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A One Health approach to managing the applications and implications of nanotechnologies in agriculture

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The need for appropriate science and regulation to underpin nanosafety is greater than ever as ongoing advances in nanotechnology are rapidly translated into new industrial applications and nano-enabled commercial products. Nevertheless, a disconnect persists between those examining risks to human and environmental health from nanomaterials. This disconnect is not atypical in research and risk assessment and has been perpetuated in the case of engineered nanomaterials by the relatively limited overlap in human and environmental exposure pathways. The advent of agri-nanotechnologies brings both increased need and opportunity to change this status quo as it introduces significant issues of intersectionality that cannot adequately be addressed by current discipline-specific approaches alone. Here, focusing on the specific case of nanoparticles, we propose that a transdisciplinary approach, underpinned by the One Health concept, is needed to support the sustainable development of these technologies.

Rapid innovation in the field of nanotechnology has produced continuous sector growth and with it, extensive risk management challenges. The volume and variety of engineered nanomaterials (ENMs) incorporated into commercial products and processes, and their unique emergent properties, have prompted significant concerns regarding the safety of ENMs for human and environmental health and highlighted the need for nanocompatible (eco)toxicological assays and dedicated risk assessment. Consequently, 'nanosafety' has been the focus of sustained research efforts for over a decade now. The term itself first appeared in the scientific literature in 2005[1], and the OECD Working Party on Manufactured Nanomaterials was established shortly afterwards in 2006. Since then, human-focused nanosafety research has been concerned with the intentional exposure of people to ENMs and in particular nanoparticles (NPs; for example, through nanomedicines, food additives and health supplements), unintentional exposure (for example, released from consumer products, including food packaging) and occupational exposure (for example, from industrial processes). By contrast, environmentally focused nanosafety research has predominantly targeted inadvertent environmental releases of NPs associated with the production, use and disposal of nanofunctionalized consumer products[2] (for example, NPs in personal care products that are released during use to household wastewater). A notable exception to this relates to the direct use of NPs (for example, nano zero-valent iron) for environmental remediation, in which case, the proposed receiving environments are already severely contaminated. As regulatory approval is typically required prior to implementing any new remediation technology, this has in effect delayed the uptake of nanoremediation technologies in many jurisdictions[3], giving risk assessors more time to conduct detailed NP risk assessment for this particular pathway prior to product deployment.

Today, the strong commercial impetus for agricultural innovation and the use of nanotechnology to enhance agricultural efficiency is bringing new priorities and challenges for both human and environmental risk researchers, assessors and regulators. The application of nano-enabled agrichemicals in plant production has been widely discussed (for example, ref. [4]). For instance, nanotechnologies could be used to control the release of agrichemicals (for example, fertilizers and pesticides), to develop target-specifc delivery systems for biomolecules (for example, silencing RNA or nucleotides) or to modify the properties of existing active ingredients (for example, replace soluble Cu with nano-CuO). These new applications will add a substantial degree of complexity to what is already a multifaceted hazard, exposure and impact scenario. In particular, the multiple levels of connectivity between human and environmental exposure scenarios in agricultural products has the potential to generate unexpected side-effects that a discipline-driven approach may fail to tackle or even recognize. This complexity brings us to a point where an inter- or ideally transdisciplinary systems-based approach[5], such as that offered by the One Health perspective, is required. This is not only needed to ensure safety is understood and researched across and beyond disciplinary boundaries; it is also necessary if we aim to develop safer-by-design agri-nanotechnologies that are both environmentally sustainable and socially robust.

The status quo

The current regulatory frameworks and discrete human and environmental nanosafety research communities are areas that should be targeted for improvement.

Immature safety governance frameworks for NPs. One of the key overarching challenges facing nanotechnology industries, including agri-nanotechnology, is that a clear and transparent framework for risk governance remains lacking despite more than a decade of technological innovation in the field[6–8]. Despite the significant research progress towards understanding ENM hazards and risk, there is still no harmonized basis for ENM risk governance across different sectors this knowledge can be useful for. Given the lack of specific regulatory frameworks, the field of nanosafety has increasingly turned towards the development of safety-by-design approaches[7,9]. Commendable as it is to actively pursue risk reduction during the design phase, this approach alone is insufficient for adequately ensuring safety and broader governance frameworks are still required[10]. One of the first steps towards achieving harmonized cross-sectorial risk governance

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of nanotechnologies is data sharing[11]. This transfer of knowledge across different nanotechnology fields is needed not only to advance nanosafety research, but also to support the development and implementation of reliable frameworks for risk assessment and decision-making and to facilitate risk communication with relevant stakeholders (for example, industry, regulators, insurance companies, civil society organizations and the general public)[7,8]

The European Commission's recent call to develop transdisciplinary risk governance frameworks based on a clear understanding of nanotechnology risks, management practices and societal perceptions is a positive sign of moving beyond the current status quo of immature and underdeveloped cross-sectorial governance[12]. Under this call, three large international projects (RiskGONE, NanoRIGO and Gov4Nano) have recently received financial support and it will be worth monitoring their outputs for their potential to provide sound overarching frameworks for nanotechnology risk governance. Nevertheless, even the establishment of overarching cross-sectorial frameworks is not all that is needed if we are to achieve good governance of agri-nanotechnologies. Deeper changes in the way research and risk assessment are conceptualized and performed are also required.

