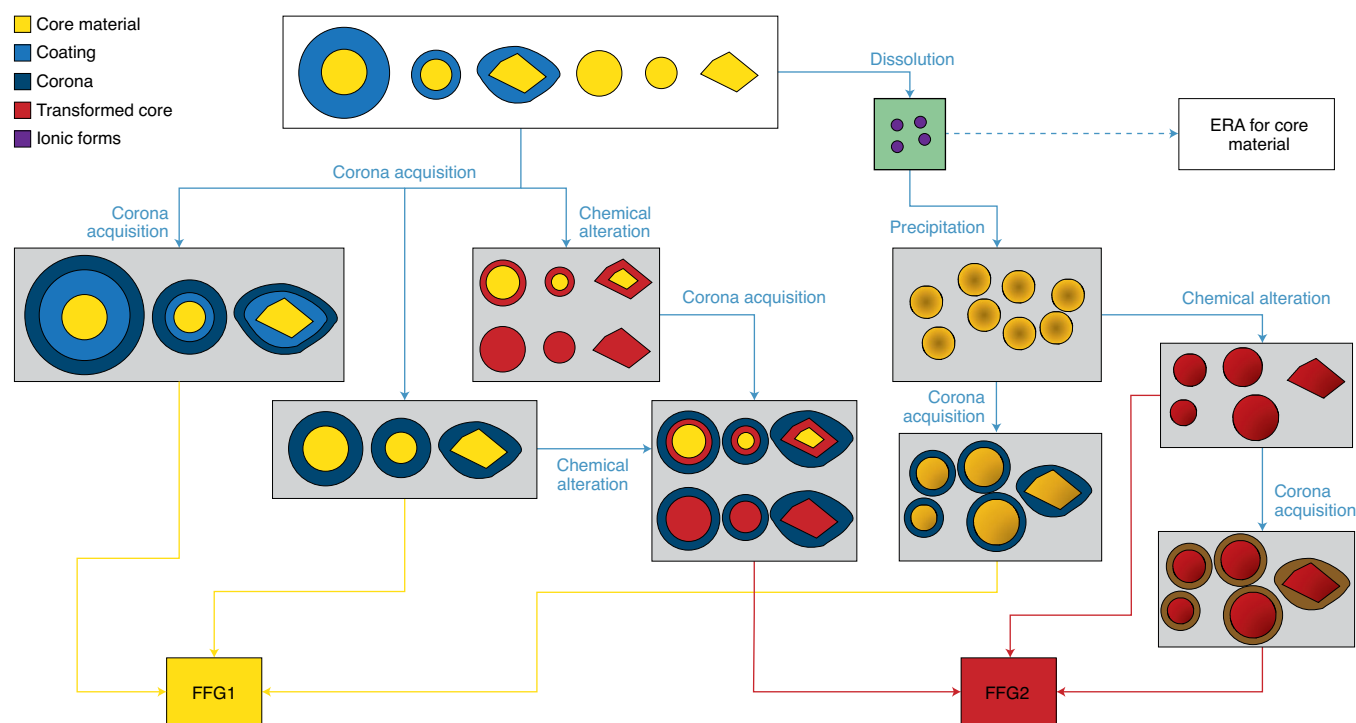


Fig. 2 | Conceptualization of the functional fate pathway and functional fate grouping approaches. In the environment, different manufactured ENMs (top box) of identical composition have different form (in this case size, shape and surface coating); when entering a waste or environmental reactor these ENMs undergo different transformation processes as labelled on relevant blue ‘reaction’ arrows; transformations lead to changes in ENM form and may lead to further transformations that ultimately result in the generation of different functional fate groups (FFG1, chemically untransformed with corona; FFG2, chemically transformed with corona) whose individual members may have started life with very different compositions/properties but who have been transformed into functionally similar groups (yellow and red ‘FFG assignment arrows’). ENMs within a FFG are expected to behave similarly in terms of subsequent fate behaviour and hazard profiles for ERA, while fate and hazard between the different FFGs are expected to be different.

earthworm bioturbation to silver ENM transport in soil⁸¹ suggested that in areas of moderate to high earthworm density (>150 individuals m^{-2}), bioturbation may be a key vertical transport process. This, coupled with their role in producing macropores¹⁰³, suggests an important role for earthworms in ENM soil transport.

