

Nanotechnology and artificial intelligence to enable sustainable and precision agriculture

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1 **Nanotechnology and Artificial Intelligence to Enable Sustainable and**
2 **Precision Agriculture**

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8

9 **Abstract**

10 Climate change, increasing populations, competing demands on land for production of biofuels, and
11 declining soil quality are challenging global food security. Finding sustainable solutions requires bold
12 new approaches and integration of knowledge from diverse fields, such as materials science and
13 informatics. The convergence of precision agriculture, whereby farmers respond in real-time to changes
14 in crop growth, with nanotechnology and artificial intelligence offers exciting opportunities for
15 sustainable food production. Coupling existing models for nutrient cycling and crop productivity with
16 nanoinformatics approaches to optimize targeting, uptake, delivery nutrient capture and long term
17 impacts on soil microbial communities will allow design of nanoscale agrochemicals that combine
18 optimal safety and functionality profiles.

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25 **Introduction**

26 The Green Revolution, i.e. the 3rd Agricultural Revolution, which occurred between the 1950s and
27 1960s, dramatically increased global agriculture productions yield thereby avoiding the spread of
28 famine and malnutrition. However, the world population has also grown by more than 5 billion since
29 the beginning of the Green Revolution, entailing a continuous growth of crop production. The global
30 agriculture and food security sector is facing a wide spectrum of challenges such as low crop yields,
31 declining soil health and fertility, low use efficiency of agrochemicals due mainly to excessive use of
32 fertilizers and pesticides, shrinking arable land *per capita* and diminishing freshwater availability for
33 irrigation¹. Moreover, climate change, as arising from increasing atmospheric CO₂ concentration
34 leading to rising temperature, is likely to further affect the resilience of agricultural soils and their
35 ability to sustain productivity and ensure food security for an increasing human population².
36 Nanotechnology offers great potential to enable precision and sustainable agriculture, the opportunities
37 and challenges of which have been discussed in several recent reviews covering strategies to enhance
38 crop nutrition and smart plant sensors^{3, 4, 5}. Using nanotechnology, the delivery of fertilizer⁶ can be
39 tailored by targeting to specific tissues / organisms and stimuli-responsive release, as well as
40 potentially improving nutrient use efficiency (NUE) by releasing the nutrient slowly for plant uptake⁷.
41 Nano-enabled agriculture is expected to target pests more efficiently using lower amounts of pesticide⁸
42 thereby avoiding widespread impacts on soil health and biodiversity, and improving soil function and
43 nutrient cycling *via* soil microbiome enhancement (optimization of nitrifying/denitrifying bacterial
44 communities). Longer term applications include development of smart “sensor” plants, whereby the
45 plant itself is adapted, using targeted delivery of nanomaterials (NMs), for sensing abiotic stress⁹. As
46 with all new technologies however, the risks must be evaluated in parallel with the benefits, and indeed
47 several NMs have been identified to cause negative changes in soil community structure, e.g, TiO₂
48 NMs cascading negative effects on denitrification enzyme activity and a deep modification of the

49 bacterial community structure after just 90 days of exposure to a realistic concentration of NPs (1 mg
50 kg⁻¹ dry soil)¹⁰, while studies with Ag NMs, which are well-known for their antimicrobial activity have
51 shown that the extent of impact on soil community composition over 90 days are affected by exposure
52 time and physicochemical composition of soil as well as the type and coating of the NMs¹¹. Thus, an
53 important caveat at the outset of this review is that NMs represent a very broad spectrum of
54 chemistries, compositions and physicochemical properties, which are dynamic and evolving as the
55 NMs interact with their surroundings, and as such generalisations regarding their applications in
56 agriculture are difficult, and predictions of long-term effects are challenging currently.

57 However, as noted in the aforementioned reviews^{3,4,5}, the development of nanotechnology for
58 agricultural applications is still at an early stage and is moving forward quite slowly. Significant
59 differences may exist between nanotechnology-based pesticides and conventional pesticides, including
60 altered bioavailability, sensitivity, dosimetry, and pharmacokinetics^{12, 13}. Challenges and barriers
61 include limited understanding of plant-NMs interactions, limited methods for efficient delivery of NMs
62 to plants and soil, risks of potentially hazardous effects of NMs to human health from accumulation of
63 NMs and active ingredient residues in edible portions of plants⁴, and to long term soil quality and soil
64 health from accumulation of NMs and their degradation products in soil and resultant potential
65 alterations in microbial biodiversity¹⁴. There is an urgent need to address these barriers and achieve a
66 true win-win scenario, whereby improved agricultural production, reduced environmental pollution
67 from agriculture and lower costs for farmers can be achieved synergistically. A one-health approach to
68 nano-agriculture was proposed by Lombi et al., that requires interdisciplinarity and the bridging of
69 human and environmental health research¹⁵. Computational approaches including artificial intelligence
70 (A.I.) and machine learning (M.L.) modelling will undoubtedly play critical roles in the progress of
71 nano-enabled agriculture, and are already starting to gain regulatory acceptance for NMs safety
72 assessment.

73 The application of computers and artificial intelligence (A.I.) in agriculture is not new – for
74 example, articles addressing software for integrated resource management¹⁶, image digitization for soil
75 and crop science¹⁶, and light and temperature monitoring and control for plants¹⁷ were published 35
76 years ago! The rise of remote sensing and integration of remote sensing data into decision support tools
77 for contemporary farming systems is expected to improve yield production and management while
78 reducing operating costs and environmental impact¹⁸. Agricultural systems models have emerged over
79 the last 50 years, spanning field, farm, landscape, regional, and global spatial scales and engaging
80 questions in past, current, and future time periods. Integrated agricultural systems models combining
81 grasslands and cropping models, livestock models, pest and disease models and risk behaviour models
82 are also emerging, although data gaps exist across all aspects, hampering their implementation¹⁹.
83 However, the convergence of A.I. approaches and nano-enabled agriculture is in its infancy and as
84 such the current perspective aims to stimulate the development of this important area.