A disconnect between human and environmental nanosafety. Currently, most nanosafety researchers operate within two distinct epistemic communities[13,14]. On the one side, the human health risk community has a primary interest in mammalian cells, tissues and organisms (for example, lymphocytes, skin and mice), while on the other side, environmental health risk researchers focus predominantly on other branches of the tree of life (for example, single-cell organisms, plant tissues, invertebrates and fish). Until recently, there has been limited direct collaboration and knowledge exchange between these communities, despite the clear potential for value. The reasons for this limited interaction across the communities becomes apparent upon considering key differences in the challenges they face.

Environmental nano-risk challenges. The identification of relevant environmental exposure scenarios, or 'problem framing' as defined by Bos et al.[15] and Owen and Handy[16], has been highly challenging in itself due to the largely incidental/accidental nature of the release of many NPs to the environment. Moreover, the key characteristics that are known to be relevant to NP toxicity (for example, size, surface identity, shape, aggregation and so on[17,18]) effectively need to be considered as dynamic properties once NPs enter natural receiving environments, even when working with simple standardized test environments[19]. As a result, determining the environmental relevance of NPs is not a trivial matter. For instance, one could argue that silver sulfide NPs should be prioritized for risk assessment rather than the pristine metallic silver NPs used in product formulations because silver sulfidation is a dominant process that occurs rapidly under a wide range of environmental conditions, significantly changing the core chemistry of the particles[20,21]. Nevertheless, most ecotoxicity testing has been done using pristine metallic silver NPs. Similarly, the surface functionalization of pristine NPs is also known to change substantially once they are exposed to ambient environments, but this process is rarely simulated or considered in laboratory studies[22]. Despite these complexities, potential environmental release scenarios have been developed and employed to derive predicted environmental concentrations (PECs) of ENMs in the environment using advanced modelling approaches such as probabilistic material flow analysis[23]. These results go some way towards filling the knowledge void, but are very difficult to verify empirically due to the extreme challenges in detecting and quantifying ENMs in complex environmental matrices[24,25]. New developments in single-particle time-of-flight mass spectroscopy may provide a way out of this impasse analytically, at least for the more simple environmental matrices[26], but in many contexts, a reliance on modelling will almost certainly remain. ENM hazard characterization is also highly problematic in the environmental context because even though protocols have been developed[27], the continuous, and difficult to reproduce, transformations of ENMs in the environment (from dissolution to agglomeration and changes in composition and surface properties) make this task particularly challenging. In addition to the scientific challenges involved, the determination of environmental hazard is also complicated by the diverse range of values that have to be navigated when defining what constitutes environmental harm and deciding how to handle scientific uncertainty and ambiguity[28].

Human nano-risk challenges. Strategies for toxicity testing are essential in human hazard and risk assessment[29] and toxicity can be investigated in silico, in vitro or in vivo. Oxidative stress has been shown to be an underlying mechanism of possible toxicity of ENMs, causing both immunotoxicity and genotoxicity. However, novel toxicity pathways, particularly epigenetic toxicity, have been also suggested[30,31]. This means that various toxicity testing strategies may be selected. Human health ENM risk assessment also necessarily involves consideration of multiple exposure pathways (inhalation, ingestion, dermal absorption or injection) and may differ considerably depending on the source of exposure. For instance, the development of nano-enabled drug delivery systems will be subject to safety requirements that differ from those needed for food additives.

Food additives are a particularly relevant example in the context of this article as one of the potential risks associated with the use of nano-agrichemicals relates to the possibility that they could be present in plant materials for human consumption[32]. In other words, both food additives and agrichemicals are intentionally added during food production, albeit at different stages. The topic of ingested NPs has recently been reviewed previously[33]. Currently, it appears that only a few types of NPs are specifically used as food additives: TiO_2 (as a whitening agent), SiO_2 (as a filler) and nano-Zn and Fe oxides (as dietary supplements). Sohal et al.[33] reported that 39 studies published between 2007 and 2017 met the selection criteria for inclusion in their review and of these, only 21% used food grade ENMs for testing. This is rather surprising and indicates that in the emerging area of nano-risk assessment for agrichemicals, there is a need to establish clear recommendations for toxicological/risk assessment investigations[33]. Even though only a limited range of ENMs are relevant in the context of direct human exposure through food, the risk assessment of these materials is far from complete and consolidated. For instance, a recent article reporting possible chronic intestinal inflammation and carcinogenic effects from TiO_2 (ref. [34]) prompted the French government to consider banning this widely used pigment from foodstuff[35].

The relatively low level of connection between human and environmental nanosafety research has occurred partly due to the limited relevance of environmental exposure pathways (not including nano-industry working environments) to human exposure (Fig. 1). Human exposure typically occurs through inhalation, ingestion, injection/insertion and skin absorption[36]. Excluding occupational exposure, dermal exposure occurs through cosmetic and sunscreen use, and from medical preparations, although the mechanisms and extent of this exposure pathway are not fully understood and an increasing number of studies indicate that ENMs, including NPs, are incapable of overcoming the intact skin barrier[37]. This pathway is also likely to vary considerably on the basis of individual habits, sex, age and other socio-economic factors. The inhalation pathway is the most significant route for occupational exposure to NPs, with inhalation of sprays and therapeutics quantitatively less important at present[38]. The ENM ingestion pathway is dominated by food additives used to change/mask taste, texture and appearance. However, incidental release of ENMs from