ENMs that are ingested by organisms and accumulated into tissues may also be biogenically transformed under physiological conditions to new forms and states¹⁰¹. For example, in earthworms internalized particulate Ag was found following exposure to both Ag ENMs and Ag ions⁹². The similar form found for these ENMs suggests that earthworms not only alter ENMs biogenically, but may also produce nano-sized particulates from the ionic metal, potentially as part of a detoxification strategy¹⁰⁴. Similar effects have been found in isopods (woodlice) exposed to Au ENMs. In this case, the Au ENMs found in the organisms were smaller than those used for the exposure. Furthermore, ionic Au exposure also resulted in the presence of 60 nm Au particles formed in situ. As Au ENMs are generally considered poorly soluble in simple media, this suggests an active biological process for dissolution and particle ripening in some biota indicating a role for organisms as reactors for ENMs.

Principle 9—Modelling should focus on the discrete set of processes that truly drive transport, transformation and bioavailability. Experience with other chemical classes suggests that not all reactions and/or transformations that influence the behaviour and fate of ENMs need to be considered in order to provide useful exposure predictions. For example, soil metal chemistry can be modelled using empirical expressions with minimal variables that effectively represent only the most important underlying

reactions¹⁰⁵. For nano-specific exposure modelling, it seems reasonable to focus on the dominant processes, as this can reduce the required effort. Cross comparisons of outputs and sensitivity analyses for models designed to operate at different tiers can be useful in this respect, as they may identify a key variable describing a transformation or transport processes not represented in a lower-tier model. This would allow targeted efforts to improve the accuracy and realism of simplified models only where most useful.

Within nano-specific exposure assessment, the majority of the dominating reactions will, with some uncertainty, often be inferable from general chemistry^{106,107}, colloid theory^{66,108,109} and from bulk ENM characteristics²⁰. Experimental studies and modelling can, therefore, focus on quantifying only functional properties relevant for specific ENM fate. For example, the potential persistence of a metal and metal oxide ENM against dissolution indicates the likely importance of heteroagglomeration as the key fate process, while for ENMs subject to rapid dissolution (in the order of hours), heteroagglomeration is unlikely to be key. For those persistent ENMs, heteroagglomeration rates in one reactor, for example, wastewater treatment, would be expected to be similar to those in another, for example, surface water, as long as floc concentrations are accounted for. For ENMs subject to rapid immobilization but relatively slow dissolution, for example in soils and sediments, dissolution rate may be key for biotic exposure and impacts^{88–90,96,97,110}. There are still some remaining situations in which processes are currently largely ignored in fate modelling due to a lack of knowledge about their importance. This applies, for example, to the processes of downward transport and detachment in soils, which has been found in column tests, albeit at low rates^{85,111}. In such situations, research is required to establish a case for inclusion or exclusion of such

parameters in fate models as compared to other potentially important processes such as bioturbation⁸¹.

Principle 10—The required and/or achievable precision of model parameters is orders of magnitude and so standardized testing (with standardized soils and waters) is justified in this context.

Most ENM exposure predictions are currently less precise than those for conventional chemicals and will likely remain so. Models for conventional chemicals rely on equilibrium constants whereas ENM modelling often relies on dynamic (kinetic) fate descriptors, such as α ⁷⁵, for which quantifications are usually less precise compared to thermodynamic descriptors¹¹². This measurement uncertainty is due, for example, to issues arising from the need to make multiple quantifications over time for kinetic descriptors compared to only a single assessment for a thermodynamic descriptor. Consequently, it currently seems wiser to apply constants pertaining to bulk characteristics for predicting form and state changes in untested conditions, instead of using one of the numerous reported nano-specific fate descriptors derived from studies under different specific conditions^{113,114}.

Sensitivity analyses of ENM exposure models have shown that attachment efficiency, α , is one of the most important parameters for PEC estimation, especially in freshwater systems⁷⁰. However, this is only the case if α is within certain ranges where PECs are most dependent on changes in α . For example, in freshwaters, α must attain or exceed critical values at which PECs become most sensitive, as below these there is likely to be little if any effect on fate from variations in α . This is because of the co-occurrence of transformation and/or dissolution reactions that change ENM properties⁷⁰. A very high attachment efficiency (0.1–1.0) in any reactor mostly implies that ENMs are poorly available, transport identically to the natural particles or flocs they are associated with and therefore travel only short distances in soils or similar to the suspended matter in surface waters. Here, small differences in the actual value of α only have a minor effect and values below 0.001, which indicate a long relevant lifetime of free (not heteroagglomerated or soil-associated) ENMs, remain difficult to determine. Given the inaccuracies in determining α , only order of magnitude differences in values of attachment would be expected to have a relevant effect on fate.