85 The rapid pace of the development of nanotechnologies, the enormous diversity of physico-
86 chemical properties of NMs and their dynamic interactions with, and transformations, by their
87 surroundings (e.g., corona formation, dissolution, sulfidation etc.^{20, 21}) leads to the need for *in silico*
88 approaches to predict and assess their safety²². Nanoinformatics is a powerful way of relating the
89 nanostructural features with functional properties based on data-driven A.I. and M.L. approaches^{22, 23},
90 ²⁴. Nanoinformatics emerged a decade ago in the context that development and implementation of
91 nanotechnology in the real world requires the harnessing of information at the nexus of environmental
92 and human safety, risk assessment and management, physiochemical properties and function. With A.I.
93 and M.L. enabled *in silico* risk assessment²⁵, NMs grouping and classification²⁶, and safe-by-design²⁷
94 NMs design, as well as for predictions of NMs corona formation²⁸ and consequences for cellular
95 attachment and uptake^{29, 30, 31}, nanoinformatics has played significant roles in the area of nanosafety and
96 nanomedicine, while there is also ample scope of nanoinformatics in nano-enabled agriculture that has

97 not been explored, including for prediction of NMs interactions with and impacts on rhizosphere
98 secretions, NMs transformations before and during uptake and translocation, NMs impacts on soil
99 microbial communities and for predictions up plant uptake following foliar application. Experimental
100 data are emerging in all these areas^{32, 33, 34}, and a dedicated effort to integrate and curate this data, and
101 present it in a format suitable for modelling is currently underway by the authors in the scope of their
102 nanoinformatics e-infrastructure projects NanoCommons and NanoSolveIT³⁵. Coupling these
103 approaches with existing models for nutrient cycling³⁶, NUE³⁷ and crop productivity³⁸ and the
104 aforementioned agricultural systems models into an overall Integrated Approach for Testing and
105 Assessment (IATA) will allow co-optimisation of NMs for use in agricultural systems that combine
106 safety and functionality profiles enabling precision agriculture.

107 In this perspective, emerging applications of nanotechnology and nanoinformatics in agriculture
108 and gaps in current understanding are outlined. Key research areas are identified where the application
109 of A.I. will support the effective implementation of nanotechnology in agriculture, with a view to
110 enhancing productivity and protecting or improving environmental quality. Current applications of A.I.
111 in agriculture, in nanotechnology broadly, and in nano-enabled agriculture are also outlined, along with
112 identification of key areas where their convergence and integration can accelerate the development of
113 sustainable nano-enabled precision agriculture.

114

115 **Current challenges in agriculture**

116 With an ever increasing human population under a decreasing per capita agricultural land
117 globally³⁹, a key challenge is to optimize productivity whilst ensuring the conservation of soil health
118 and the protection of environmental quality. Agrochemicals (fertilizers and pesticides) enabled an
119 increase in productivity such that half of us are alive today due to the invention of industrial ammonia
120 production and its use as a fertilizer globally. However, the intensification of agriculture for enhanced

121 productivity resulted in extremely poor NUE globally (<50%)^{40, 41}. Poor NUE under an excessive
122 fertilizer use culture thus poses a serious threat to environmental quality as large amounts of nutrients
123 are lost into water and air causing eutrophication and greenhouse effects. For example, agriculture
124 contributes nearly 11% of global greenhouse gas emissions⁴². Nitrogen (N) and phosphorus (P)
125 fertilizer use in agriculture is one of the main drivers behind the breach of the safe planetary boundaries
126 for these elements that could trigger irreparable damage to the environment⁴³. Rockstrom et al.
127 recommended a reduction of reactive N use in agriculture from 150 Mt N y⁻¹ to about 35 Mt N y⁻¹
128 globally to ensure sustainability⁴³. Such a reduction can only be achieved through a combination of
129 approaches including targeted nano-enabled delivery of fertilizer to match plant demands to avoid
130 excessive losses, development and availability of low-cost in situ nutrient sensing technology to help
131 farmers plan fertilization efficiently, introduce rotations into agriculture to recover the health and
132 fertility of soils, utilize farm yard manure and slurries for meeting nutrient demands and identifying
133 crop breed that are efficient in nutrient uptake and even fixing atmospheric N₂ directly or through
134 enhance symbiosis are some of the key measures to enhance NUE, reduce excessive fertilization and
135 the subsequent losses of reactive N from cultivated soil⁴⁴. Unlike N, available terrestrial P reserves are
136 non-renewable and the current losses of available P from agriculture to water (rivers and oceans) is 10
137 times the pre-industrial and agricultural intensification era⁴³. This unsustainable use of P fertilizer in
138 agriculture is thus posing a risk to global food security⁴⁵, while causing eutrophication of fresh and
139 coastal water bodies, together with N⁴¹.

140 The grand challenge in agriculture is therefore that of optimizing usage efficiencies, timing and
141 targeting of fertilizer use to enhance and sustain crop production and while simultaneously reducing
142 amounts of fertilizers used and losses to environments external to agricultural catchments. While
143 regulatory and voluntary fertilizer use policies in Europe and USA have resulted in reduction of losses
144 to water, an overall enhancement in NUE was not achieved⁴⁶. Recent efforts to enhance NUE include

145 utilization of biofertilization to enhance microbial biodiversity⁴⁷, and application of a range of N
146 management tools across the growing season including soil testing, plant tissue testing, spectral
147 response, fertilizer placement and timing and vegetative indexes (leaf area index, and Normalized
148 Difference Vegetation Index (NDVI)) through A.I. enabled drones, handheld sensors, and satellite
149 imagery⁴⁸. Rockstrom et al. suggested that substantial N and P fertilizer use reduction can protect the
150 planet from breaching resilience thresholds, if such reductions can still ensure productivity⁴³.

151 Gopal agricultural yields are also impacted by crop loss due to competition from weeds, insect
152 damage and plant diseases. Weed competition causes 34% of crop loss on a global scale, while
153 microbial diseases and pest damage also cause 34% of crop loss⁴⁹. The application of synthetic
154 herbicides and pesticides thus increases yields (reduces crop loss) and, in the case of herbicides
155 containing N, P and K, improves food quality through enhanced nutrient uptake and retention⁵⁰;
156 however, these agrochemicals, which are designed to kill, also cause severe adverse impacts on the
157 health of human and non-targeted organisms and soil fertility, and result in contamination of water, soil
158 and air⁵¹. Mis-use of agrichemicals on poor quality soils, soil degradation as a result of farming
159 intensification, shrinking water availability and decreasing water quality, and globalization of diseases
160 have led to low resilience of agriculture systems.⁵² Moreover, climate changes such as elevated
161 atmospheric CO₂ levels and increasing temperatures also potentially impact the future of agriculture.⁵³

