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Nano Impact Statement: Comprehensive life cycle impact assessment (LCIA) of engineered nanomaterials (ENMs) and nano-enabled products requires quantification of impacts associated with conventional chemical *and* ENM releases. However few published assessments to date address nano-scale emissions, which precludes use of LCIA to identify the most significant environmental and human health 'hot spots'. This frontier review summarizes recent advancements and challenges in LCIA for ENMs, focusing on human and ecotoxicity impact assessment models, and identifies recent nano-specific environment, health, and safety literature with promise to inform LCIA model development. Throughout, the manuscript calls for closer collaboration between experimental investigation and modeling research such that experimental data collection is prioritized according to the greatest life cycle uncertainties and modeling needs.

One sentence to accompany TOC art:

There is an opportunity to facilitate responsible nanotechnology research and development through improved collaboration between life cycle modeling and experimental efforts.

Coordinating Modeling and Experimental Research of Engineered Nanomaterials to Improve Life Cycle Assessment Studies

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Abstract: Life cycle assessment (LCA) – a comprehensive modeling framework used to identify environmental and human health impacts associated with products, processes, and technologies – is increasingly recommended for emerging nanotechnologies. LCA applied prospectively can guide design decisions and enable reduction of future impacts. A growing literature describes the potential for LCA to inform development of safer nanotechnologies, for example by identifying the manufacturing inputs or processes with the greatest potential for improvement. However, few published studies to date include all life cycle stages in part because of uncertainty regarding engineered nanomaterial (ENM) releases and impacts, which precludes comprehensive environmental assessment of nano-enabled products. Life cycle impact assessment (LCIA) converts emissions into environmental damages through linked fate-exposure-effect models that require robust experimental data and a mechanistic understanding for each of these components. In the case of ENMs, there are pertinent knowledge gaps, high uncertainties in experimental data, and disagreement regarding the suitability of existing fate, exposure, and effect models. This frontier review summarizes recent advances in human and aquatic ecotoxicity LCIA for ENMs and calls for greater coordination between LCA modelers and experimentalists, including those that study fate and transport, environmental transformations, occupational exposure, and toxicology, to inform responsible development of nanotechnology, enabling ENMs to reach their full potential.

Introduction

The historical focus on designing for function without a complementary focus on hazard has led to the unintended environmental and human health consequences of widely utilized substances such as asbestos and dichlorodiphenyltrichloroethane (DDT), motivating a more proactive and comprehensive approach to evaluating emerging chemicals, materials, and products. The potential widespread use of engineered nanomaterials (ENMs) and nano-enabled products for applications in diverse sectors (e.g., health care, consumer products, electronics, national defense, and environmental remediation) is coupled with concern over adverse impacts upon exposure to humans and the environment. Releases of ENMs can occur at multiple stages along the life cycle of a nano-enabled product, for example as uncontrolled emissions during ENM synthesis, wear-and-tear during use, or from waste management facilities processing nano-wastes and nano-enabled products. The chemical and physical form of the emissions varies along these points, as does the potential for human or ecological exposures, which necessitates a life cycle perspective when approaching issues of holistically designing safer nanomaterials. In addition to the potential adverse impacts of emitted ENMs themselves, there are concerns from non-nano emissions associated with nano-enabled products. For example, the formation and potential release of harmful polyaromatic hydrocarbons and volatile organic compounds during carbon nanotube (CNT) synthesis.[1, 2] As such, an approach that is pro-active, life-cycle based, and uses multiple criteria is necessary to identify potential unintended consequences and contribute to responsible development of ENMs and nano-enabled products.

Life cycle assessment (LCA) is one such approach that has been recommended by the National Nanotechnology Initiative[4] and the National Research Council[3, 4] and is increasingly applied for ENMs and nano-enabled products. LCA, widely used in the chemical and product

manufacturing sectors, is a systems-level methodology for evaluating environmental and human health impacts associated with a product or process. LCA methods have been prescribed in a series of international standards[5, 6], and consist of four steps: (1) goal and scope definition, where the unit of analysis and system boundary of the study is established; (2) life cycle inventory (LCI) modeling, which accounts for each discrete energy and material input and emission across the life cycle of the product – including activities such as mining, processing of primary materials, manufacturing, use, transportation, and disposal; (3) life cycle impact assessment (LCIA), which uses coupled fate-exposure-effect models to translate the mass of each emission in the LCI into a quantified measure of potential environmental and/or human health impacts using so-called characterization factors (CFs); and (4) interpretation of results. LCA is a multi-criteria assessment tool, as separate CFs are applied for each substance and across a variety of impact categories such as global warming potential, ozone depletion, human toxicity and ecotoxicity, as presented in Figure 1.

