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Life cycle considerations of nano-enabled agrochemicals: Are today's tools up to the task?

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Environmental Significance Statement

Engineered nanomaterials (ENMs) are used as agrochemicals or in agrochemical formulations. It is prudent to assess the lifecycle benefits and risks of such direct applications of ENMs in agriculture to widespread utilization. This perspective identifies nano-specific challenges of using the existing life cycle assessment (LCA) framework to evaluate the net environmental impacts or benefits of using ENMs compared to existing agrochemicals. Potential models, experiments, and methodologies to fulfill the data requirements of an LCA are discussed with the intent to guide ongoing research and development of nano-enabled agrochemicals.

Life cycle considerations of nano-enabled agrochemicals: Are today's tools up to the task?

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Abstract

Engineered nanomaterials (ENMs) used as fertilizers, pesticides and growth regulators will involve direct application of large quantities of ENMs to the environment and products intended for human consumption. Assessing their life cycle environmental impacts to mitigate unintended consequences poses several challenges. In this perspective, we identify obstacles to the application of life cycle assessment (LCA) for evaluating environmental tradeoffs of nano-enabled agrochemical applications. These include: (1) defining functional units that represent the function provided by nano-enabled agrochemicals and that are proportional to the scale of the study (nano-scale vs. field scale), (2) limitations in availability of comprehensive data necessary to inform life cycle material flow (resource use and emissions) for inventory development specific to nano-enabled agrochemical applications, (3) human and environmental exposure and effects data relevant to the agricultural context for impact assessment models, (4) spatial and temporal dependent components that can affect the results of an LCA of nano-enabled agrochemicals, and (5) high data uncertainties and the possibility of their reduction through collaborative efforts between life cycle practitioners and experimental researchers using anticipatory decision-based models. While several of these challenges are experienced in LCA of emerging technologies generally, they are highlighted herein due to a unique or heightened relevance to the use of ENMs in agriculture applications. Addressing challenges in these areas are intended to inform research prioritization to ensure safe and sustainable design, development, and implementation of nano-enabled agrochemicals.

Keywords: Environmental nanotechnology, Agriculture sustainability, Emerging technologies

Introduction

Meeting future global food demand in an environmentally sustainable manner is challenged by a multitude of factors. Rapid growth in population (projected to increase by 30% in 2050[1]) and increased economic prosperity, especially in developing countries,[2,3] constantly drives demands for high-value foods (e.g., fruits, vegetables, meat) and processed agricultural products.[4,5] Adverse effects of increasing climate variability on agro-ecological conditions[6,7] (e.g., extreme weather patterns affecting cropland yields[8,9]), and our intensive and inefficient utilization of water, energy, and nutrients hinder progression towards environmentally sustainable agriculture. These inefficiencies and their subsequent environmental burdens are most salient in crop production. For example, global annual consumption of primary macronutrients, nitrogen (N) and phosphate (P_2O_5) fertilizers, reached approximately 110 and 42 million metric tonnes in 2014, a nearly 830% and 289% increase, respectively, from 1961.[10] At the same time, nutrient use efficiencies have remained at an average of 50% or lower for N[11] and 10-15% for P.[12] This inefficient use of nutrients results in millions of tonnes of nutrients entering surface and groundwater, negatively impacting aquatic and terrestrial ecosystems by causing eutrophication, groundwater contamination, and undesirable changes to soil chemistry and microbial communities.[13] Pesticide application is also inefficient;[14,15] approximately half of pesticides applied are ultimately found in surface or groundwater bodies.[16] The buildup of pesticide residuals can decrease populations of pollinators and predators for natural pest control and plant protection, increase resistance, decrease fish populations, and negatively affect bird and mammal growth and reproduction from direct and indirect (food consumption) exposures.[14,15,17]