162 Nanotechnology applications in the agricultural sector have great potential to improve all
163 aspects of crop production, that is, to increase crop production yields and resource use efficiency whilst
164 reducing agriculture-related environmental pollution, thereby ensuring global food security whilst
165 ensuring future agricultural sustainability. Coupling existing models for nutrient cycling and crop
166 productivity with A.I. and machine learning to optimize targeting, uptake, delivery, nutrient capture
167 and soil microbial composition will allow design of nanoscale agrochemicals that combine optimal

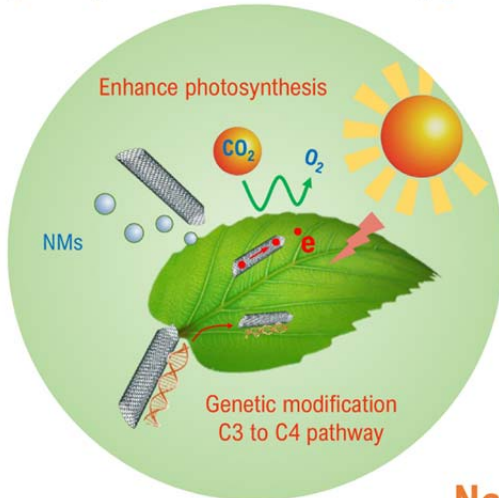
168 safety and functionality profiles and implementation of nano-agricheicals into mainstream
169 agricultural systems management.

170

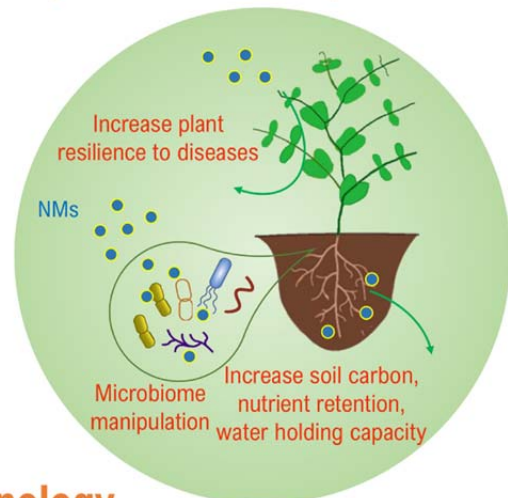
171 **Current applications of nanotechnology in agriculture**

172 Nanotechnology offers the benefit of reducing costs of fertilization at farm level directly and at global
173 level, indirectly, through reduction in environmental damage and environmental clean up costs
174 associated with agriculture-derived pollution. More importantly, enhancing NUE through
175 nanotechnology application in agriculture is a promising intervention technology that could
176 revolutionize and modernize agriculture making it precise and targeted. **Figure 1** summarises 4 key
177 areas where nanotechnology is, and will continue to, improve the precision and sustainability of
178 agriculture.

Improve production rates and crop yields

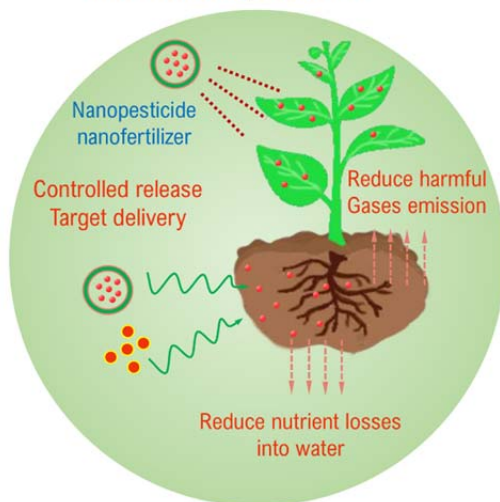


Improve soil health and plant resilience

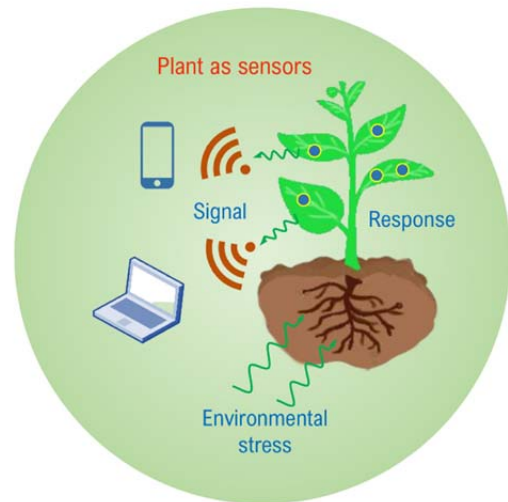


Nanotechnology In agriculture

Improve resource use efficiency
and reduce pollution



Plant as sensors



179

180 **Figure 1.** Applications of nanotechnology in agriculture, focusing specifically on crop production
181 (agronomy). Most are still at research stage, due to uncertainties regarding safety, and complex and
182 emerging regulatory processes for approval of agricultural chemicals, including plant protection
183 products, biocides and fertilizing products or plant biostimulants.

184

185 ***Increasing crop yields and production rates***

186 The Green Revolution relied highly on the traditional agronomic factors including use of synthetic
187 fertilizer and pesticide coupled to rainfall patterns or irrigation, and breeding technology. Instead of

188 increasing intensity and doses of those activities, improving the “efficiency” in agriculture is a more
189 realistic strategy to realise significant enhancement of crop yield and production rates whilst avoiding
190 overuse of natural resources and reducing agricultural pollution, ensuring a win-win-win future.
191 Nanotechnology is undoubtedly one of the most promising approaches that can achieve this goal.

192 One promising way to enhance crop yield is using ‘plant nanobionics’, a recently coined term
193 referring to the approach of designing NMs to interact with plants in order to enhance native functions
194 or to give the plant non-native functions⁹. A key focus is to improve the efficiency of photosynthesis,
195 an essential process occurring in plant leaves which uses solar energy to produce sugar from CO₂ and
196 water for plant growth. Photosynthesis efficiency can be enhanced by improving the efficiency of the
197 photosynthetic enzyme ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO). A pioneering
198 study found that TiO₂ NMs promote the photosynthesis rate by activating the RuBisCO carboxylation
199 process, potentially the result of the photocatalytic activity of TiO₂ NMs⁵⁴. More recently, root
200 application of carbon dots (CDs) was found to enhance RuBisCO activity thus improving the
201 photosynthesis efficiency and carbohydrate production in *Arabidopsis thaliana*⁵⁵, leading to 20%
202 increase of plant yield; this enhancement of plant growth was also demonstrated for several other plant
203 species such as soybean, tomato and eggplant. The overlapping adsorption of CDs with chloroplasts at
204 420 ~ 700 nm and the photo-induced electron donating and accepting properties of CDs are considered
205 to contribute to the enhanced photosynthesis efficiency. Other NMs, such as multiwalled carbon
206 nanotubes (MWCNTs)⁵⁶ and CeO₂ NMs have also shown potential for improving plant photosynthesis
207 under stress conditions^{57, 58}. CeO₂ NMs can scavenge free radicals such as hydroxyls in mesophyll cells
208 thereby improving plant tolerance to stress and photosynthesis.