Kinetic parameters may, in theory, vary with different reactor chemistries. However, it is unlikely that the current imprecise methods we have for determining these parameters will systematically capture this variance at a resolution sufficient to impact on modelled fate. Functional, strictly standardized testing to determine ENM fate parameters with only one or a limited number of media is, therefore, justified because it is unlikely that more extensive, and thus more costly testing, will contribute to more precise modelling¹¹⁵. The development of standardized testing protocols, for example, via the Organisation for Economic Co-operation and Development, is needed to allow stakeholders to efficiently and consistently parameterize exposure models. Current knowledge suggests that heteroagglomeration and dissolution are the processes for which standardized protocols would be most useful, although there is value in knowing other potential fate process rates such as transformation rates and bioturbation rate for soil fate assessments.

Integrating ENM exposure modelling in ERA

Understanding of environmental fate processes for ENMs has advanced significantly over the past decade. Much of course remains to be done, not least to ensure that methods and models remain applicable to new generations of ENMs. However, knowledge about ENM fate processes, at least for the most commonly researched materials, is now at a level where construction of ENM exposure models at a similar range of complexities, as we know for

conventional chemicals, is possible, and indeed has already been done to a degree^{116,117}. Available categories of tools include:

- Material flow analysis (MFA) models that predict releases to all waste and environmental compartments, but have limited consideration of further fluxes or transformations³⁸.
- Spatially and/or temporally resolved process based models that predict environmental concentrations within one compartment, including transformations and transport within that compartment (that is, mechanistic fate models)^{19,58,118}.
- Models that simulate the distribution of ENMs across multiple environmental compartments, including biota at steady state or with some dynamic aspects^{119–121}.
- Uptake of ENMs in organisms applying physiological based kinetic biotic uptake models using rate constants for adsorption, distribution, metabolism and excretion (ADME) processes not based on equilibrium partitioning^{22,89}.

Ultimately, the integration of ENM-capable fate and exposure models into ERA frameworks will depend strongly on the requirements of particular regulatory regimes and the requirements of expert, regulatory and industry stakeholders. In order to shape the discussion, we here use an illustrative, generalized approach comprising three tiers termed ‘low’, ‘intermediate’ and ‘high’ to identify the features of exposure assessment tools that may be used for different tiers within an ERA framework. Table 1 and Fig. 3 summarize the general features of a modelled exposure assessment that might be seen at each tier and provides examples of tools that could find use in the ‘intermediate’ and ‘high’ tiers, with the assumption that the lowest tier would encompass primarily thermodynamically-derived predicted values.

The ‘low’ tier emphasizes very simple calculations of exposure, using ‘worst case’ estimates of release and aiming to produce conservative estimates of PECs that do not rely on quantitative knowledge of key transformation processes or their rates. Furthermore, the environmental scenario should be defined as simply as possible, with an emphasis on minimizing or removing the need for knowledge on rates of transfer between compartments. For example, based on assessment of environmental release points, PECs could be calculated on the basis that all the material enters the environmental compartments that it could potentially enter. In the extreme case, where information on release points is poor or unknown, PECs could simply be calculated for all environmental compartments for which assessment is needed, without any consideration of release pathways. In this situation, the definition of the environmental scenario is limited to the capacity of the receiving compartments (for example, soil mass, freshwater volume). There are currently no widely recognized models that take such a simplified approach for fate assessment. Simplified models, such as the Swiss Precautionary Matrix for Synthetic Nanomaterials¹²² and LICARA nanoScan¹²³, which exist for risk assessment, have limited consideration of exposure. Nonetheless, such approaches may be simple enough to be implemented outside a formal modelling tool, for example, in a spreadsheet.

The ‘medium’ tier generally includes multimedia models covering different environmental compartments, but that lack a high degree of spatial and/or temporal resolution. Such models provide a balance between ease of calculation and environmentally realistic process descriptions. Scenarios represented should include the important ENM fate processes, but data requirements should not be too onerous. Such models can be steady state or can include some dynamic aspects, noting the limitations of applying steady state calculations for ENMs as highlighted earlier. Here, rates of ENM transformation can be placed within the context of environmental residence times, guiding the simplified assumptions to be used. For example, for dissolving ENMs the rate of dissolution could be

Table 1 | Summary of general features of release estimation and fate modelling and relevant approaches and models for application and use within an illustrative three-tier environmental risk assessment framework