Figure 1

Recent reviews summarize the accomplishments and critical challenges encountered in the application of LCA to the study of ENMs and nano-enabled products.[7-9] These reviews draw several important conclusions including: 1) the majority of nano LCA studies to date are cradle-to-gate and do not include use or end-of-life considerations and 2) ENM releases are not commonly considered at any stage, which is in part due to the lack of inventory data and characterization factors for ENMs, as well as the significant uncertainty in use- and end-of-life stages[7-9]; 3) initial incorporation of this critical information, as it becomes available, can be facilitated by using existing tools and experimental data[9]; 4) many nano LCAs are constrained to mass-based functional units, which is inappropriate for quantifying product functionality

comparisons as is standard in LCA[8]; and 5) given the previously identified shortcomings, much can be learned from qualitative or screening-level assessments.[7, 9] This is not an unusual state of affairs for the assessment of emerging technologies[10], as environmental modeling tools are routinely adapted to incorporate new substances and experimental data.

Nano LCA studies to date have been informative though remain limited in scope. As noted previously, the work has largely focused on indirect impacts, such as ENM production and manufacturing of nano-enabled products, while excluding assessment of nano emissions from products or in pure form (particularly in the use and end-of-life stages).[7-9] For example, recent cradle-to-gate studies on nanocellulose[11, 12] and graphene[13] compare the environmental impacts of alternative production processes to identify the least burdensome process. Studies of carbon nanotubes (CNTs) call attention to the high resource and energy intensity of their production, associated with the high temperatures, pressures, and low reaction yields typical of CNT synthesis processes, particularly single-walled CNTs.[1, 14] Yet, when considering these manufacturing impacts within the context of a product that contains small amounts of CNTs, such as a semiconductor device, the contribution of CNT manufacturing to the overall life cycle impacts of the product may be minimal.[15, 16] This is similar for metallic nanoparticles, in which the life cycle impacts have been found to be dominated by bulk metals such as gold and silver, whose mining and refining is energy intensive.[17, 18]

The few efforts to incorporate ENM emissions into life cycle studies examine the relative impacts of production and use- or end-of life phases by adapting current LCIA methods. A recent comparative LCA of three nano-enhanced paints included TiO_2 emissions and ecotoxicity impacts using recently published characterization factors (although nano silver and silica were omitted), to show net improvement if TiO_2 was substituted for other active ingredients and paint

lifetime increased.[19] Another study investigating the ecotoxicity of single-walled CNTs found that production impacts due to non-nano emissions were orders of magnitude greater than the impacts of CNT releases under a realistic release and environmental fate scenario.[20] Furthermore, the behavior of ENMs in the environment is influenced by the chemistry of the surrounding media, such as pH, dissolved organic carbon (DOC), and ionic strength. For example, silver nanoparticles have been shown to react rapidly with sulfur, resulting in decreased Ag^+ release and ecotoxicity impact potential.[21, 22] In addition to these exogenous factors, ENM fate, exposure, and toxicity are influenced by a number of physical and chemical properties associated with their nano length scale, including large surface area, chemistry, reactivity, charge, morphology, and agglomeration state.[23, 24] These factors, vitally important to describing ENM behavior, are notably different than the current modeling considerations of molecules rather than particles, which present a challenge in directly utilizing or adapting current models. One exception is that of particulate matter (PM), for which several methods[25-28] consider size by using different CFs for PM 2.5 – 10 μm in diameter (PM_{10}) and PM less than 2.5 μm ($PM_{2.5}$); nonetheless this approach does not account for heterogeneity in PM composition, morphology, or reactivity. Demonstrating the complexity of this effort, a recent analysis accounts for the heterogeneity of PM by developing more than 2,700 distinct characterization factors for the complex components of PM, and concludes that if less-harmful particles such as salt aerosols are omitted, established methods significantly overestimate PM impacts.[29]

Despite the progress in nano LCA described above, the capabilities of the current life cycle impact assessment models remain inapplicable in a comprehensive and universal manner to ENMs and the products they enable. Experimental studies pertaining to ENM transport, fate and transformations in the environment, occupational safety, and nanotoxicology continue to advance

149 such that significant data and expertise are available to inform LCIA. Nonetheless, ENM-specific
150 impact assessment models or CFs are not included in any commercial or publically available
151 LCIA packages. Given the large number of ENMs, release scenarios, surface modifications, and
152 possible permutations of these characteristics, there exists a need to prioritize data collection[30]
153 and improve model parsimony. Table 1 compiles prominent life cycle concerns associated with
154 several commercially relevant ENM classes and calls attention to their similarities and
155 differences pertinent to LCIA. The final column in Table 1 suggests those midpoint impact
156 categories most relevant to the given ENM class based on the product categories, potential for
157 release, exposure routes, transformations, and mechanisms of biological activity. It becomes
158 clear that certain impact categories are more relevant for certain ENM classes and life cycle
159 stages as indicated by the frequency of appearance throughout the table (e.g., human and
160 ecotoxicity categories).