209 Enhanced photosynthesis can also be achieved by broadening the range of solar light that can be
210 absorbed by plant leaves. Plants can naturally only absorb visible light in the range 400 ~ 700 nm with
211 energy conversion efficiency less than 4%. Single walled carbon nanotubes (SWCNTs) are capable of

212 capturing a broad range of solar light covering ultraviolet, green and near-infrared. Seminal work by
213 Giraldo et al. found that SWCNTs can insert into the thylakoid membrane, and that the formed
214 assemblies enabled a higher rate of electron transport and augmentation of photosynthesis in leaves due
215 to the semi-conductive nature and wide light absorption ability of SWCNTs⁹. Using SWCNTs as a
216 carrier also enabled gene-delivery into chloroplast, a structure that is hard to target using current (often
217 liposome-based) methods⁵⁹, to improve light capture efficiency. The nanotubes also prevented the non-
218 native DNA from integrating into the plant genome thus avoiding consumer concerns over genetically
219 modified crops. Importantly, the delivery efficiency is plant species independent and may help with
220 high-throughput screening of plants to identify phenotypes with desired functions, e.g., optimised
221 photosynthesis efficiency. For example, it could facilitate the engineering of C3 crops (e.g., rice, wheat)
222 to use the C4 pathway (e.g., maize), which have nearly 50% higher light use efficiency and higher N
223 and water use efficiency than C3 pathway plants.

224

225 ***Improving resource use efficiency and soil health***

226 As discussed by Lowry et al.⁴, NMs and nanotechnology could also improve the use efficiency of natural
227 resources whilst reducing agricultural derived environmental pollution, which is one of the main pillars
228 of the sustainable vision. Crop yield is highly dependent on external inputs of N, P and potassium (K)
229 and micronutrients (e.g., B, Fe, Mn, Cu, Zn) into the agricultural land. The overall NUE by plants
230 currently stands at less than 50% globally⁴⁰, with the rest retained in soil, leached into water, or emitted
231 into air, causing detrimental environmental impacts. Engineered NMs offers great opportunity to
232 improve NUE *via* nano-based smart delivery platforms, i.e. so-called controlled release and targeted
233 delivery for efficient plant uptake⁶⁰, or through NM influence on microbial communities and their
234 nitrogen fixing abilities⁵⁵. For example, using hydroxyapatite nanoneedles as carriers of urea can
235 remarkably slow the release rate of urea from the nanohybrid surface, which can lead to better yields at

236 50% lower application rate and reduced hydrolysis of urea and hence lower emission of ammonia into
237 the air.⁶ Such a system could also deliver pesticide active ingredients more efficiently thus reducing the
238 amount of pesticides needed. For example, nano copper pesticides show four orders higher efficacy
239 against bacterial blight on pomegranate at 10^4 times lower concentrations than that recommended for
240 copper oxychloride⁶¹. Nanotechnology also allows the nutrients or pesticides to be delivered only at the
241 target position, such as the plant rhizosphere. These strategies reduce the use of fertilizers and
242 pesticides which would reduce the waste of natural resources and synthetic agrochemicals whilst also
243 protecting soil health by lowering the input of contaminants. In addition to avoiding emissions from
244 agrochemicals, Lowry et al.⁴ also pointed out that selective removal or recovery of nutrients from
245 contaminant water and waste streams using nanotechnology provide additional opportunities for
246 improving NUE. NMs applied to soil have been shown to alter the microbiome activity and
247 abundance⁶², thus could potentially be used to intentionally alter the signaling and community structure
248 of microbiome (e.g., N fixing bacteria) to enhance the availability of nutrients to plants. It is also
249 possible to increase the population of beneficial symbiotic bacteria (endophyte) to enhance crop
250 productivity; however, as noted by Lowry et al., achieving this requires better understanding of the
251 connection of soil and plant microbiome and the plant physiology involved⁶³. One promising approach
252 to address these knowledge gaps, and facilitate development of initial A.I. models, could be soilless
253 growth systems such as hydroponics⁶⁴, where introduction plant growth-promoting rhizobacteria and
254 use of multi-element sensors and interpretation algorithms based on machine learning logic to monitor
255 the availability of nutrients/elements in the hydroponic solution and to modify its composition in
256 *realtime*⁶⁵, are feasible in the near term and the lessons learned can then be translated to more complex
257 soil systems.