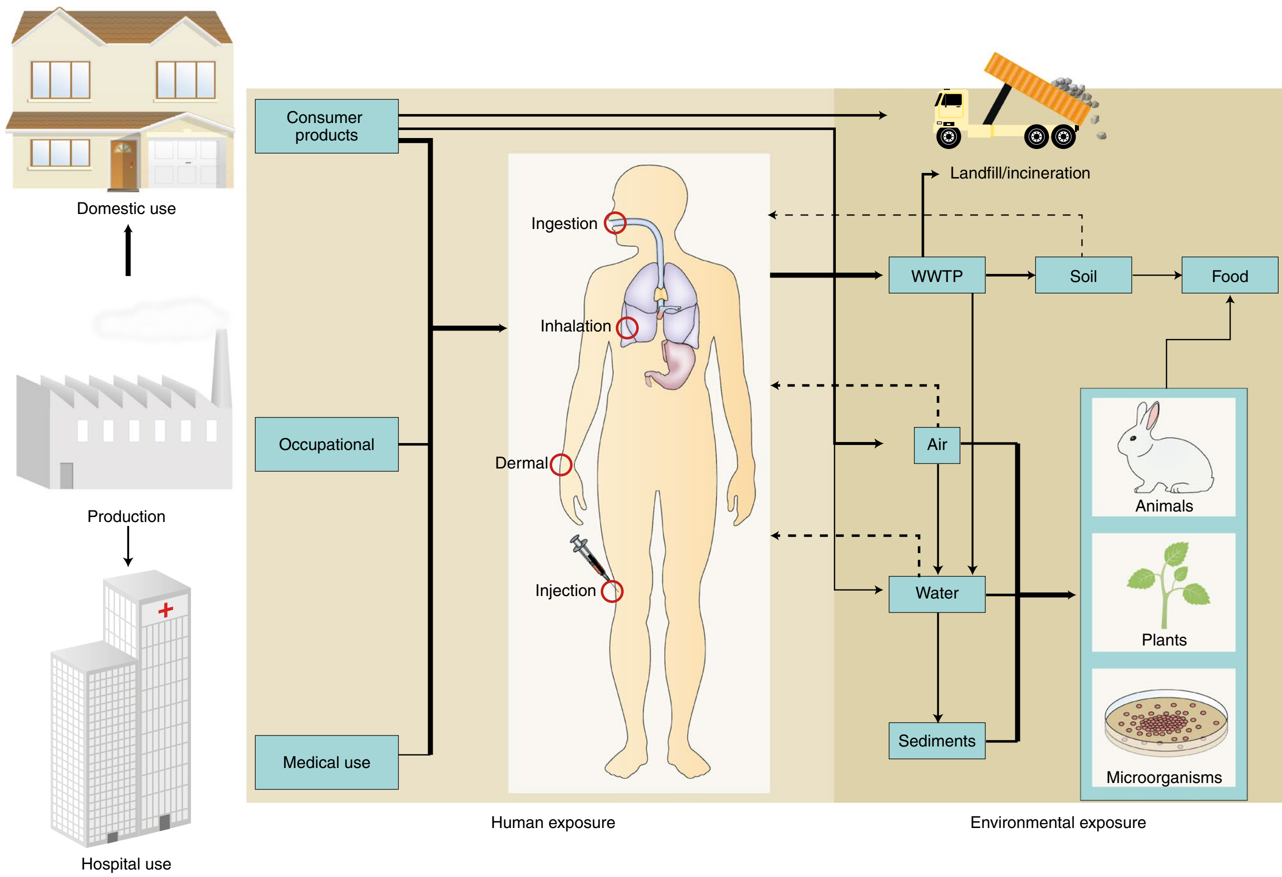

Fig. 1 | Human and environmental exposure pathways not considering agri-nanotechnology. The solid lines indicate the main exposure pathways while the broken lines are theoretical, and currently most likely negligible, exposure pathways. WWTP, wastewater treatment plant.

lipsticks, packaging materials and NPs used for delivery of drugs and other compounds and in beverages also contribute to this pathway[39]. Direct injection of NPs for imaging or clinical treatment or exposure to implants that have been nanofunctionalized is highly person-specific. Overall, it must be concluded that the natural environment (that is, excluding working environments) is likely contributing relatively little to human exposure at present, with the strongest link apparently being through food grown on soils that receive wastewater biosolids, which in most cases is the primary environmental exposure route[40].

Due to these inherent differences in focus in the early days of nano-risk assessment the status quo in nano-risk research and assessment became characterized by a separation between the fields of human and environmental nanotoxicology. Despite the very significant research efforts in both, cross-disciplinary interactions and information exchange has been comparatively limited, even with respect to analytical techniques, where an immediate benefit is apparent[41]. Moreover, even though risk assessment frameworks that cover both human and environment aspects have been developed[15] their application still typically remains discipline-specific with little interaction between assessors in different areas. This is perhaps not surprising in the case of ENM risk assessment as a lack of cross-fertilization between human and environmental toxicology has long been recognized even in more established fields of research. For instance, the potential to use human pharmacology data in ecotoxicology has been advocated for a considerable time[42] but only a limited number of examples are present in the literature (for example, ref. [43]).

A strategy for environmental risk assessment of NPs recently put forward[44] demonstrates the current approach for the environmental nanorisk community. It involves material characterization, release, fate and exposure modelling (to obtain PECs), hazard characterization (to derive predicted no-effect concentrations; PNECs) and risk characterization (often by comparing PECs and PNECs). This framework is conceptually similar to those used to assess other potential environmental pollutants but with additional challenges due the complexity of NPs and their behaviour in the environment. A similar framework can be used for human risk assessment[15]. However, these two approaches have not been integrated to date.