	Risk Assessment Tier		
	Low	Intermediate	High
Release estimation			
Release rates and receiving environmental compartments	Identification of receiving compartments Likelihood of release to each receiving compartment	Per-compartment, time-independent or time-dependent release rates	Per-compartment, time-dependent, spatially distributed release rates
Release factors	Unity (that is, all material produced/used is released) or standard release factors	Standard release factors, or refined release factors based on measurements	Refined release factors based on measurement and with spatial considerations (for example, regional/local scale)
Release forms	No	Simple consideration of form (for example, mean size or size distribution on release) if data available Worst cases (for example, all dissolved, all pristine)	Multiple
PEC estimation			
Fate process parameters	Not required	Compartment-specific	Compartment-specific. Possibly explicit dependence on environmental parameters (for example, pH)
Inter-compartmental transfer rates	No-losses from compartment only, if turnover rate defined	Constant or time-variable	Time-variable
Consideration of form and state	No	Simple consideration of form (for example, mean size or size distribution on release) if data available Form and state changes via process algorithms	Multiple forms and states Form and state changes via process algorithms
Spatial and/or temporal resolution	Lumped by compartment Possibly compartment subtypes (for example, soil types)	Lumped by compartment Possibly compartment subtypes and/or nested scales (for example, local, regional, global)	Yes Problem-dependent choice of spatial extent and resolution
Steady state or time-variable	Steady state if a turnover rate is used, time dependent if not	Either	Time-variable only
Example fate models			
Underlined models developed or updated in the NanoFASE project	No model — simple calculation	SimpleBox4nano, MendNano, NanoFate, GuideNano	NanoFASE (soil and aquatic), LOTOS-EUROS (atmosphere), Dale et al. ⁵² (freshwater), NanoDUFLOW (freshwater)

compared with hydrological residence time to guide the choice of hazard assessment of the ENM or its dissolved form. Models in this tier, such as SimpleBox4Nano¹²⁰, MendNano¹¹⁹ or nanoFATE¹²¹ are likely to be of greatest use for most common application in prospective nano-specific ERA. For example, the SimpleBox4Nano¹²⁰ tool is based on the regulatory approved model SimpleBox. Features such as a potential for regulatory acceptance, more limited data requirements and more realistic process assumptions have been identified by stakeholders as key features for adoption of ERA exposure, hazard and risk assessment models¹²⁴.

'Higher' tier assessments should be occupied by multimedia spatiotemporal modelling providing high resolution spatial and temporal exposure data for multiple compartments. To date, there has been little emphasis on spatiotemporally explicit multimedia modelling, beyond some limited adaptation of existing models⁷², although there have been useful developments within the freshwater environment¹¹⁸. This lack of progress is most likely due to the complexity and driving data requirements for such

modelling and the complexity of modelling the soil compartment. The NanoFASE (Nanomaterial Fate And Speciation in the Environment; European Commission Horizon 2020) project has filled this gap with the creation of a spatiotemporally explicit multimedia model of fate, speciation and bio-uptake applicable to soils, surface waters, sediments and biota (nanofase.eu/show/the-nanofase-water-soil-organism-model_268/). When coupled to a spatiotemporal release database and an atmospheric deposition model, such as LOTOS EUROS⁵⁸, for the first time a 'whole picture' assessment of ENM fate and exposure under realistic environmental conditions becomes possible. The use of such models is likely to be relatively unusual, more bespoke and less formalized than for lower tier tools. This is due to the need for specialist knowledge, for example in relation to data requirements for transport modelling (catchment hydrology and large-scale atmospheric transport). Such more-complex models are best viewed as research tools appropriate for specialized application at higher tiers of fate and risk assessment, whereas models at lower levels will be sufficient for the majority

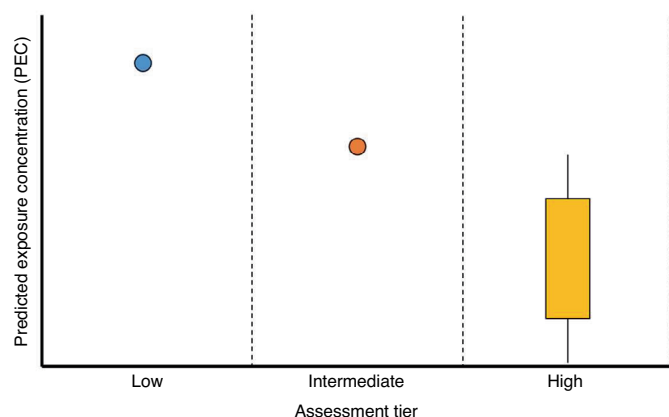


Fig. 3 | A general illustration of the trend in PEC across the three tiers of the illustrative risk assessment. This theoretical case provides a general illustration of the trend in PEC across the tiers, from a conservative worst case single value estimate in the low tier, via more realistic single value estimates in the intermediate tier, to the highest tier, where the PEC is a range of values, reflecting spatial and/or temporal variability (see Table 1 for more detail).

of regulatory requirements¹²⁴. Nonetheless, this type of modelling system can potentially be oriented towards more routine use by the provision of standardized scenarios and driving data sets, and simplification of outputs to focus on regulatory requirements.