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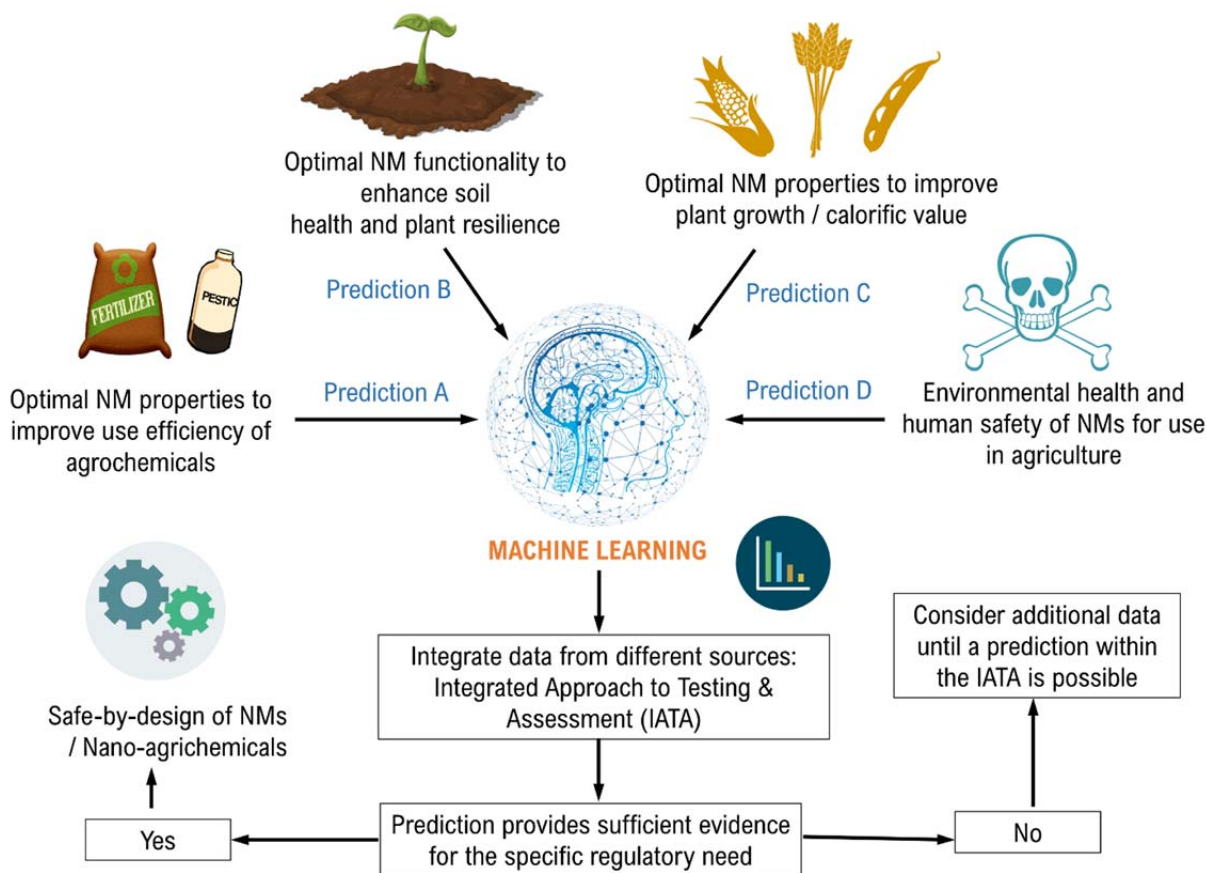
259 ***Improving management of soil health and plant growth***

260 Nanotechnology can also enable smart sensing of undesirable ambient biotic (plant pathogens, weed
261 competition, insect damage) and abiotic (drought or flooding, high salinity, extreme climate) stressors,
262 thus improving management effectiveness to reduce crop loss, which is a major challenge in global
263 agronomy. Nanotechnology based approaches for monitoring plant stress and resource deficiencies has
264 been recently reviewed by Giraldo et al⁵. For example, the secretome of microbes, fungi, rhizosphere
265 and plants are rich in information about the organisms adaption to their environment, and offer a means
266 to probe changes in the environment, or stress responses *via* secretion of biomarkers^{63, 66}. Developed
267 inventories of secreted proteins under normal, biotic and abiotic stress conditions revealed several
268 different types of novel secreted proteins, such as leaderless secretory proteins potentially involved in
269 the defense/stress responses, which could be explored (including computationally, see later sections for
270 details) for use as biomarkers⁶³. Molecule specific NMs-based sensors could be designed to detect
271 metabolites and root exudates to monitor crop growth status. Remote and real time detection of plant
272 pathogens or pests is also possible using NMs sensors, which could greatly reduce the use of pesticides,
273 especially if coupled with stimuli-responsive release^{67, 68}. Stimuli responsive sensing systems can
274 deliver agrochemicals only when it is necessary in response to environmental changes such as shortage
275 of nutrients, extreme pH conditions, elevated temperature or CO₂. These strategies will greatly improve
276 agronomic management and resilience of agroecosystems to stress, especially under changing climate
277 conditions.

278 In order to maximise the use of NMs in agriculture and agronomy, however, there are some
279 concerns that need to be addressed, including the potential toxicity of the NMs to non-target organisms
280 and adverse impacts on ecosystems^{69, 70}, their persistence and mobility in the environment and that of
281 their break-down or transformation products. As with all agrochemicals, concerns about potential
282 residues in edible portions of plants also need to be addressed, as part of an overall risk assessment of
283 nano-enabled agrochemicals⁶⁸. Since the use of NMs in farmland will require large quantities of NMs,

284 the synthesis of which requires high energy input, evaluating the cost of NMs production and the
 285 benefit trade-offs should be considered in the development of NMs for application in agriculture.

286 While in terms of both risk and application of NMs, current studies in the lab, mesocosms and
 287 field are expensive, time-consuming and complicated, limiting the range of conditions that can be
 288 varied systematically. Results are often hard to conclude because the interpretation of the results is
 289 influenced by factors such as experimental procedures, protocols, duration, NMs types, doses, soil
 290 types and plant species. Integrating of the existing data, albeit with gaps and limitations, and
 291 supplementation with predictive modelling and machine learning approaches, including Bayesian
 292 networks^{71,72}, for example, which can be dynamically updated as new knowledge emerges, into IATA
 293 offer exciting new directions; development of a nano-agriculture IATA case study utilising the OECD
 294 IATA case study approach⁷³ to seems like a logical next step (**Figure 2**).



295

296 **Figure 2.** Application of machine learning in risk assessment and safe-by-design of NMs and their
297 extension to support nano-enabled agriculture, building on advances in both nanoinformatics and
298 agricultural systems modelling. Integrating different modelling and experimental approaches, *via* an
299 IATA, will lead to enhanced prediction power and faster and safer implementation of precision nano-
300 enabled agriculture.

301

302 **A.I. and machine learning for agronomy**

303 *A.I. and machine learning approaches*

304 As computer power increases, and the value of data as knowledge to be exploited is realized more and
305 more, A.I. and machine or deep learning approaches are emerging as means to identify patterns in large
306 datasets that are predictive of future outcomes. One of the most widely used approaches involves neural
307 networks algorithms, which use an unbiased subset of the total available data as the training set to
308 develop a model that makes predictions using the rest of the data and the validity of the predictions are
309 evaluated to ensure that they could not arise randomly. The size and range of the dataset used to train
310 the model provides the limits to its predictive power, or its domain of applicability – models cannot
311 predict reliably outside their range of data. Box 1 describes the various types of data-driven machine
312 learning models, among which are models that link structure or properties (e.g. of a chemical) to
313 specific effects or impacts on the environment, so called Quantitative Structure Activity (or Property)
314 Relationship models (QSARs / QPARs)⁷⁴, and Bayesian Networks (BNs) which are a powerful tool for
315 incorporating uncertainty into decision support systems⁷⁵, by providing a basis for probabilistic
316 inference and facilitating assessment of changes in probabilistic belief as new evidence is entered into
317 the model. The larger the dataset available to train a machine learning model, the more powerful it will
318 be – typically in drug discovery or chemoinformatics for example, models will utilize data from
319 thousands of different chemicals to develop a prediction. Similarly, genomics and related approaches,

320 where hundreds of thousands of datapoints are available, allow generation of strong gene interaction
321 networks and assessment of effects of specific genetic perturbations, for example used to understand
322 gene regulation networks in plants⁷⁶.