The development and adoption of agri-nanotechnologies arguably brings new impetus and opportunity to transcend the current human and environmental health nanosafety divide. Indeed, failure to do so may potentially lead to large gaps and oversights. Emergence of unexpected side effects due to unrecognized system continuities often occurs when breakthrough technologies with multiple points of contact between the human and ecological spheres are introduced but assessed according to separate disciplinary-based expertise. In the case of agri-nanotechnologies, we argue that an interdisciplinary and ideally transdisciplinary approach, such as that embodied in the One Health concept, is both appropriate and necessary.

One Health

One Health is an approach to research and collaboration where multiple disciplines—working locally, nationally and globally—unite in the quest to attain optimal health for humans, animals and the environment, recognizing that each of these entities are integrated within a system[45]. It is also an approach in which different types of stakeholders are recognized as having important roles and knowledge to effect change within the system. This approach has proven particularly important in the area of (microbiological) food safety, zoonoses and antimicrobial resistance[46]. It has been endorsed by the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE) and numerous national governments. In the context of this article, the FAO definition is relevant as it includes food safety as well as human, animal and environmental health: "The One Health vision is a unifying force to safeguard human and animal health, to reduce disease threats and to ensure a safe food supply through effective and responsible management of natural resources."

Here we will briefly introduce the concept of One Health as applied to antimicrobial resistance as there are several parallels with the use of agri-nanotechnologies. Rapidly evolving and spreading antibiotic resistance is a complex phenomenon driven by antimicrobial use, for different reasons and with different degrees of need, in human health, and in the animal, environmental and food sectors[47]. In particular, the inappropriate use and overuse of antibiotics in human medicine[48] and as growth promoters in animal husbandry, as well as insufficient treatment of waste streams, have come under increasing scrutiny for their role in driving the rapid development and transmission of multidrug-resistant pathogens[49]. For instance, the use of antimicrobials for animal production has been reported to represent about 80% of the total antimicrobials used in the USA[50] with global predictions indicating a significant increase in their use due to growth in consumer demand for livestock products[51]. There is now broad consensus that transfer of antimicrobial resistance occurs between food-producing animals and humans[46] with increasing evidence that human activities increase the environmental resistome[52,53].

The advent of agri-nanotechnologies has the potential to significantly increase the direct release of ENMs into the environment and add a significant pathway of exposure to humans through the food chain. This has several similarities to the issue of antimicrobial resistance: (i) it provides an exposure continuum and interlinkages between human, animal, environmental and food health; (ii) it is both driven and mediated by agricultural activities and (iii) it is driven by increasing demand for food production (fuelled largely by increased demand for animal-based products[54] and large food waste in affluent industrialized nations) and compounded by population growth.

The first point above is particularly significant as it drastically changes the exposure scenario depicted in Fig. 1, where the main exposure pathways to human and environmental endpoints are separate or have minimal feedback loops. Given the introduction and widespread use of agri-nanotechnologies (limited to plant production in this article), a much more complex exposure scenario can be envisaged (Fig. 2). In particular, large-scale release of agri-nanotechnologies could significantly increase human exposures in various ways. First of all, through the 'contamination' of the food chain with the ENMs used for their production. This of course will be a function of a number of socio-technical parameters such as their partitioning and persistence both pre- and post-harvest, the impacts of food processing and cooking, diet, legislation, information available, acceptance to consumers and so on. However, if the direct and intentional application of nanotechnologies to agricultural environments increases substantially, other indirect pathways of exposure due to the leaching, spray-drifting and runoff of NPs to non-target environments may become significant. In either scenario, it is likely that the NPs to which humans are exposed could be substantially different to the pristine NPs that are used in the original agri-nanotechnologies. This also represents a distinction and complication in comparison to the status quo where most of the human exposure at present is due to largely pristine NPs used directly in food, beverages or biomedical applications. Moreover, whereas current human exposure through food and beverages is limited to relatively few classes of ENMs, the range of agri-nanotechnologies that will be developed will be much more diverse and, in some cases, will directly carry toxic substances (that is, nanodelivery system for pesticides).

Such an increase in the complexity of the possible pathways of exposure and the multiple points of contact between human, animal, environmental and food domains highlights the relevance of the One Health concept and the value in adopting an interdisciplinary approach to risk research and assessment. This is essential to identify opportunities for health improvements and optimize risk mitigation strategies over-riding compartments and discipline divides[55]. Furthermore, such an approach would offer the opportunity to identify potential indirect benefits of agri-nanotechnologies, which may otherwise be overlooked. Examples of complex, indirect risk-and-reward questions that may be best studied using a One Health approach include:

- Could mass commercialization of antimicrobial NPs and their potential use in agriculture undermine their biomedical potential by driving the environmental development/spread of antimicrobial resistance?
- Could NPs increase colloid-facilitated transport of pesticides to water bodies and contaminate the (human) food chain?
- Could agri-nanotechnologies increase the efficiency of agrichemicals to a point where they reduce off-target effects on non-target organisms (including humans)?
- Could nano-enabled agrichemicals offer novel mechanisms or exposure pathways that make them more efficient but increase the range of non-target organisms or organs affected, or act as carriers of other pollutants?
- Could agri-nanotechnologies substantially reduce the carbon footprint of agriculture with corresponding benefits for environmental and human health?