Various solutions exist to improve efficient use of fertilizers and pest control. One example is genetically modified crops, which have raised public concern[18–21] and the ecosystem risks remain unresolved.[22,23] Others include hydroponic or other highly engineered cultivation practices, which can suffer from significant resource and energy demands, and extreme vulnerability to contamination, impeding their widespread adoption.[24–26] Recent reviews suggest the potential of engineered nanomaterials (ENMs) to enhance crop yields, protect against pests, improve agrochemical use efficiency, and lower environmental impacts associated with agriculture production.[27–29] These increased efficiencies stem from advancing capabilities to provide the agrochemicals (i.e., fertilizers and pesticides) *when* and *where* they are needed.[30] Advances include manipulation of particle physicochemical properties, such as surface charge[31] and surface ligands[32], to control uptake and translocation of nanoparticles in plants. Developments in slow-release nano-enabled fertilizers promise higher utilization efficiencies and thus, reduced environmental damage from leaching and runoff.[33–35] Applications of ENMs to plants have indicated both beneficial and inhibitory effects.[36,37] For example, multiple studies have seen benefits from application of ZnO nanoparticles to plants, showing increase in root and shoot length,[38] biomass,[38,39] germination rate,[38,40] and rhizospheric microbial population.[38] Similar improvements were seen for nano-TiO_2 applications, such as enhanced rubisco activity, photosynthesis rates, chlorophyll content,[41,42] and growth rate.[41,43,44] Yet other studies caution the use of these same ENMs and report reductions in biomass and soil enzyme activity,[45] and lower biomass and diversity of soil bacterial communities.[46] These contrasting reports are not unique to nano-agriculture. It is a familiar challenge to the environmental nanotechnology community because differences in experimental conditions (e.g., dose, plant species studied, hydroponic vs soil exposure, growth stage of the plant and exposure period) and ENM properties (e.g., particle size, shape, composition, surface area, surface chemistry) are often not reported, and can lead to contradicting results.[36] Combined with the broad range of environmental conditions to consider in agricultural settings, there are significant challenges to systematically assessing the benefits and risks of nano-enabled agrochemicals.

Environmental impacts of agrochemicals cascade across the life cycle, from raw material acquisition, fertilizer and pesticide production, to their use phase impacts, and finally, end-of-life (namely, unintended release to the surrounding environment).[47] Given that current studies focus narrowly on the use phase – mostly assessing the direct effects of ENMs on plants - there is a need for wider system-level analyses to capture system-wide benefits and impacts. Life cycle assessment (LCA) is a systems-level tool, that has been previously used to evaluate the benefits and risks of nano-enabled applications (e.g., textiles[48–50] and batteries[51–53]), providing valuable information that directs research focus towards certain stages of the life cycle with the greatest impact or opportunity for improvement[50,54–56] as well as in defining the design space within which net benefit realization is possible.[56–59] Similarly, in an effort to increase awareness of environmental impacts of agriculture, LCA has been applied to the study of food systems since the early 1990s[60], including processed food products, dairy and meat production, crop-based agriculture, food packaging and food waste.[60–65] There are intrinsic challenges to applying LCA to both agriculture[64] and nanotechnology[66–69] in every step of the analysis based on the data availability, variability and uncertainty.

This perspective utilizes the identified challenges of both agriculture and nanotechnology LCA to provide the necessary context in discussing unique challenges specific to the critical intersection of 'nano' and agriculture. Further, the advantages of applying a life cycle approach to assess the potential of nano-enabled agrochemicals at early stages of technology development are explored. The focus is on nano-enabled agrochemicals for crop production because (i) significant gains are promised to be realized through tangible improvements in efficiencies, and (ii) the direct application of these products to croplands and the indirect non-nano emissions from upstream processes can both negatively affect both human health and the environment. Discussion of these challenges is organized around and follows the progression of LCA phases, (i) goal and scope definition, (ii) life cycle inventory (LCI), (iii) life cycle impact assessment (LCIA), and (iv) interpretation. Opportunities for methodology development and guidance to overcome the identified challenges are proposed to support future endeavors in applying nano-enabled agrochemicals, and develop a path to a more sustainable agricultural sector.

Defining agricultural functional units and system boundaries that account for ENM addition

A critical challenge of LCA in agriculture is the choice of the functional unit (FU), which relates the inputs and emissions of the system under study for quantification and creates a comparable basis for a wide range of systems. The FU decision also relates to the type of LCA, be it attributional or consequential.[60] In an attributional approach, overall environmental burdens associated with the life cycle of a product or a system are identified in accordance with the inputs and emissions directly corresponding with the FU.[70] A consequential LCA involves concepts of decision support tools, and evaluates direct and indirect environmental burdens as a result of a change in market demand for the FU.[70] Consequential LCA has been especially useful in identifying the effects of adopting bioenergy technologies on land use change,[71–74] an impact that is specifically germane to agricultural processes. For crop-related agricultural practices, mass of the final product ready for consumption (kg) or mass of crop produced per unit of area at farm level (kg/ha), or area of occupied land (ha) are most commonly used as FUs.[60,64] Others have considered the water footprint of crops (m^3/kg),[75] protein, energy, and nutrient density to account for the "function",[76–79] or economic value as the FU.[60,64]

Addition of different types and concentrations of agrochemicals affect the nutrient composition of plants.[80,81] This suggests the need for a quality indicator or a quality corrected FU[82] (correcting yields by e.g., nutrient density, protein and oil content, depending on the crop) in LCA of food products. Research has shown that ENMs have the potential to alter nutritional composition of plants as well, yet the mechanism by which these changes are induced are not well understood.[83–86] Further research is required to identify the nano-specific properties that elicit unique crop responses to inform decisions on appropriate FUs for nano-enabled agrochemicals, especially in a comparative narrative. Integrating nano-specific aspects and quality metrics in FUs will ensure any benefits gained from reducing environmental impacts by the introduction of nano-enabled agrochemicals is not at the cost of inferior agricultural products.