Box 1. The main types of Machine Learning algorithms, and examples of their application in agriculture and/or nanomaterials design and safety assessment⁷⁷

- **Supervised Learning.** This algorithm consists of a target outcome (dependent variable) to be predicted from a given set of predictors (independent variables), generating a function that maps inputs to desired outputs. The training process continues until the model achieves the desired level of accuracy on the training dataset, and is then tested on the test dataset that was not involved in the training procedure.
Examples of Supervised Learning: Regression, Decision Tree, Random Forest, K nearest neighbours (KNN), Logistic Regression
Applications in agriculture and agronomy: A KNN algorithm was used to predict water retention at -33- and -1500-kPa matric potentials, using a hierarchical set of inputs (soil texture, bulk density, and organic matter content).
*Applications in NMs design, safety and interactions*⁷⁸: KNN algorithms have been applied to develop a predictive QSAR model for NMs cellular association based on their physico-chemical properties and adsorbed protein corona, as a means to understand the drivers of NMs toxicity⁷⁹.
Potential applications in nano-enabled agriculture: could be applied to prediction of acquired biomolecule coronas (rhizosphere secretions, foliar sections and biont) and their evolution during NMs uptake into plants; for prediction of NMs transformations and impacts on soil or foliar bionts. As part of IATA could be integrated with water retention models to predict NMs mobility in soil.
- **Unsupervised Learning.** In this algorithm, there is no target or outcome variable to predict. It is used for clustering data into different groups.
Examples of Unsupervised Learning: A priori algorithm, K-means.
Applications in agriculture and agronomy: A segmentation algorithm, inspired from an image-processing region-merging algorithm, for delineation of discrete contiguous management zones has been developed that is applicable to high- or low-density irregular data sets, such as yield data⁸⁰, and can identify coherent management units to facilitate differential crop management.
Applications in NMs design, safety and interactions: K-means clustering has been applied to signal processing of spICP-MS raw data (used for characterisation of NMs size and to distinguish particulate versus ionic fractions for quantification of NMs dissolution, uptake etc.) to discriminate particle signals from background signals, leading to a sophisticated, statistically based method to quantitatively resolve different size groups contained within a NM suspension⁸¹.
Potential applications in nano-enabled agriculture: could be applied to prediction of NMs transformations under different soil and climate conditions; for prediction and clustering of efficacy of nano-enabled agrichemicals and NUE of fertilisers. Integration with crop management approaches could be applied to determine optimal nano-agrchemical application strategies.
- **Reinforcement Learning.** The machine is trained to make specific decisions. Using trial and error, the machine learns from past experience and tries to capture the best possible knowledge to make accurate decisions.
Example of Reinforcement Learning: Markov Decision Process.
Applications in agriculture and agronomy: A smart agriculture Internet of Things system based on deep reinforcement learning has been developed to increase food production using deep reinforcement learning in the cloud layer to make immediate smart decisions such as determining the amount of water needed for irrigation to improve the crop growth environment⁸².
Applications in NMs design, safety and interactions: A recent example used Kohonen networks⁸³, or self-organising maps (SOMs), to visualise sets of silver and platinum NMs based on structural similarity and overlay functional properties to reveal hidden patterns and structure/property relationships. Visual inspection of the SOMs revealed a strong structure/property relationship between the shape of silver NMs and the energy of their Fermi level, and a weaker relationship between shapes with a high fraction of (111) surface area and the ionisation potential, electron affinity and electronic band gap. Both energy levels and crystal structure or exposed crystal face are linked to NMs reactivity and toxicity⁸⁴.
Potential applications in nano-enabled agriculture: initial applications in hydroponics as part of realtime responsiveness to changes in nutrient and microbial compositions and integration with NMs structure-property relationships under different environmental and local conditions to optimize release rates and

323

324 ***Current A.I. and machine learning in agriculture***

325 A 2018 review of the use of machine learning in agriculture has classified the application areas into (a)
326 crop management, including applications on yield prediction, disease detection, weed detection crop
327 quality, and species recognition; (b) livestock management, including applications on animal welfare
328 and livestock production; (c) water management (daily, weekly, or monthly evapotranspiration rates);
329 and (d) soil management such as prediction-identification of agricultural soil properties⁸⁵. Application
330 of Bayesian Networks to agricultural systems has been a challenge to date however, as there is often
331 insufficient data for computing the prior and conditional probabilities required for the network⁷⁵.

332 In terms of the key areas identified for improvements in crop production, process based
333 machine learning models (e.g., the SPACSYS model⁸⁶) for plant growth, incorporating assimilation,
334 respiration, water and N uptake, partitioning of photosynthate and N, N-fixation for legume plants and
335 root growth⁸⁷, are emerging and being constantly improved. With increased understanding of the
336 processes, and the availability of intervention strategies such as precision nanoagrochemicals, the
337 potential of machine learning for optimisation of agroecosystems has never been higher; integrating
338 machine learning, simulation, and portfolio optimization can inform decisions and support selection of
339 optimal seed (e.g., soybean) varieties to grow with resolution at the level of a specific farm with its
340 individual crop rotation history rather than at regional scale based on soil type and quality⁸⁸. Indeed, a
341 very recent review of the potential impacts of A.I. on the achievement of the UN sustainable
342 development goals (SDGs) suggested that A.I. will be an enabler for SDG2 on sustainable agriculture,
343 but highlights generally that the pace of development of A.I. may have implications in terms of a lack
344 of regulatory oversight and insight, which could potentially result in gaps in transparency, safety, and
345 ethical standards⁸⁹.