MFA models warrant a special mention in the context of nano-enabled ERA. They place a strong emphasis on an understanding of the flows of NEPs and ENMs through the product value chain and managed waste systems prior to environmental release. For 'standard' MFA models, consideration of inter-compartmental transport and further fate processes tends to be rather simple and on a par with 'low' tier exposure models. However, the detailed consideration of the product value chain makes MFA models potentially useful for deriving compartment-specific release rates of ENMs and NEPs for fate modelling at higher tiers. Recent developments include models capable of providing estimates of release forms²⁹ (including explicit modelling of ENM transformations in waste streams¹²⁵), providing probabilistic estimates of uncertainties for release rates¹²⁶, and producing spatial and temporal predictions^{125,127}. These advances bring recent MFA models in line with 'medium' tier exposure models, though it should be noted that ENM transformations within the environment are not commonly modelled. In general, MFA models should play a central role in coupling knowledge of ENM and NEP production, use and environmental exposure.

The state of the art in exposure assessment for ENMs has developed sufficiently to allow (1) the framing of a tiered approach to progressively incorporate nanospecific fate processes into modelling approaches at increasing levels of complexity and realism; (2) the use of information on key fate descriptors to inform the selection of those key processes for inclusion into models at different tiers; and (3) mapping of the assumptions and simplifications inherent in models at each tier to understand the reliability and realism of the derived PEC, that is, a single conservative value at a lower tier, a 'realistic' worst case value at an intermediate tier or realistic spatial and temporal variability values at the higher tier (Table 1 and Fig. 3). By starting from the lifecycle of an NEP (Fig. 1), estimates of the fractions of ENMs emitted directly to the environment and released after transformation through waste infrastructure can be modelled based on physiochemical properties, colloid theory, environmental characteristics and key functional assay results. Such functional assays would serve for example, to quantify a specific process rate for an ENM in a given system¹²⁸. In countries with well-developed

waste infrastructure, the larger proportion of inputs will most often enter the environment via waste systems where they may transform to a less reactive form or state to partially mitigate risk before their release. In contrast, in countries with less developed waste infrastructure, a greater proportion of ENMs may enter the environment either directly or after minimum treatment and, hence, may be in more reactive, and potentially more hazardous forms. Within these regional contexts, the principles outlined above can be used as a practical way forward to reduce the insurmountable level of complexity inherent in environmental exposure assessment, while still achieving predictions of the dynamic behaviour of ENMs to a suitable level of accuracy, for example, at least within orders of magnitude.

For regulatory assessment for a new ENM variant of an existing material, it will generally be sufficient to use tools that provide PECs at limited spatial or temporal resolution based on consideration of only key processes. Indeed, these new ENMs will likely follow the same 'functional fate pathways' as the previously assessed material, especially since coating and size will usually have only secondary effects on the core when exposed to the main transformation processes. Identifying the 'functional fate group' for a specific ENM from a given NEP type may allow the efficient calculation of compartment-specific PECs for this collected group of ENMs. For the ERA of future ENMs or NEPs good release estimates will still be of utmost importance for exposure modelling. Indeed, where product type and uses for a new NEP are considered comparable, it is likely that existing models can be used with modifications made only for the release estimate values and forms expected for the new products. This means that the principles of broad environmental release categories (ERC) of the REACH guidance and also the Specific Environmental Release Category (SPERC) principles used to focus ERA and PEC derivation for dissolved chemical uses can also be used for NEPs. When addressing advanced, multi-component inorganic ENMs, mechanistic based Intermediate and Higher tier fate models are likely to be useful for fate and exposure modelling, since these ENM will generally obey chemical speciation and colloidal principles that can be estimated from first principles or quantified for specific ENM and media chemistries using functional assays. The exception to this may occur for ENMs based on carbon, organic materials, polymers or hybrid ENMs, which may potentially demonstrate less predictable fate behaviours, including their interactions with organisms that warrant further focus.

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The authors declare no competing interests.

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