A One Health approach for nanosafety in agriculture

Successful implementation examples of the One Health principles and approach are emerging in a variety of contexts. For instance, Boqvist et al.[56] recently reviewed the One Health issues related to microbiological food safety in Europe, and Lammie et al.[49] summarized the progress on addressing antimicrobial resistance. This latter study also provided an excellent overview of the numerous implementations of One Health principles in national and global policies, testifying to the fact that, at least in the area of antibiotic resistance, these principles are actively being translated into operational and legislative outcomes. For instance, nations worldwide are increasingly moving to restrict and ban the use of key antibiotics as growth promoters in animal husbandry as it is now clear that this practice can inadvertently increase antibiotic resistance in human and animal pathogens[57].

Despite the successes to date, operationalizing a One Health approach in any new area of research presents significant challenges. Lebov et al.[58] have recently provided a framework for One Health that includes a case study based on the application of biosolids in agriculture. This example is highly relevant in the context of this paper as the risk of contamination of the food chain and potential effects on human and environmental health when biosolids are inappropriately used in agriculture are not dissimilar to those that can be envisaged in the case of unregulated adoption of agri-nanotechnologies. We have therefore used the proposed framework[58] to begin a theoretical conceptualization of what a One Health approach for agri-nanotechnologies may involve. The approach of Lebov et al.[58] includes a conceptualization phase and a planning phase. In the case study provided, the planning phase includes data sourcing as a substantial amount of information is already available regarding potential risks related to biosolids use in agriculture. In

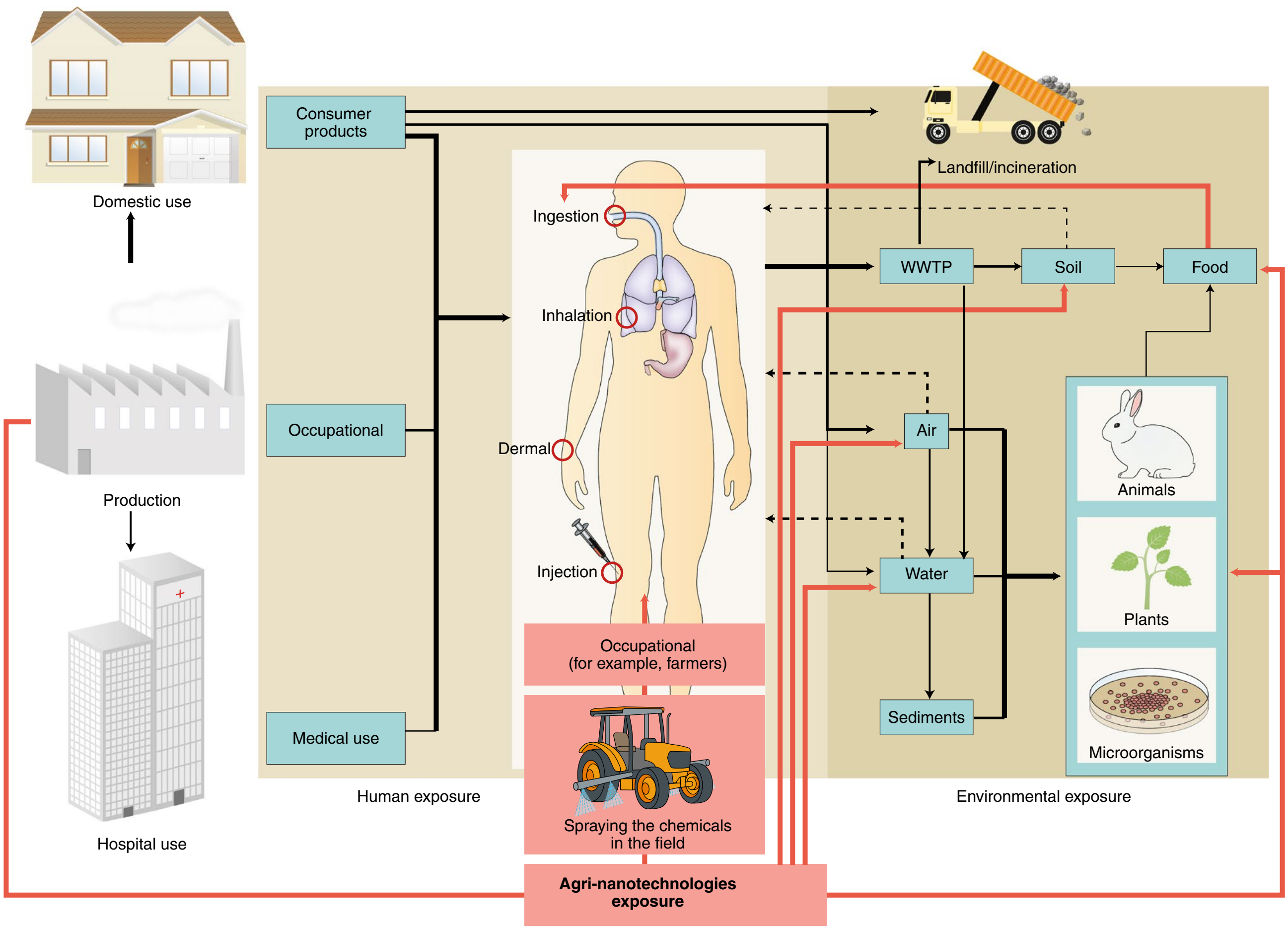

Fig. 2 | Human and environmental exposure pathways become much more complex when agri-nanotechnologies are added to the scenario reported in Fig. 1.

the case of agri-nanotechnologies, where the information available is still limited, planning and execution should be separated (Fig. 3).