346 *Nanoinformatics models applicable to nano-enabled agriculture*

347 The application of machine learning in NM risk assessment, and for design of “safe” and
348 environmentally friendly NMs, is also an area of intensive research in the last few years. For example,
349 nanoQSAR models linking specific NMs properties to uptake by, and impacts on, cells or organisms
350 are emerging, as well as models that allow determination of surface functionalizations that enhance (or
351 decrease), for example, protein binding and/or cellular association (as a pre-requisite for
352 internalization⁷⁹), and can be applied for design of targeting strategies in precision nano-agriculture.
353 Similarly, extending advances in nanomedicine to precision nanoagriculture will facilitate the design of
354 optimized controlled release agrochemicals^{90,91}. For example, deep learning employing an automatic
355 data splitting algorithm and the evaluation criteria suitable for pharmaceutical formulation data was
356 developed for the prediction of optimal pharmaceutical formulations and doses⁹². From an agricultural
357 perspective, understanding the factors (NM, plant, soil, climate etc.) that control the release rate of
358 active ingredients, and the factors driving transport of the carrier can influence selection of formulation
359 parameters. Such data-driven models require significant amounts of data to train and validate them,
360 which is certainly a barrier to their current development, although significant work is underway in the
361 nanosafety arena broadly to develop optimized workflows for data and metadata generation (e.g.
362 utilizing Electronic Laboratory Notebooks), annotation with relevant ontological terms mapped to the
363 data schema of the receiving databases and automated upload to nanosafety knowledgebases⁹³, which
364 in the medium term will facilitate the aggregation, integration and re-use of nanosafety and nano-
365 agriculture related datasets.

366 As noted above however, there are significant concerns regarding the safety and risk of NMs
367 that must be addressed before their widespread intentional application to the environment can be
368 sanctioned, and there are tight regulatory processes for approval of agrochemicals⁹⁴. A recent review
369 has assessed the regulation of pesticides for risk assessment and the potential use of *in silico* computer-

370 based chemical modeling technologies to facilitate risk assessment of nano-enabled pesticides⁹². This
371 review concluded that while quantum chemistry is an appropriate tool to characterize the structure and
372 relative stabilities of organic compounds isomers, for studying degradation processes pathways, and *via*
373 use of quantum descriptors for QSAR development, a reevaluation for their suitability for nano-enabled
374 agriculture is needed.

375

376 **Challenges and barriers to precision nano-agriculture**

377 Although nanotechnology demonstrates high potential in a wide range of applications in agriculture, it
378 is still primarily at the research stage. There are many challenges to be overcome to move this area
379 forward from basic research to full commercial scale application. This includes lack of mechanistic
380 understanding of the interaction at NM-plant-soil interface and NM uptake and translocation in plant
381 vascular structure and organelles; insufficient understanding of the environmental safety and human
382 health risks of intentional NM application; lack of soil and large scale field study to demonstrate the
383 efficacy of NMs under realistic scenarios; and an unclear balance between adoption of a new
384 technology and the low profit margin in agriculture, and the aforementioned challenges regarding
385 collection and harmonization of the datasets needed for development of A.I models.

386 Long term studies at ecosystem level under environmentally relevant conditions are currently
387 lacking. For example, silver-, zinc- and copper-based NMs show the potential to be applied as efficient
388 pesticides or fungicide; however, the potential impact on non-target organisms (e.g., beneficial plant
389 rhizosphere bacteria, worms) and long term impacts on soil quality are not known. Although
390 nanofertilizers may enhance the NUE, effects (e.g., alteration of the content of carbohydrates, macro-
391 or micro- nutrient) of NMs on the nutritional quality of food have been reported⁹⁵ and need to be
392 assessed systematically and predictive models need to be established. NMs might accumulate in seeds
393 and the potential to cause transgenerational effects^{96,97} are largely unknown. The presence of NMs may

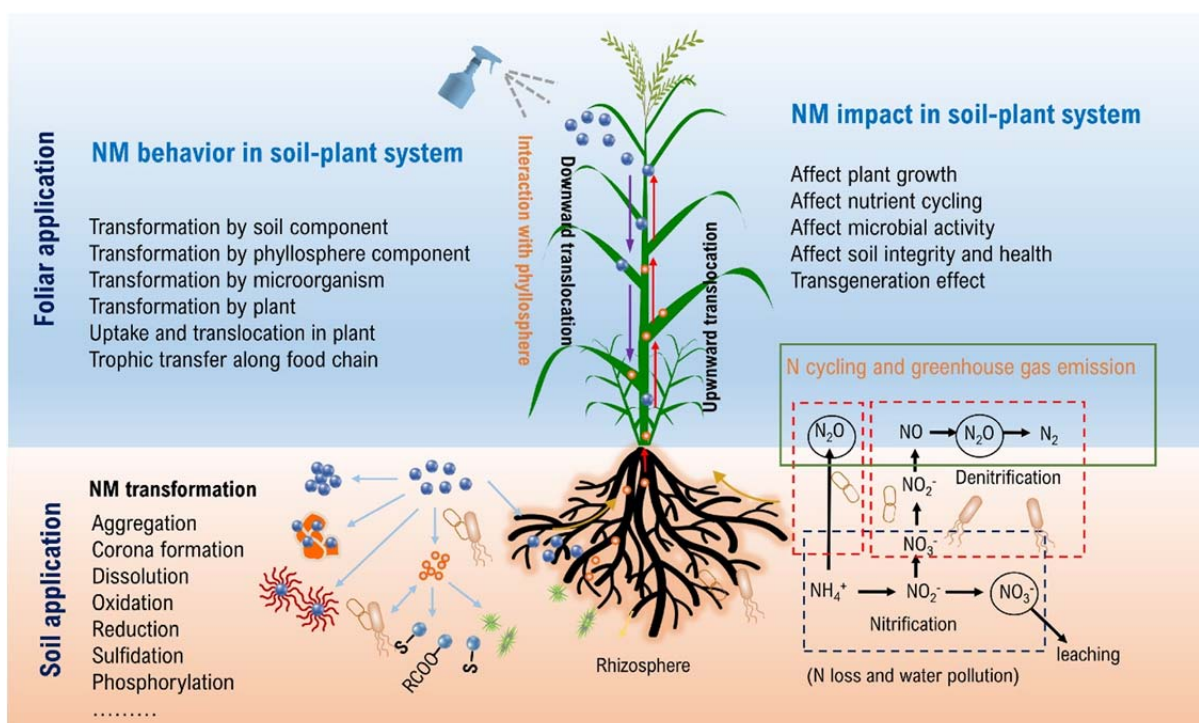
394 cause enhanced uptake of contaminants by plants, e.g. by binding to the NM surface and co-transport,
395 and may amplify their adverse effects^{98, 99}. Such co-effects need to be fully understood.