161 Table 1

162 The need for environmental research prioritization is not unique to ENMs and nano-
163 enabled products, but rather is shared by other emerging technologies. Meaningful inclusion of
164 ENM releases, fate, exposure, and effects in LCIA models can be accelerated through
165 coordinated efforts between experimentalists and life cycle modelers. Specifically, cooperative
166 efforts early in experimental design can tailor data collection toward the greatest modeling
167 uncertainties while fostering development of innovative modeling approaches. In particular,
168 there is a need for sensitivity analyses of LCIA models to identify which parameters are most
169 influential to model results and then integrating these data needs into experimental design to
170 narrow specific uncertainty ranges. These data needs and modeling advances are discussed first
171 as they relate to ENM releases (treated as environmental emissions in the life cycle inventory)

and second to development of nano-specific characterization factors (life cycle impact assessment). While this review identifies many nano-LCIA experimental and modeling challenges, it cautions attempts to create nano-specific models that are overly detailed and have limited utility for risk modeling or decision making. Rather, coordination between both experimental and modeling approaches can enable iterative sensitivity analyses, direct data sharing that can identify which uncertainties are significant while others may be revealed as low priorities for further investigation, and inform experimental designs and priorities according to the greatest life cycle uncertainties.

Quantifying and Characterizing Life Cycle Releases of ENMs

Estimating the quantity and characteristics of ENM releases is the first step in LCI modeling, which tracks the mass and receiving compartment (e.g., air, water, soil) of all emissions across the life cycle. Initial global estimates of ENM emissions[31, 32] have since been improved through increased geospatial resolution[33] and site specificity such as waste water treatment plants[34, 35] and end-of-life disposal activities such as incineration.[36] In addition to considering emissions at the global scale, ENM emissions are likely to differ across end-use applications and the physiochemical characteristics of emitted ENMs may change in each life cycle stage. Several recent studies consider potential ENM releases from select product classes including personal care products,[37, 38] composite materials,[39, 40] and paint formulations.[41, 42] Since it is impracticable to include all possible permutations of raw, transformed and composite ENM emissions, there is active discussion regarding which physicochemical properties of ENM emissions are most important to characterize and how these may be integrated into mechanistic impact assessment models.[43]

Incorporation of ENM properties, namely shape and size, in LC inventory modeling was recently recommended in addition to mass and chemical composition[44] that are currently considered for conventional chemicals. This approach stops short of tracking changes in ENM morphology and physiochemical properties when released from different products and life cycle stages – for example the loss or gain of surface functional groups – that will influence their fate, exposure, and toxicity potentials. This is problematic, as LCI modeling of conventional chemicals sums the total mass of each emitted material across all life cycle stages, implicitly assuming that releases from manufacturing, use, and end-of-life are environmentally equivalent. Thus, experimental efforts to quantify life cycle ENM releases should prioritize commercially-relevant nano-enabled products and explore the extent to which environmental residence times, bioavailability, and toxicity change across the life cycle or with different surface modifications. This can inform LCI modeling by identifying which ENM emissions and release scenarios are suitably different to necessitate distinct LCI entries and those that may be grouped into one entry with minimal increases in uncertainty.

Toward the Development of Nano-specific Characterization Factors

LCIA begins with classification of all emissions according to the impact categories to which they contribute, followed by quantification of their relative impact through characterization factors (CFs). CFs provide a quantitative measure of the impact potential associated with each emission, and are calculated per unit mass emitted to a specified environmental compartment. The consensus model USEtox[45, 46] is recommended practice for human and aquatic ecotoxicity impact assessment[47], and has recently been adapted – as discussed in greater detail below – to estimate CFs for several ENMs. CFs are calculated as the product of:

1. Fate factor (FF), which represents the fate, transport, and residence time of an emission in each environmental compartment, and is obtained through simplified multi-media box models,
2. Exposure factor (XF), which accounts for intake by multiple species and/or humans through known exposure routes, including ingestion and inhalation, and
3. Effect factor (EF), which represents the aggregated toxicological response of multiple organisms or humans upon exposure to a known dose.

Experimental data and mechanistically appropriate models are required to calculate each of these factors and to reduce the high ENM parameter and model uncertainty. In the following sections the relatively small but growing body of literature advancing LCIA of ENMs is reviewed, with a focus on published methodological improvements arising from the sustained interest in the environmental impacts of ENMs.