The conceptualization phase is critical as it includes both the problem/hypotheses definition and the identification of collaborating teams. Although definition of hypotheses and objectives within individual areas can be a relatively simple task if they fall within a specific discipline, the strength and the challenge of a One Health approach lies in the intersectionality aspects. It is at this level that unexpected issues can be raised, which would otherwise be overlooked by one-dimensional approaches. This also means that technical knowledge, which remains a conditio sine qua non in risk assessment, needs to be integrated with knowledge of consumer behaviour, food trends, economic incentives and political necessities to provide a holistic understanding of complex issues. In other words, hypotheses at the intersection of different domains require interdisciplinarity or even transdisciplinarity rather than simply multidisciplinarity. According to the definitions provided by Choi and Pak[59] this requires moving beyond the simple assemblage of different forms of disciplinary expertise (multidisciplinarity) toward the analysis, synthesis and harmonization of knowledge from different disciplines into a coherent whole (interdisciplinarity). However, an interdisciplinary approach would still have significant limitations as this would still be limited to a largely academic discourse. Knowing the real risks of (nano-)agrichemicals to both human health and the environment would improve when there is a better understanding of how farmers use and apply them. Do they follow the recommendations provided and if not, why not? What are the social, economic and ecological pressures they face that may mean they do not follow the rules assumed during risk assessment or mandated by risk management? Similarly, how do chemical companies communicate the safety requirements? How are these then passed on by suppliers or extension officers? Is this sufficient? In this context, the final goal of a One Health project would extend to include the integration of natural, social (including economic) and health sciences in a humanities (or legislative) context together with the inclusion of a range of other relevant stakeholders such as research funders, farmers, civil society organizations and local community groups (transdisciplinarity[60]).

Hypotheses that are commonly tested in human, environmental and animal health in relation to nanotechnologies are reported in Fig. 3, along with examples of questions that could arise from the intersectionality of these areas. This clearly does not represent an exhaustive list but should provide some example of the type of interactions that can be addressed through a One Health approach. Lebov et al.[58] suggest the use of visualization to explore potential intersections between disciplines. This could be accomplished using causal diagrams or directed acyclic graphs[61] for instance; these are often used in clinical settings and risk assessment. To some extent, the definition of these key questions will drive the composition of the collaborative teams required through an iterative process. In taking a One Health approach, such teams should not be limited to scientists or researchers but should also involve stakeholders such as practitioners, policymakers, managers and community members. In the case of agri-nanotechnologies, this would also include farmers, relevant industry representatives and consumers.

The planning phase possibly represents the most challenging stage of the investigation as by their very nature, One Health study designs are complex and have to cover different disciplines

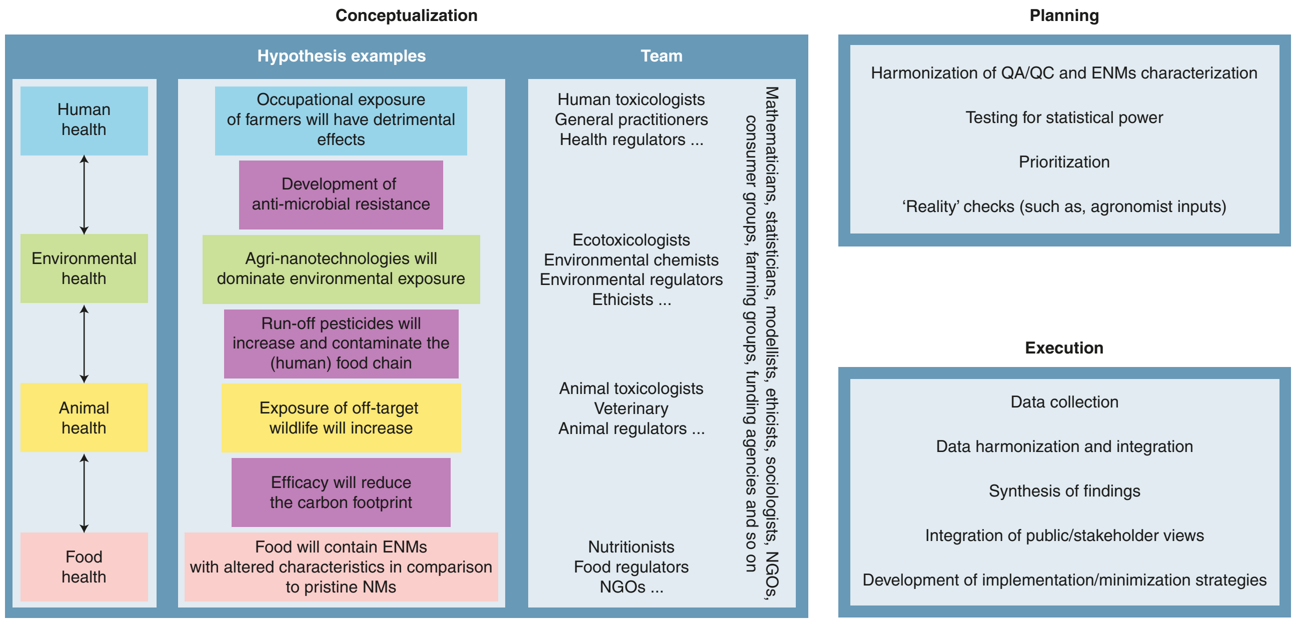

Fig. 3 | A possible One Health framework for the risk assessment of agri-nanotechnologies. The purple hypotheses are representative examples of One Health issues while the other boxes are more directly linked to a specific health area (for example, limited intersectionality). NGOs, non-governmental organizations.