Results from LCA can be used to inform design of ENMs for specific applications when the FU is defined to capture unique aspects enabled through their use (e.g., size, crystal facet, surface chemistry). This is further important in comparative scenarios since different quantities of ENMs may be required to provide the same function (size dependent toxicity of silver nanoparticles illustrates the nano-specific functions,[55] for example). Any LCA comparing nano-enabled agrochemicals to non-nano alternatives requires moving away from nano-induced effects to reach a common denominator, encompassing a larger system that is representative of the performance of all scenarios (e.g., nutrient use efficiency, plant protection efficiency). The choice of FU is ultimately dependent on the goal of the LCA, and it may even be necessary to consider multiple FUs to capture all of the potential environmental outcomes of a system under study.[87–89]

Designing nano-enabled agrochemical experiments with life cycle inventories in mind

LCA can be pursued using either process-based or economic input-output (EIO) models. The EIO model uses economic activities in a supply chain to estimate material and energy requirements of an economic sector. While EIO-LCA has been applied (independently and in combination with process-based LCA) to both agriculture[90,91] and nanotechnology[49], there is concern regarding the suitability in applying it to nano-enabled agrochemicals. This is due to the incompatibility of the highly aggregated EIO database[92] and the not yet generalizable and heterogeneous nature of ENM applications to agriculture. Evaluating the environmental and human health burdens of nano-enabled agrochemicals for crop production using process-based LCA requires extensive data to create a comprehensive LCI. This includes all inputs (e.g., energy, materials) and outputs (e.g., gaseous, solid and liquid emissions to the various environmental compartments – water, soil, atmosphere) for every process across all life cycle stages, including raw material extraction, manufacturing of chemicals and ENMs and their associated co-products, application of additives and other natural resources to cropland, as well as any transportation between stages. Information on many industrially mature chemicals and additives, and conventional production methods for various crops are already available within commercial databases. The current data gaps related to *nano-specific* processes (Figure 1) emerge as early as the ENM manufacturing stage. Limited data on ENM manufacturing is a well-established challenge[66–69] and data that is available is primarily at lab- rather than industrial-scale complicating comparisons with conventional manufacturing processes. Further, ancillary inputs/outputs, such as energy or water use, nano and non-nano emissions during production, or process yields, are rarely available. Such information is required to comprehensively determine impacts from ENM production.

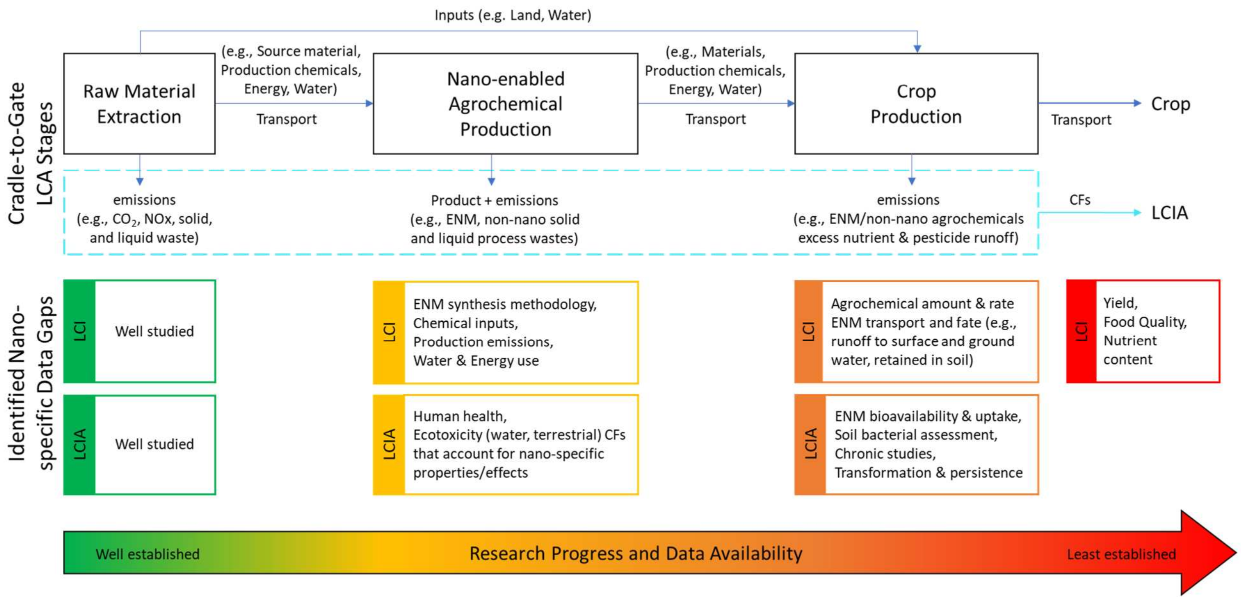

Figure 1 – Cradle-to-gate process-based LCA of crop production, and identified data gaps associated with addition of nano-enabled agrochemicals.