Fate Factor: Modeling Environmental Transport and Residence Times of ENMs

LCIA fate models – for example the European-developed USES-LCA 2.0[48, 49] used in ReCiPe[50] and the consensus model USEtox[45, 46] now adopted by TRACI[25] – rely on multi-media mass balance models following a fugacity approach.[51] The applicability of this approach to ENMs, which is based on equilibrium partitioning coefficients originally developed and applied to organic pollutants, is the subject of recent scrutiny and debate.[52-55] Use of equilibrium partitioning coefficients as an indicator of ENM fate may be misleading given that ENM suspensions violate key thermodynamic assumptions associated with use of equilibrium partitioning coefficients.[55] To address this critique, several fate models developed specifically for ENMs[56-59] – described in greater detail in Dale et al[53] and Scheringer et al[60] – replace partitioning assumptions with elements of colloid theory. Nonetheless, substitution of colloidal models

requires simplifying assumptions and does not reduce model uncertainty. Thus, informed, skeptical use of partitioning-based models remains a recommended practice until further research validates one approach over another.[54] Following this reasoning, several recent nanomaterial fate models employ partitioning approaches with ENM-specific data and size-dependent binning[61, 62] of results. This presents LCIA model developers with a decision of how best to evaluate the fate of ENMs using existing models or by developing ENM-specific models based on limited understanding.[7]

To date necessary, albeit minor, modifications to existing LCIA models have been made to account for both model and parameter uncertainty in FF calculations for ENMs, and focus largely on freshwater aquatic residence time for CNTs[20, 63, 64] and TiO_2.[65] Miseljic and Olsen[7] simply assume a FF equal to one day for nano Ag and TiO_2 ENMs, citing lack of information and likelihood of rapid transformation, aggregation, and sedimentation. Other studies account for removal through aggregation/agglomeration by comparing scenarios of fixed percentage removal,[20] modeling FFs probabilistically based on the wide range of published parameter estimates,[64] or with qualitative discussion of uncertainty.[63] Salieri et al.,[65] make the most significant modifications to USEtox by: 1) developing a simplified heteroaggregation model and exploring scenarios of alternative attachment efficiencies, and 2) binning TiO_2 ENM emissions based on particle size and calculating distinct FFs for each size range. Aside from aggregation and deposition, none of these analyses quantitatively consider other ENM transformations or surface modifications – for example, stabilization of CNTs by natural organic matter[66] or sulfidation of nano Ag.[21] A probabilistic approach may capture some of this uncertainty and material variability[20, 64] though not mechanistically, and further experimental investigation is necessary to validate one fate modeling approach over another.[67]

While there is significant uncertainty surrounding current ENM fate modeling approaches, experimentalists can expedite resolution that is more appropriate for a given class of ENMs. Future LCIA model development should assess the sensitivity of CF results to those mechanisms relevant to ENMs, including removal, stabilization and transformations for separate classes of ENMs since their behavior can be markedly different (e.g., carbonaceous vs nanocellulose vs metal and metal oxide ENMs). Those physicochemical properties that most determine fate for each ENM class should then be required in specifying ENM emissions in the life cycle inventory. In addition, adjustments made to existing models, such as USEtox, should aim to include these nano-relevant removal pathways, including aggregation and settling.

Exposure Factor: Quantifying the Fraction of ENMs Available to Humans and Organisms

For conventional chemical emissions, exposure modeling in (eco)toxicity impact assessment relates the residence times of an emission in each compartment to the intake fraction by people or biota, called the exposure factor (XF). The presently available version of USEtox includes human exposure via inhalation and ingestion of plants, meat, fish and dairy products, but does not yet include workplace, indoor, or dermal exposure routes. For conventional pollutants, inhalation dominates for air-phase releases or emissions to water that are volatile, whereas consumption exceeds inhalation only in cases of low volatility and high lipophilicity.[68] Exposure to aquatic organisms is modeled as the dissolved fraction of an emission, where partitioning to suspended solids, dissolved organic carbon, and biota (again, calculated using equilibrium partitioning coefficients) decreases the bioavailable fraction of the emission.[69] None of these approaches are designed for nanomaterials, for which aggregation influences the number of free particles and their effective size, density, and diffusion rates.[70] Thus mass and particle concentrations reported and administered in many *in vivo* studies may overestimate the delivered

dose.[71] LCIA exposure models for ENMs could adopt additional dose-conversion calculations[72], potentially taking guidance from recent protocols coupling experimental characterization of life cycle ENM releases with dosimetry modeling[73]. Human exposure research has focused on consumer[74-76] and occupational settings[77] with strong guidance for ENM inhalation XF and CF calculations recently described in Walser et al[78].