and include knowledge from a range of different stakeholders. Harmonizing quality controls/assurance procedures, characterization protocols (also a key point in ENM studies) and ensuring that experimental designs provide sufficient analytical and statistical power for the different endpoints investigated requires considerable coordination. Furthermore, it is to be expected that, despite these harmonization efforts, data will be diverse and will include both quantitative and qualitative information as well as measured and modelled data. Hence, statistical and mathematical strategies at this stage may be necessary for ensuring that the available information can usefully be combined and used to test the hypotheses set in the conceptualization phase. The planning phase, and the execution phase that follows, should also try to leverage the range of technical expertise available across disciplines, which could provide a significant advantage over discipline-specific studies. For instance, specific ENM characterization or analytical requirements could be serviced by one or a few specific teams with the most appropriate expertise. This would result, at the same time, in more comparable and robust datasets.

An inclusive framework such as the one described here would also have the advantage of bringing together all the necessary stakeholders to ensure that the most appropriate implementation/minimization strategies are developed and acted upon in order to promote appropriate risk governance. For instance, in the case of nano-agritechnologies, farmer groups could play a critical role not only in the planning and execution phases but also in the implementation of a One Health strategy as recently argued through the Farmer First Health Paradigm[62]. Engaging with public and stakeholder views and combining these with more analytical processes such as risk assessment has been advocated in frameworks for responsible innovation[60,63,64] and in the development and use of various deliberative/analytic models for decision-making[65–68]. Experience with these types of integrative approaches can also be brought to bear on the development of a One Health perspective and framework.

Indirect benefits of adopting a One Health perspective

Bringing together a diverse community of researchers and stakeholders has several indirect benefits that could progress the development and safety of nanotechnology applications in agriculture.

One area that would be boosted in importance under a One Health perspective is what we would call 'comparative nanotoxicology'. Many have argued that a thorough understanding of the nano-specific mechanisms of action and toxicity is required before ENMs with improved characteristics (that is, high efficacy and low toxicity) can be consistently developed[22,69,70]. Yet studies that compare, side by side, the mechanisms of action or toxicity in environmental and human endpoints are virtually absent from the literature although a few review articles cover both human and environmental toxicology (for example, refs. [71,72]). For instance, a literature review comparing the toxicity of Ag, ZnO and CuO NPs on the basis of various environmentally relevant test species and mammalian cells in vitro revealed that toxicity varied by up to four orders of magnitude between endpoints[73]. This variation could be due to genuine differences in susceptibility between the tested organisms/cells or to the variation in toxicity of the NPs tested in the different studies (due, for instance, to size, surface chemistry or shape). However, it cannot be excluded that confounding factors due to differential interaction of the NPs with experimental materials (for example, media and containers) also play a role. These operationally defined issues have been reported in the literature[74–76] but more needs to be done to get to the core of the differences in toxicity that have been observed. To tackle this issue in 2017 the so called Malta Initiative was launched, with the aim to speed up validation and adaptation of nanospecific OECD test guidelines for physico-chemical properties, acute toxicity and systemic and chronic effects against humans and ecosystems[77].

A One Health approach could create the conditions for comparative nanotoxicology to progress rapidly. This is an essential step before a safe-by-design approach can prove successful. In fact, while safety by design has gained much attention in the area of ENMs development and many see it as a promising approach[78,79], it has also been argued that safety by design is hardly achievable at this stage as "there is no reliable and complete body of knowledge on the risks of ENMs that can simply be incorporated into design processes"[10]. A complete body of knowledge would arguably have to include the sort of unexpected and intersectional issues that can only be comprehensively addressed through comparative nanotoxicology and a One Health approach. While there are some new initiatives, such as the NanoREG2 (http://www.nanoreg2.eu) project that will take important steps forward by developing large databases collating results from numerous projects on human and environmental nanotoxicology, for comparative nanotoxicology to deliver valuable inputs to risk assessment and regulation, further steps beyond the collation of information will be required. The information will, for example, need to be systematically compared and new empirical investigations designed on the basis of the findings.

A One Health perspective would also greatly facilitate the exchange of knowledge and expertise between medical- and agri-nanotechnologists. For instance, nanodelivery systems have been a focus of intense research for their potential to control the release of drugs and stabilize labile molecules (for example, proteins, peptides or silencing RNA) from continuous degradation[80]. Although it is likely that the same principles can be applied to plant systems[81], the development of nanotechnologies to enhance crop productivity is, comparatively, in its infancy[4]. To date, research in this area is mainly related to nanoparticulate soil fertilizers and encapsulated herbicides[82,83]. This research activity pales in comparison to the depth of knowledge already generated about the potential use of nanomedicines for drug delivery in humans. There is therefore clearly the potential for significant advance through an increased level of interaction, knowledge sharing and knowledge co-creation across these fields.