Data scarcity and uncertainty increases significantly for the use phase (here, crop production), where current studies on nano-enabled agrochemical use predominantly evaluate the direct effects of the ENM to a specific plant in a laboratory setting. Information provided in studies such as these typically include ENM concentrations, experimental procedures, and the immediate observed effects (e.g., root/shoot elongation, increased germination rate, increased biomass, and effectiveness rate for pesticides). Yet, the nano-specific data (e.g., ENM flows) that is necessary to include the use-phase LCI is not available (Figure 1). This would include for example, the amount and frequency of application (input), retention (e.g., in the crop or soil) and emission of the ENM (e.g., in the eluent or runoff) as well as the conventional resource flows, including fertilizer and water. These material flows are necessary to inform comprehensive life cycle inventories and reduce uncertainty in the resulting impacts. While the specific focus of studies may differ (i.e., the boundary of the system and the chosen FU), these material flows - which complete a mass balance for any material, product or process, quantify critical resource use and the compartments where they exist (e.g., taken up by the plant, remaining in the soil, emitted to the atmosphere or surrounding aqueous environment) are a critical underpinning of a comprehensive LCA that produces informative and actionable results. Given the diversity of ENMs, crops and conditions, the development of such a dataset requires an extensive library of field-scale experimental data.

A review of literature on nano-enabled agrochemicals to affect crop growth reveals a diverse range of ENMs (e.g., urea-hydroxyapatites, metals, metal-oxides and carbon-based nanomaterials) are used to induce effects in germination rates, total biomass, and yield (Table S1 in the Supplemental Information, SI). The experimental conditions and the measured outcomes from these studies were different in every case. When applying the LCA framework (Figure 1) to these studies, the gap in information (indicated by N/A, Table S1) necessary to complete the resource inventory (i.e., mass balance of chemicals and ENMs) is identified as the primary challenge.

As this nano-enabled agrochemical research develops, the incorporation of more complex and larger plot-scale experiments that track ENM flows would allow for added data realism and reduced uncertainty. The utility of larger-scale experiments for studying ENM behavior has been established through the use of mesocosms that simulate the behavior of ENMs in natural freshwater wetland environments.[93–100] Useful information gained from similarly designed agricultural studies include, but is not limited to, ranging ENM application doses and modes of application, tracking ENM uptake and utilization efficiency, uptake into edible components, crop yield data, plant health and food quality, effects on water utilization efficiency, and ENM emissions to the environment and corresponding ecotoxicity.

Incorporating ENM-specific environmental behaviors into impact assessment models

Deriving any form of environmental impacts (human health or ecological) from chemical emissions requires information on three primary components: chemical fate, exposure concentration, and toxicity.[101] For common life cycle impact assessment (LCIA) models (e.g., IMPACT 2002+,[102] ILCD,[103] Recipe,[104] and TRACI[105]), these elements are combined into characterization factors (CFs) that quantify relative environmental impacts of a unit emission. A critical shortcoming is that models used to calculate CFs in LCIA methodologies are designed for organic chemicals,[66–68] making them ill-suited for assessing the environmental impacts of ENMs[106] due to the fact that ENMs behave more similar to colloids than chemicals in the environment.[107] Examining the structure of the consensus model, USEtox,[108] provides useful insight into the critical limitations of applying LCA to evaluate nano-enabled agrochemicals. USEtox determines the toxicity CF (including ecotoxicity and human toxicity) as the product of the fate factor, exposure factor, and effect factor. Challenges in determining each of these factors for ENMs are discussed, and specific issues regarding the application of nano-enabled agrochemicals are highlighted:

Fate factor: USEtox uses a multimedia transport model containing various regionalized compartments of air, water and soil as interconnected well-mixed boxes that exchange and contain contaminants. It is a steady state mass balance model, assuming *equilibrium partitioning* for organic compounds between dissolved organic carbon, suspended solids, sediment particles, and soil particles and water within a phase. First order inter-media mass transfer and degradation processes with respect to mass are assumed. This has worked adequately for many organic contaminants, but additional considerations are required for ENMs that behave more like particles than organic chemicals.