No published ENM ecotoxicity CFs mechanistically account for uncertainty in exposure modeling. Several studies adopt the precautionary assumption that 100 percent of ENM emissions are bioavailable[65,7] while others apply Monte Carlo sampling across published partitioning coefficient ranges.[20, 64] Similar to FF calculations, none of these studies directly account for ENM transformations and how these may influence exposure estimates. Reported XF values for CNTs span approximately six orders of magnitude,[63] suggesting that research directed towards elucidating exposure mechanisms and improving resolution in XF calculations can substantially reduce CF uncertainty. Only one study calculates XF for human toxicity using USEtox, and concludes that – regardless of emission compartment – ingestion of CNTs through consumption of fish and plants significantly exceeds intake through inhalation.[63] Nonetheless, like chemicals, exposure through inhalation may be significant in the case of localized high-concentrations of ENMs (e.g., occupational settings), and LCIA model developers should continue to improve existing workplace studies[79, 80] and build consensus and wider adoption of recent guidance.[78, 81, 82]

Effect Factor: Linking Toxicity Data to Adverse Environmental and Human Health Impacts

For conventional chemicals, toxic effect modeling in LCIA is one of the greatest contributors to uncertainty in CF calculations. The effect factor (EF) represents potential adverse human and environmental health impacts derived from the toxicity of the emission, and is based

on extrapolation from animal models or multi-species toxicity data, respectively. Quantification of (eco)toxicity effects is based on chemical hazard indicators such as average LC or EC_{50} values obtained from experimental measurement of the concentration at which the effect was observed in 50% of the population. ReCiPe and USEtox rely on the same toxicity databases,[83] in which coverage of conventional chemicals is oftentimes incomplete or based on relatively few data points.[84] Extensive human health and ecotoxicological testing of all new chemicals to determine inherent toxicity characteristics is not feasible due to the number of new substances introduced daily, the time it takes to conduct reviews, and the prohibitive economic and social costs of testing, particularly *in vivo*.[85, 86] These challenges are exacerbated in the context of ENMs, where even less data are available and the role of transformations and colloidal behavior may require modifications to existing testing protocols.[87, 88] The few early studies calculating EFs for ENMs use ENM-specific toxicity values reported in the literature to build multi-species sensitivity distributions following USEtox guidelines.[45] Similar to XF and FF, calculating EF probabilistically as demonstrated in application to CNTs[20, 64] provides one pathway to address parameter uncertainty in reported EC_{50} values. Furthermore, enhanced mechanistic understanding, specifically increased resolution of toxic modes of action (TMoA) and reduced inter-species uncertainties, has been shown to contribute orders of magnitude uncertainty to EF calculations for conventional chemicals.[89-91]

In addition, there are several challenges to obtaining reliable data for ENMs using conventional toxicological assays. First, many nanomaterials are insoluble and thus, have a tendency to rapidly agglomerate and settle out of solution. This makes dosimetry determination challenging, as discussed previously. As it relates to the EF specifically, insoluble ENM behavior hinders determination of the actual delivered dose – a topic that remains under critical review[70,

[92, 93] – because the delivered dose likely differs from the mass-based concentration of ENMs in the system. Alternative approaches to estimating the delivered dose include on the basis of number of particles (#/L) or total surface area of the particles (m^2/L).[94, 95] Another challenge to utilizing conventional toxicological assays to study ENMs is that carbon-based ENMs have been shown to interact with many of the commonly used dyes and essential nutrient compounds leading to false readings from fluorescent quenching and organism growth inhibition, respectively.[96, 97] Combined, these make the applicability of high throughput screening (HTS) – a rapid, highly automated approach to *in vivo* and *in vitro* toxicity testing – across all ENM classes virtually impossible. Still, HTS offers a promising avenue for efficient data collection and has provided useful results for certain classes of ENMs (e.g., metal and metal oxide).[98-101] Finally, there is mounting concern over the relevance of the studied toxicological endpoints under extremely high ENM concentrations and relatively few studies that consider the transformed or weathered ENMs that may be of greater relevance to actual release scenarios.[102-104] Impacts of ENM releases combined with experimental investigations that demonstrate the importance of ENM transformations in environmentally relevant conditions[102, 105-107] can motivate improvements to latent issues in LCIA. Specifically, LCIA toxicity modeling tends to exclude impacts of transformation byproducts, inclusion of which has been shown to significantly alter EF estimates for conventional chemicals.[108]

While there remain several challenges for insoluble ENMs, there is increased evidence for a distinct difference in the magnitude of toxicity of released ions upon dissolution of nanomaterials compared to the parent nanomaterial, and is particularly true for silver nanoparticles (with enhanced surface area to volume ratio and thus, more surface atoms, nanomaterials undergo dissolution more rapidly than their compared to their bulk