Another area where adopting a transdisciplinary One Health perspective will be important, is in navigating the acceptance for agri-nanotechnologies in the public domain. The social acceptance of nanotechnologies has not suffered from the same high level of public criticism and political debate as that experienced by biotechnologies. This is perhaps partly due to the fact that nanotechnology innovation has to date primarily focused on creating new materials rather than altering living beings or food systems. In some parts of the globe there has also been significant investment in public outreach and engagement activities early in the development of nanotechnology development, policy and funding programmes, and although many of these efforts may be criticized for using limited conceptualizations of 'the public'[84] or simply working to legitimate existing investments in the field[85], these efforts may also have impacted the levels of public criticism[86–89]. However, a large-scale, intentional distribution of ENMs into agricultural environments, especially to enhance crop productivity, could certainly generate similar concerns for nanotechnologies as those raised against GMOs. A recent study in the US[90] shows that public perceptions of GMOs are, for example, correlated to a tendency to support labelling of nano-enabled products, and food is always a culturally charged domain to enter. At present, various surveys testing the consumer knowledge of food-relevant nanotechnologies show that understanding in the general population is low[91–94]. Multiple studies have shown that willingness to pay for nano-enabled products and nanofoods is largely influenced by perceived benefits[95] and trust in the food industry[96]. Willingness-to-pay studies have, however, also shown a reluctance to pay more for nanofoods even if there could be health benefits[32]. Frewer[97], who recently reviewed the literature on consumer acceptance and rejection of emerging agrifood technologies, concludes though that consumers are not necessarily averse to technological development in the agrifood sector. This means that social acceptance rests on a complex interaction of factors that includes a weighing of costs and benefits, an assessment of the quality and sufficiency of the available information and the level of trust in the producers of both the nanoproducts and the associated safety knowledge. Adopting a One Health perspective can help this process by actively recognizing the interconnected nature of social and biological systems and working to incorporate both different disciplines and stakeholders in knowledge building and decision-making processes.

A One Health perspective could also facilitate the development of appropriate regulatory frameworks for nano-agritechnologies. The regulation of nanotechnologies has been fraught with challenges[28]. This is even the case for the food sector despite the limited number of materials currently employed as food additives[98]. For instance, a recent article documented the struggle of the Australian regulatory authority to even acknowledge the use of ENMs in Australian foods until 2015[99]. The use of ENMs in agriculture is even more complicated since it needs to consider safety for humans and farmed animals (through occupational exposure and food/feed) and the environment.

It could be argued here that in the case of plant protection products (PPPs, such as pesticides and herbicides) the current regulation could be sufficient as 'new chemistries' already require extensive human and environmental risk assessment before a product can enter the market. However, simply relying on the current approach used for PPPs may in fact not be sufficient in this case because:

- It is not clear whether the use of nanocarriers would require comprehensive new testing of specific formulations.
- It is uncertain whether existing chemistries, and a simple change in particle dimensions, would trigger a need for new testing or not (for example, in the case of Zn and Cu oxides that are already commercially available as micronized products for which the 'chemistry' would not change).
- At present, nanospecific, standardized testing protocols are not available in many jurisdictions.

Nanomaterials are known to easily change characteristics as they move through different environmental compartments and these transformations are far from being understood at the level required to perform robust risk assessment.

These remaining questions and uncertainties regarding the regulatory status of many NPs used in agrifood settings, the level of scrutiny being applied, and the reliability of the available knowledge mean that regulating nano-agrichemicals according to existing systems alone may be insufficient. Indeed, there are indications that the situation may be equivalent to testing an organic pesticide without considering the properties of its degradation products.

Finally, it could also be argued that current regulatory requirements for PPPs have also found to be lacking in several cases. The massive loss of insect biodiversity and the impacts of this on broader ecological health being one current example indicating that pesticide regulation has not been as effective as we need it to be (for example, ref. [100]). A One Health approach to the emerging issue of NP use in agriculture could open the way to developing a more holistic approach to pest and pesticide management in agriculture.

Challenges for the future

The One Health concept has been very successful in drawing together disparate research, surveillance and mitigation activities, and players in the fields of zoonoses and antimicrobial resistance. However, as recently reviewed[101], there is still a long road ahead as a number of barriers prevent the One Health approach from reaching its full potential. Some of the most obvious barriers relate to the abatement of disciplinary divides and the creation of knowledge between various stakeholders with different backgrounds and interests such as scientists, farmers, regulators, industry, NGOs and consumer groups.

Despite these challenges, a One Health approach to complex problems and systems can provide a way to engage multiple disciplines and actors to ensure a more comprehensive perspective. In the case of agriculture and food systems, we argue that it is essential to include actors engaged in the system in practice (such as farmers, agronomists, extension officers and so on) to assist decision-making regarding NP use and regulation. This is both to obtain more complete knowledge of the system and to ensure that any recommendations for management actions are viable and likely to be enacted.

It is clear that since agriculture is, and always has been, a socio-ecological system, the assessment of new technologies entering into it, requires the integration of different forms of knowledge. To overcome the barriers already recognized in the pursuit of One Health perspectives, crucial steps to advance this approach in the case of agri-nanotechnologies will include: (i) pursuing better communication, cooperation and integration between the fields of human and environmental toxicology, (ii) harmonizing nanometrology and testing protocols and collating consistent datasets spanning both human and environmental toxicology, (iii) stimulating comparative toxicological studies and learning, (iv) actively engaging the public and stakeholders in research and innovation, and (v) bringing together regulators from different areas (for example, food, medicine, agrichemicals, veterinary and so on) to contribute to the development of a transdisciplinary risk governance framework for nanotechnology.

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