Unlike dissolved organic compounds, ENMs do not readily equilibrate between phases. Rather, their fate is usually defined by particle physicochemical characteristics and the environmental conditions using kinetic models.[109,110] To account for these differences, process-based multimedia models for ENMs have been developed, including Rednano,[111] SimpleBox4Nano[112] and MendNano.[44] Recent developments in this field are providing dynamic models,[113–115] including an updated nanoFate model.[110] Utilizing the SimpleBox4Nano model to derive toxicity potentials of nano-TiO_2 is the first reported application of these newer dynamic models.[116] These models uniquely account for hydrology, land use effects and realistic release scenarios[117] as well as the fraction of ENMs that are dissolved, free and aggregated . While these dynamic (non-steady-state) spatially-resolved models are likely capable of predicting exposures to ENMs, they become extremely data intensive when considering the direct environmental application of nano-enabled agrochemicals, requiring environment- and particle-specific data: nano-enabled agrochemical use and emissions data, land-use statistics, and sediment loads, for example. While some ENM transformation rate data is available for surface waters, much less is available for agricultural soils – a primary receiving compartment of nano-enabled agrochemicals.[118] Collaborative efforts between experimentalists and modelers will enhance identification of the ENM physicochemical characteristics and environmental properties that most affect their fate in agriculturally-relevant media,[109] with the goal of reaching a consensus model for determining the fate factor of ENMs.

Exposure factor ***:*** The exposure factor aims to estimate the bioavailable fraction of a given compound. For ecotoxicity, the exposure factor for freshwater ecosystems is calculated by assuming emitted organic or inorganic chemicals partition (equilibrium) or dissolve between the available phases based on the compound's hydrophobicity (i.e., partitioning coefficient, K_{ow}). Exposure to organic chemicals in aquatic environments is estimated based on the dissolved fraction of the chemical. For this category of chemicals exposure factor can be derived from $XF = \frac{1}{1+K_{sus}\frac{C_{sus}}{1000}+K_{doc}\frac{C_{doc}}{1000}+BAF\frac{C_{biota}}{1000}}$ where knowing the concentration of chemical associated with suspended matter (C_{sus}), dissolved organic carbon (C_{doc}) , and biota in freshwater (C_{biota}), the suspended solid-water (K_{sus}) and dissolved organic carbon-water partitioning coefficient (K_{doc}), and bioaccumulated fraction of the chemical in fish (BAF) are required. For metals, the exposure factor is the truly dissolved fraction, which is the sum of free metal ion and dissolved inorganic complexed metals, over the total mass. The model relies on four decades of research for creating empirically derived exposure equations with limited regard for mechanistic insight.[119] For human toxicity the model currently considers possible direct (e.g., inhalation and ingestion via drinking water) and indirect (e.g., through consumption of produce and animal products) exposure pathways, and the exposure factor is determined by quantifying the intake fraction of the compound by humans from the total concentration available in an environmental compartment.

In contrast to conventional chemicals, determination of the ENM bioavailable fraction based on USEtox criteria remains an ongoing pursuit.[54,120,121] Specific to assessing the risk of nano-enabled agrochemicals, it will be critical to obtain a mechanistic understanding of ENM uptake by plants from soils or leaves, and translocation throughout, for example.[122] Seminal work in this area provides evidence of ENM uptake and transport through plant vasculature[123], but the dependence of uptake levels on plant species, specific particle characteristics (e.g., surface area, surface chemistry), and/or environmental conditions is not yet fully understood. Further, exposure models of nano-enabled agrochemicals should account for sorption of ENMs to soil particles, ENM interactions with soil microorganisms, ENM transformations and transport under different environmental conditions (e.g., drought vs frequent rainfall events). Given the wide range of agricultural conditions it is imperative to account for the role of soil properties (e.g., type, pH, saturation level, dissolved organic matter content) when determining the bioavailability of ENMs, not only to plants, but to soil invertebrates and the soil microbiome.[124] Transformation of ENMs in soil also affects the ENM speciation and bioavailable fraction in receiving water bodies from leaching and runoff. Despite the emergence of a few nano-specific models,[112,125–129] persistence and bioaccumulation of the nano-enabled agrochemicals in higher trophic level species and their translocation through the food chain is not well studied and information on worker exposure during application of agrochemicals is not yet available. Including these important exposure pathways in determination of the exposure factor requires further research into potential unique pathways for nano-enabled agrochemicals and validation of exposure levels.

Effect factor*:* For ecotoxicity, the effect factor is derived from the *chronic toxicity* of materials to at least three categories of freshwater aquatic species (e.g., algae, crustacean and fish). For a freshwater ecosystem, it is obtained by calculating the geometric mean of empirically derived EC_{50} values for freshwater species (EC_{50} for each species is the concentration of a substance that induces effects in 50% of the test population). The ecotoxicity effect factor focuses on freshwater toxicity only and does not include terrestrial and marine life effects, even though the latter are likely sinks for many ENMs[119] and particularly relevant to agricultural applications of ENMs. For human toxicity, the effect factor is defined as the sum of cancer and non-cancer impacts from inhalation and ingestion. It is derived from the ratio of the intake fraction for each exposure route (inhaled or ingested) to their respective cancerous and non-cancerous ED_{50} values, which is the effective dose that affects 50% of the test population.