354 counterparts).[103, 109] A recent meta-analysis comparing the ecotoxicity of three soluble ENMs –
355 nano Ag, CuO, and ZnO – to their ionic counterparts found that the ENMs displayed reduced
356 toxicity in the majority of studies and exceed the ionic form only in worst case scenarios.[110]
357 Thus, studies that assume a fixed percentage ionic release from ENMs[18, 111] and rely on existing
358 EFs and CFs for ionic metal potentially overestimate toxicity impacts. To this end, there is the
359 opportunity for enhanced resolution of environmental and human health impact evaluation of
360 ENMs. With the currently available data it is possible to develop novel or update current effect
361 models that will elucidate relevant obstacles and therefore, be able to direct future toxicological
362 data acquisition.

363 ***Catalyzing Research Synergies to Inform Development of Safer Nano-Enabled Products***

364 The numerous data gaps, high uncertainty in experimental protocols and published
365 parameter estimates, and rapid evolution of modeling approaches leaves development of robust
366 LCI data and ENM-specific impact assessment models an ongoing endeavor. The possible
367 permutations resulting from the large number of ENMs, associated surface modifications, and
368 release scenarios creates a need for research prioritization that can be facilitated through greater
369 coordination between modeling and experimental approaches. The early efforts reviewed herein
370 point to innovative LCIA modeling approaches that, in the absence of clear mechanistic
371 understanding, have combined probabilistic uncertainty modeling with scenario development to
372 produce actionable results. In outlining where recent experimental advances can inform
373 modifications to CF calculation for ENMs this review identifies several specific
374 recommendations for experimentalists and LCA modelers to coordinate research agenda to
375 streamline progress toward responsible development of nano-enabled products.

1) It is of critical importance to include ENM releases in nano LCA studies – despite uncertainties of current models and data – to assess the relative magnitude of ENM emissions within broader life cycle impacts.
2) Rather than adopting one fate modeling approach (e.g., either partitioning or colloidal), LCIA method developers should evaluate the sensitivity of FF and CF results to the choice of fate model as a way to prioritize further experimental investigation.
3) Robust impact assessments rely on relevant information being included in the life cycle inventory. Size and morphology have been recommended in specifying ENM emissions. In addition to identifying ENM attributes that govern property-hazard relationships, we recommend a consensus process around which ENM attributes are important in determining ENM fate and subsequent inclusion of these attributes during the life cycle inventory stage.
4) Not all life cycle impact categories are of equal concern when considering direct environmental and human health impacts of ENMs, especially under different release scenarios. As such, it is suggested to build consensus regarding priority categories and release scenarios for which nano-specific characterization factors will most improve understanding of these impacts.
5) Experimental investigations should follow an analytical sequence that considers first, the potential and likelihood of ENM release at each life cycle stage, the transport and fate of the released ENM (in parent, transformed, and/or complex matrix form), exposure of the released ENM (including appropriate dosimetry considerations), and finally, the effect (adverse or otherwise) caused by exposure to the delivered dose.

6) LCIA of ENM-enabled products requires more detailed characterization of ENMs as they are released from products (e.g., aged, transformed, composites) and overtime, as opposed to the raw or pristine forms.

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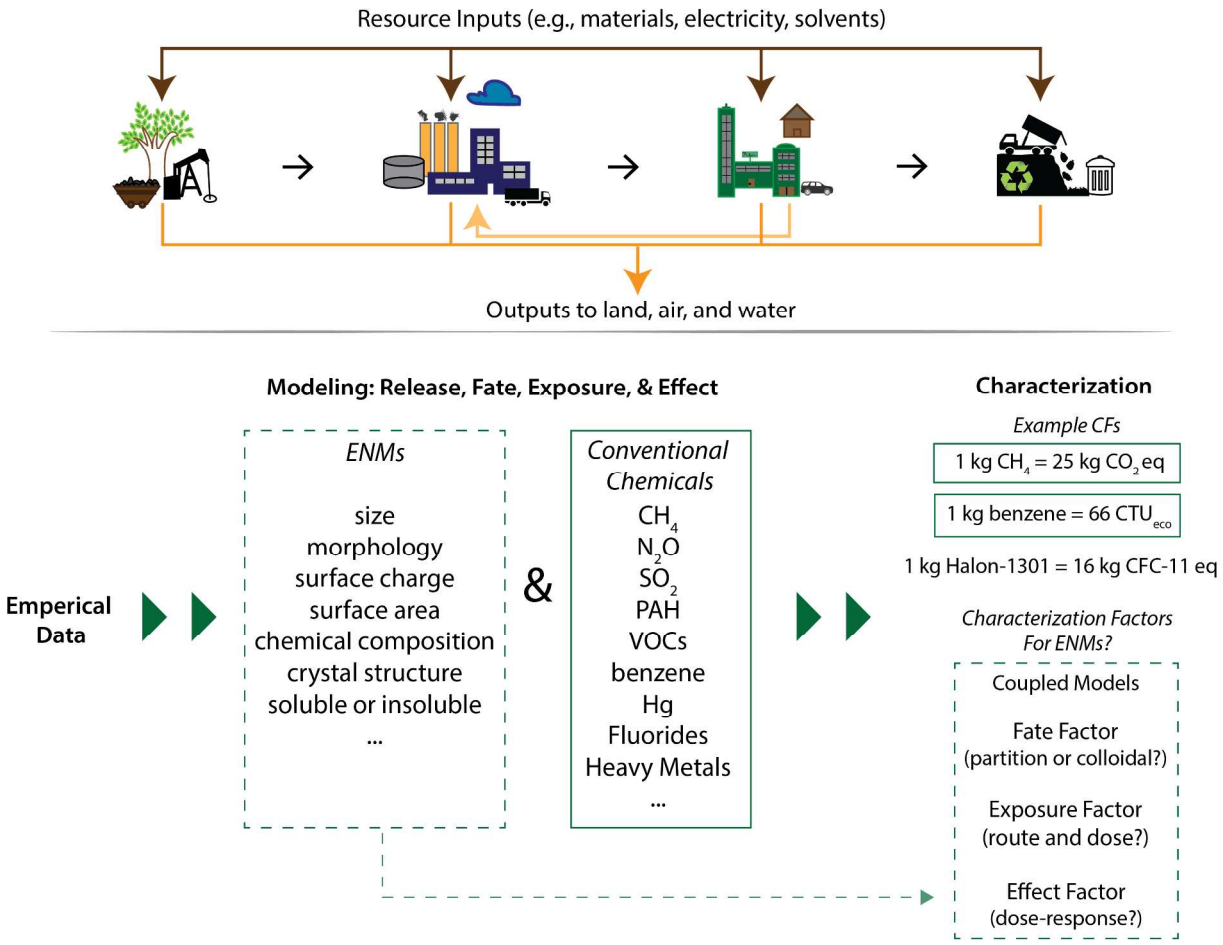

Figure 1. Schematic representation of the life cycle stages and overview of the life cycle assessment (LCA). Life cycle inventory analysis quantifies resource use and emissions across the product life cycle and mid-point impact assessment uses characterization factors to convert LCI entries into environmental and human heath damages. Dashed lines in the schematic represent active research areas in need of greater coordination between experimental and modeling efforts as it related to nanomaterials and nano-enabled products. eq = equivalents. CTU_{eco} = comparative toxicity units for ecotoxicity.

Table 1. Compiled overview of six engineered nanomaterial (ENM) classes*, including the respective primary applications and relevant sectors, potential benefits realized by enabling products with the nanomaterial, potential release and exposure routes, relevant transformation mechanisms, and primary life cycle impact indicators of interest.

ENM Class	Primary Applications & Sectors	Potential Realized Benefits by Nano-Enabling	Potential Release and Exposure Routes	Relevant Transformations and Mechanisms	Primary Life Cycle Impact Indicators of Interest
Nano-Silver [95, 112-115]	*anti-odor textiles* (e.g, sheets, towels, shirts, socks, pants) *composites* (e.g., hospital equipment, washing machine, cosmetics) *wound dressings* *Antimicrobial surfaces* (e.g., paints, coatings) *filters* (e.g. for air/water purification & sterilization) *catalyst* (e.g., CO oxidation) *consumer electronics*	Reduced laundering Prevention of bacterial and viral transmission Faster wound healing Improved access to potable water Increased reaction time (decreased energy barrier)	*Manufacture:* occupational exposure during handling *Use Phase:* release of nano-silver and Ag^+ ions from products *End of Life:* release of Ag^+ from WWTP effluent; low hazard concern when in non-ionic form (e.g., Ag_2S, AgCl)	Oxidation of Ag^0 to Ag^+ leading to: Sulfidation (Ag_2S) Chlorination (AgCl) Re-precipitation of nano-Ag upon reduction of Ag^+ disruption of biological function (e.g., via ROS production, extra- and intra-cellular Ag^+ interactions)	*Raw Materials & Manufacture* Global Warming Potential Fossil Fuel Depletion Mineral Resource Depletion Human Toxicity *Use & End of Life* Terrestrial, Freshwater & Marine Ecotoxicity Human Toxicity Non-Carcinogenics