The following three suggested improvements to the current form of the effect factor are discussed as a way to enhance the applicability to nano-enabled agrochemicals. First, assessment of ENM ecotoxicity for agriculturally relevant applications should include terrestrial organisms, given that soil is the direct receiving compartment for many agrochemicals and ENMs have demonstrated negative effects on soil microbial communities,[46,130] earthworms and other soil invertebrates,[124,131–133] and plants.[127,134,135] Of particular importance to agriculture are ENM impacts on the phytobiome (i.e., rhizobia, soil and plant microorganism that provide critical ecosystem services for plants). The second suggested focus area is an issue pertaining to ENMs generally, but is especially pertinent to agricultural settings; that is, enhancing the appropriateness of current toxicity protocols, which are not designed for nano-specific time- and environment-dependent transformations. Further, they do not capture the influence of ENM colloidal behavior and therefore, likely overestimate exposure concentrations.[120] Third, it may not be appropriate to aggregate different species effects in the HC_{50} value and for different forms of the same ENM (e.g., different size silver nanoparticles) since ENM toxicity cannot be generalized over multiple species and questions still remain regarding the underlying nano-specific features that drive ENM reactivity and toxicity.[135] This suggests a potential disaggregated approach to effect factor determination, specific to the organism and ENM (composition and other distinguishing characteristics), which merits careful consideration to determine the appropriate tradeoff between gains from added specificity and the practicality of model complexity.

These suggestions are also applicable to human effect factor determination. Added challenges with human toxicity include data availability relevant to inhalation pathways (e.g., worker exposure), relevant synergistic effects, and the added uncertainty associated with extrapolating toxicity data from aquatic or animal studies (especially for carcinogenic effects).[136] These are not specific to nano-enabled agrochemicals however, the application of ENMs in agriculture introduces exposure to new species and ENM forms. Reaching consensus on standards for and prioritization of agriculture-specific ENM toxicity assays is suggested to overcome these existing challenges and accelerate the applicability of LCIA to nano-enabled agriculture.

Including spatiotemporal components in benefit-impact evaluation

Variability is engrained within agricultural processes as they are spatially and temporally heterogeneous. Spatiotemporal challenges of LCIA has been an ongoing area of research.[137–141] Spatially differentiated,[140] and spatiotemporal models[142] have been developed for agricultural practices, but are not universally implemented in a standard LCIA framework. The addition of ENMs to agriculture introduces another level of uncertainty to these processes. For example, ENM environmental transport, fate and concentrations are location-specific, affected by ecosystem characteristics such as geology and topography of the land, the regional climate and extremes of climate variability, and properties of receiving water bodies. Additionally, time-dependent transformations, agglomeration and sedimentation are also relevant in ENM behaviors. At a systems level, as is the case with all chemicals, spatiotemporal concerns become relevant for nano-enabled agrochemicals because benefits and impacts to the environment are realized at different stages of the life cycle, in geographically different locations, and across a wide range of timescales. This spread of potential impacts and benefits over the spatiotemporal spectrum challenges our ability to fairly assess the tradeoffs of nano-enabled agrochemicals. Further, the application of ENMs as a solution to reducing environmental impacts of agriculture (e.g., eutrophication) is only feasible when the economic benefits of avoiding said burdens (e.g., excess nutrients) outweighs initial costs to growers. This is also a location-specific component of a system-wide analysis since legislation and/or incentives on agriculturally relevant emissions can range from county-to-county and state-to-state. Consequences of potential increased efficiencies and enhanced yields through technological advancements of nano-enabled agrochemicals can cascade across locations, influencing land-use change by either repurposing the land once used for agriculture or bringing marginal lands into service, which will subsequently affect the conditions of that ecosystem.

Anticipatory-LCA to guide environmentally favorable ENM development

LCA is inherently retrospective as it relies on life cycle inventory data from mature industrial processes.[143] There is significant scarcity and uncertainty in globally available and comprehensive inventory data in the early stages of research and development,[144] making it difficult to apply conventional LCA tools for quantifying the environmental impacts of emerging ENMs for use in agriculture.[145] Furthermore, incorporation of uncertainty analysis is not universally included in LCA; the use of deterministic values[146–148] in the results mask the underlying data uncertainty and undermines the confidence in the findings to inform decisions on the choice of an environmentally preferred emerging ENM.

A series of National Research Council reports[149–151] have examined the challenges associated with managing emerging technologies in an environmental of data scarcity. Each report emphasizes the importance of relating environmental analysis to specific management *decisions* that orient technologies towards environmental preferable outcomes. Nonetheless, existing practices in LCA present several obstacles to adoption of "decision-directed" approaches.[149] Foremost among these is the emphasis on absolute, versus relative assessments. In an absolute assessment, inventories and midpoint estimates are benchmarked to either pristine or existing background conditions. In normalization of inventory results, which is an essential step for interpreting the results of LCIA, conventional practice is to divide the inventory estimates associated with the study functional unit by existing emissions levels on a global or regional (e.g., European Union) scale. The result is a dimensionless ratio that expresses the fraction of overall emissions that can be attributed to the activity under study. This approach, called *external* normalization,[152] examines the function under study in the context of existing environmental conditions that are outside the scope of the decision-maker. Several studies have now revealed the biases that are introduced by this external normalization approach that may mask information especially important to decision-makers.[152–154]

Alternatively, the *anticipatory* approach applies *internal* normalization[155] that benchmarks assessment of emerging technologies relative to potential alternatives, resulting in a probabilistic rank-ordering of alternatives in order of environmental preference.[156,157] Moreover, an anticipatory approach reveals a rank-ordering of uncertainties that are most important to overall confidence in the results,[158,159] which can be used by stakeholders to prioritize research [160] efforts towards identifying the preferred ENM alternative at the early stages of technology development. This decision orientation of anticipatory LCA distinguishes it from *prospective* LCA, which is another forward-looking approach to understanding the systemic environmental consequences of emerging technologies. Where prospective LCA is most concerned with making accurate forecasts of environmental impact,[161] anticipatory LCA is most concerned with steering technological development towards environmental preferable outcomes. Given the extraordinary uncertainties associated with ENMs, relative assessment for improved decision-making is likely the standard to which LCA analysts should aspire.

Summary and implications

The potential value added through the application of LCA is immense as the community considers the role of nanotechnology in advancing future agriculture sustainability. As such, opportunities for advancing the methodology are identified and suggested as potential path towards incorporating nano-specific behaviors as well as reducing the uncertainty associated with evaluating emerging technologies. Challenges to adopting a life cycle approach for assessing environmental tradeoffs of nano-enabling agrochemicals for crop production are presented herein, and build on the well-established foundation of identified challenges in LCA applied to agriculture and to nanotechnology, independently. Understanding the challenges of LCA applied to agriculture and to nanotechnology is a necessary precursor for identifying the unique challenges at the intersection of these two fields. Table 1 summarizes the overarching challenges and suggestions within each field as it relates to goal and scope definition, inventory analysis, impact assessment, as well as the particular relevance of spatiotemporal analyses and anticipatory approaches. Information presented in Table 1 was informed by a vast body of literature, which was most recently comprehensively reviewed by Notarnicola et al.[64] for LCA of agriculture, and in references 66-69 for LCA of nanotechnology

Table 1 - Identified challenges and recommendations of LCA in agriculture, nanotechnology and nano-enabled agrochemicals

	LCA of agriculture		**LCA of nanotechnology**		**LCA of nano-enabled agrochemicals**	
	Challenge	**Recommendation**	**Challenge**	**Recommendation**	**Challenge**	**Recommendation**
Goal, Scope and Functional Unit (FU)	- FU of yield (kg/acre), does not represent the function. - Deciding among economic, physical, biological and system expansion for co-product allocation. - No clear boundaries between input processes and environmental emissions.	- Include FUs that capture the function of agriculture products, e.g. nutritional content. - Need standard allocation criteria for different products. - Inclusion of impacts on soil quality, fertility, hydrology and biodiversity in the land use impact category.	- FU typically, mass-based, which does not always capture the function offered by ENMs compared to non-nano alternatives.	- In evaluating impacts of nanomanufacturing, the weight-based FU is appropriate. When comparing alternatives across the life cycle, additional functionalities of nanomaterials must be defined (e.g., size dependent toxicity).	- Addition of nanomaterials may change the nutritional composition of foods compared to bulk counterparts. Comparative LCA scenarios among nano and non-nano alternatives poses challenges in finding common functions.	- Use quality corrected FUs to account for changes in nutritional composition. - Incorporate the nano-specific property in the FU when linked to observed effects (e.g., size/shape-related growth). - Use common denominators (e.g., nitrogen use efficiency) for comparing nano and non-nano alternatives. - Compare results across multiple FUs to capture all environmental outcomes.
Life Cycle Inventory	- Insufficient landscape-level data. - Data gaps specific to pesticide and fertilizer emissions to surface water, and emissions from operation of machinery.	- Need consensus on definition of pesticide emissions and on modeling fertilizer emissions to soil and water from leaching, erosion and runoff.	- Lack of data at production level. - Variability in the available input data. - No consensus on methodology of accounting for release of nanomaterials from products.	- Need guidelines for experimentalists assessing release of ENMs. Studying characteristics of released materials. Expansion of release studies from use phase to other life cycle stages.	- Available data on use of nanoagrochemical are limited to direct effects, with no mention of other resource inputs and emissions to inform material flows.	- Incorporating field-scale experiments that track ENM/resource flows would allow for a more comprehensive data inventory.