Carbon Nanotubes [1, 20, 112, 114, 116-118]	*composites* (e.g., vehicles, infrastructure, athletic gear, protective clothing) *electronics* (e.g., memory chips, sensors) *batteries* *biomedical* (e.g., sensors, scaffolds) *flame retardant filters and membranes* (e.g., water purification & disinfection) *antimicrobial surfaces*	Light-weight high performance materials Reduced energy consumption Enhanced detection of harmful analytes Improved early detection of maladies Improved access to potable water	*Manufacture:* VOC & PAH formation; occupational exposure (e.g., inhalation) during handling *Use Phase:* release as raw material, transformed material, or as composite during wear-and-tear of products *End of Life:* release and exposure during resource recovery (e.g., electronics, plastics or fabric recycle); landfill accumulation; complete combustion during incineration	Surface transformations Agglomeration, Homo/Hetero aggregation and Settling Physical (e.g., frustrated phagocytosis) and chemical (e.g., oxidative stress) induction of adverse impacts on cells and organisms (e.g., delayed growth or hatching, developmental malformations)	*Raw Materials* Global Warming Potential Fossil Fuel Depletion Mineral Resource Depletion Human Toxicity *Manufacture* Fossil Fuel Depletion Mineral Resource Depletion Particulate Matter Formation Criteria Air Pollutants Acidification Eutrophication Human Toxicity Carcinogenics Non-Carcinogenics *Use & End of Life* Particulate Matter Formation Terrestrial, Freshwater, & Marine Ecotoxicity Human Toxicity Carcinogenics Non-Carcinogenics
Nano-TiO_2 [112, 114, 119, 120]	Nano-TiO_2 functions primarily as a pigment (i.e., whitening agent), UV protectant, and photocatalyst in: *paint* *food* *sunscreen* *deodorant* *self-cleaning coatings* *air & water filters* *environmental remediation* *dye-sensitized solar cells*	Reduced washing of exterior surfaces Reduced risk of skin cancer Improved access to potable water	*Manufacture:* occupational exposure during handling *Use Phase:* direct application (i.e., cosmetic applications), release during wear and washing *End of Life:* landfill accumulation (e.g., residual cosmetic during container disposal)	Agglomeration, Homo/Hetero aggregation and Settling Photoinduced production of reactive oxygen species (e.g., oxygen radical) causing disruption of healthy biological function	*Raw Materials & Manufacture* Global Warming Fossil Fuel Depletion Mineral Resource Depletion Human Toxicity *Use & End of Life* Terrestrial, Freshwater, & Marine Ecotoxicity Human Toxicity Non-Carcinogenics

Nano-ZnO [114, 115, 120, 121]	Nano-ZnO functions primarily as a pigment and semiconductor in: *sunscreen* *paints* *antimicrobial fabrics* *deodorant* *rubber additives* *solar cells* *LCDs*	Reduced risk of skin cancer Reduced exterior washing Realization of alternative energy resources	*Manufacture:* occupational exposure during handling *Use Phase:* direct application (e.g., cosmetic applications), release during wear and washing *End of Life:* landfill accumulation (e.g., residual cosmetic during container disposal)	Agglomeration, Homo/Hetero aggregation and Settling Oxidative stress induced adverse response Adverse impacts caused by dissolution (Zn^{2+})	*Raw Materials & Manufacture* Global Warming Fossil Fuel Depletion Mineral Resource Depletion Human Toxicity *Use & End of Life* Terrestrial, Freshwater, & Marine Ecotoxicity Human Toxicity Carcinogenics Non-Carcinogenics
Nano-CeO_x [112, 114, 122-125]	*catalyst* (e.g., methane steam reforming) *fuel additive* *polishing agent* *UV coatings & paints* *chemical mechanical planarization* *solid oxide fuel cells* *batteries*	Reduced criteria pollutants (e.g, oxidation of CO to CO_2) emissions UV blocker Bioprotective effects against oxidant injury	*Manufacture:* occupational exposure during handling *Use Phase:* release to environment from use (e.g., fuel additive, coatings) or WWTP effluent discharge *End of Life:* proper disposal and recycle of high value applications limits exposure (e.g., batteries, fuel cells)	Agglomeration, Homo/Hetero aggregation and Settling Surface adsorption (e.g., via hydroxyl groups) Storage and release of oxygen Dual oxidation state (Ce^{+3}-Ce^{+4}) gives rise to unique redox properties (e.g., oxidant and antioxidant effects)	*Raw Materials & Manufacture* Global Warming Fossil Fuel Depletion Mineral Resource Depletion Human Toxicity *Use & End of Life* Terrestrial, Freshwater, & Marine Ecotoxicity Human Toxicity Non-Carcinogenics

* ENM classes were chosen based on their production volumes, current and proposed market presence[31, 126-128]

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