Life Cycle Impact Assessment and Characterization Factors (CFs)	- Impacts of water and land use are not considered. - Health and biodiversity impacts are ignored in current LCAs.	- Implement impact categories such as land use, water use, terrestrial ecotoxicity in agriculture LCIA.	- No nano-specific CFs. - High degree of variability in toxicity data in terms of methodology, model organisms, and measured toxicity endpoints.	- Establish consensus on methodology of CF development. - A fate model that accounts for nanomaterial transformations*: aggregation, agglomeration and dissolution. (*reviews did not include nanoFate model). - Exposure models that consider bioavailable fraction of nanomaterials for toxicity, otherwise this factor should be equal to 1. - ENM fate and exposure should be integrated with toxicological assessments.	- No nano-specific CFs.	- Incorporate the newly developed nano-fate models. - Further research into behavior, persistence and fate of nanomaterial in agricultural soil. - Exposure models should evaluate sorption of nanomaterials to soil, their transformations and interaction with organisms and bioavailability. - Bioavailability should be assessed for both plants and soil invertebrates and phytobiome. - Enhance relevance of toxicity protocols and model organisms to agriculture exposure scenarios - Distinguish nano-specific characteristics driving effects and account for nano-agrochemical behavior and transformations.

Spatiotemporal Components	- Ignores effects of globalization of food supply chains. - Regional environmental impact categories (e.g. eutrophication, etc.) are location specific. - Variability in soil types, climate, seasonality, transportation among locations, and other stages of the life cycle, can affect LCA results.	- Incorporate spatially differentiated models for regional impact categories, and geo-specific data for inventory. - Use value ranges or statistical analysis to address variability. Use caution in interpreting results of comparative and process performance analyses with non-representative data.	- Not specifically mentioned in review articles. Spatial components are integrated within LCIA fate models. USEtox operates at four different spatial scales (indoor, urban, continental and global).	- No specific suggestions made by review articles.	- Benefits and impacts to the environment are realized at various geographical locations and timescales. - Location-specific legislations and incentives affect the adoption of nanoagrochemicals.	- Consider the spatiotemporal span of the gains from potential enhanced yields and resource efficiency through using nano-agrochemicals, and the subsequent effects on land use change.
Anticipatory Models	- Not specifically mentioned in review article.	- No specific suggestions made by review article.	- Not specifically mentioned in review articles.	- No specific suggestions made by review articles.	- LCA relies on data from mature processes, while nanotechnology is enveloped in uncertainty. - The use of deterministic values in the results mask the underlying data uncertainty and undermines the confidence in the findings.	- Adopt an anticipatory approach results in a probabilistic rank-ordering of alternatives by environmental preference, which allows for prioritizing of research.

A readily accessible opportunity in advancing LCA of nano-enabled agrochemicals includes the establishment of common comparative metrics (i.e., FUs) that account for either nano-specific or higher level agrochemical functions depending on the objective of the study and the type LCA (i.e., attributional vs. consequential), noting that inclusion of multiple FUs can aid in capturing all potential environmental outcomes. To address the issue of the data gaps in LCI, collaborative efforts among experimentalists and LCA practitioners can ensure that comprehensive data related to ENM and conventional resources flows are captured to inform the LCI, which typically requires dissemination of methodological details, a slight modification to the experimental design and/or additional characterization of captured eluents or crop components. Future efforts should consider pursuit of larger-scale experiments that similarly track ENM and resource flows under more realistic conditions. To determine nano-enabled agrochemical impacts, LCIA models should (i) adopt and incorporate the available nano-specific fate models with the standard LCA framework, (ii) utilize bioavailability assessments that include ENM transformations and interactions with soil, and (iii) focus on agriculturally-relevant toxicity assays (e.g., using terrestrial ecotoxicity endpoints, soil microorganisms). The addition of dynamic components can also assist in determining impacts at specific spatiotemporal levels appropriate for agricultural practices and climate conditions. Modifications of conventional LCA approaches to anticipatory models are also advised to mitigate effects of data uncertainty and facilitate decision making among ENM alternatives. The identification of critical challenge areas and outlined opportunities to enhance the applicability of LCA to nano-enabled agriculture offer guidance for ongoing research intended to advance promising ENM applications towards realizing agriculture sustainability.

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Conflicts of interest

There are no conflicts to declare.

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Nano specific challenges of applying LCA towards nano-enabled agrochemicals to assess their environmental implications are identified in this perspective.

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