396 NMs undergo numerous transformations (physically, chemically or biologically) in soils and
397 plants. For example, many metal based NMs such as ZnO, Cu and Ag tend to dissolve and release
398 metal ions, which can further react with soil and plant components such as phosphate, sulfur, chloride
399 *etc.* The original NM properties that are designed for specific application purpose might not be
400 maintained due to these processes. For example, antifungal NMs such as Ag NMs can be oxidized,
401 dissolve and sulfidized in soil environments either by interaction with the soil microbiome or within
402 plants, and the antifungal property of the Ag NMs could be reduced or diminished¹⁰⁰. Some
403 transformations might release toxic components, for example, graphene oxide was reported to degrade
404 under sunlight and release PAH (polycyclic aromatic hydrocarbon) -like compounds which are likely to
405 exhibit toxic properties and persist in the environment¹⁰¹.

406 Computational tools that can predict NM transformation processes will favour the design to
407 manipulate or even simulate directly the transformation in order to maintain the NM function or modify
408 their impacts. However, the complexity of soil chemistry and the high responsiveness of plants and their
409 secretions into the rhizosphere increase the variability and diversity of potential NM transformations
410 (**Figure 3**). Many factors are interlinked. For example, NM transformations are affected by the soil and
411 plant microbiome and the excreted extracellular polymeric substances (EPS) and plant root exudates
412 around the rhizosphere. However, plant root exudate composition and microbiome can affect each
413 other and both may be altered due to NM exposure, which can in-turn affect the NM transformation
414 processes. Changes to the microbiome will affect the N cycling processes in soil. Foliar applied NMs
415 can translocate downwards to root and interact with phyllosphere components such as microorganism
416 and leaf exudates. All of the above are also subject to further change and disruption as a result of
417 climate changes, *e.g.*, altered CO₂ and temperatures can shift nutrient cycling, alter rates of reactions /

418 transformations, change plant susceptibility to NMs and more. Therefore, the dynamic nature of the
419 whole system needs to be considered making this a perfect candidate for A.I. and machine learning
420 solutions.

421 Compared to small molecules toxicity prediction, nanoinformaticians are used to working with
422 smaller datasets (sometimes just a few NM variants), and use exposure concentrations and timepoints
423 as a means to expand the dataset. Thus, evaluation of the impact of NMs on NUE in a hydrophnic
424 system for example could evaluate a panel of 8-10 NMs and evaluate their effect alone and in
425 combination with fertilizer at different ratios and over different timescales, and determine the N
426 concentrations in the water, plant mass and emitted to air under controlled temperatures and CO₂
427 levels, which would provide a multi-factorial dataset for establishment of machine learning models to
428 predict the NUE of a new NM, as long as its physicochemical characteristics fell within the domain of
429 applicability of the model, i.e. at least one of the NMs in the training and test set had some overlap with
430 the properties of the “new” NM. If the NMs were characterised over time under the different
431 conditions, e.g., in terms of their size, dissolution, acquired corona composition, further models
432 predicting corona composition and NMs fate and behaviour could be build, identifying the key NMs
433 properties and environmental factors driving the specific effect. If data on plant growth (roots, shoots)
434 or localization of the NMs in the plants were determined, increasingly complete models of NUE versus
435 localisation in plants could be developed. System complexity can then be build by moving to soils for
436 example, where the NM characterization challenges increase, but where models for the NMs
437 environmental fate already exist, such as the NanoFASE soil-water-organism model, which predict the
438 fate of NMs in the environment²¹. Thus, the steps will be small initially, but as the datasets and models
439 emerge, their integration with other models and tools into overall IATA and agricultural systems
440 models will become feasible and achievable.



441

442 **Figure 3.** Schematic illustration of the complexity of NM behavior in the soil-plant environment and
 443 the potential impacts in soil-plant systems. Understanding and predicting these translocation,
 444 transformations, and identifying the optimal NMs forms to retain bioavailable N species in the soil will
 445 facilitate design of sustainably functional NMs for agriculture, enhancing NUE while simultaneously
 446 reducing pollution and the need for fertilizers. Coupling this with enhanced targeting and sustained,
 447 controlled release of pesticides can be facilitated using A.I. to design optimal nano-agricheicals.

448

449 **A roadmap for progress**

450 Smart and nano-enabled agriculture, combined with A.I. and machine learning capability offer an
 451 exciting convergence of technologies with the unique capability to address the overarching UN SDGs,
 452 the “improved nutrition and promotion of sustainable agriculture”. The impetus for smart agriculture is
 453 thus multi-pronged: from enhancing and sustaining productivity through nano-enabled (responsive)
 454 delivery of agrochemicals to crops, through to reduction in environmental pollution and negative
 455 human health impacts from agriculture. Agriculture’s grand challenges can only be solved if the power

456 of NMs can be harnessed safely, responsibly and sustainably. Nanoinformatics will play a vital role in
457 probing the design parameters, the plant and ecosystem responses, and their co-optimising for safe and
458 sustainable agriculture. For example, A.I. may predict NM impacts on the agricultural ecosystem and
459 their performance in improving agricultural production (NUE, reduction in air and water pollution
460 forms of key elements), by integrating experimental data from across different soil conditions and
461 different plant species/climate change conditions and NM physicochemical properties, which enables
462 safer-by-design development of nanoagricultural chemicals. Future reseach directions are outlined here
463 to address these challenges – a summary of the future research needs is given in Box 2.

Box 2 Future research needs

- Determine the long term fate of NMs including transformation, transport in soil, uptake and translocation in plants, curate this data and its accompanying metadata into NMs-KnowledgeBases and enrich it with global soil and weather characteristics, plant biology knowledge and microbial community characteristics to facilitate development of deep learning models tailored to specific NMs being developed for nano-agriculture and the local environmental conditions.
- Assess the long term life cycle impacts of NMs in agricultural ecosystems including the trophic transfer of NMs along food chains and the potential for transgenerational impacts. Integration of these datasets into the aforementioned KnowledgeBases will enable further iteration of the models, including development of Integrated Approaches to Testing and Assessment (IATA) and integrated agricultural systems models.
- Take a systems levels approach (as illustrated in **Figure 3**) since the whole ecosystem is interlinked with numerous co-variances, and feed this enhanced understanding into emerging regulatory frameworks.
- Utilise A.I. and machine learning to identify key nanospecific properties that initiate the adverse effects or beneficial function of NMs from large dataset obtained, thereby facilitating design of optimised (safe-by-design) nano-agrochemicals that are fully compliant with emerging regulations.
- Integrate models addressing different aspects of the overall challenge (physics-based, process based and data driven) through alignment of input and output parameters and development of an IATA, as shown

schematically in **Figure 2**.

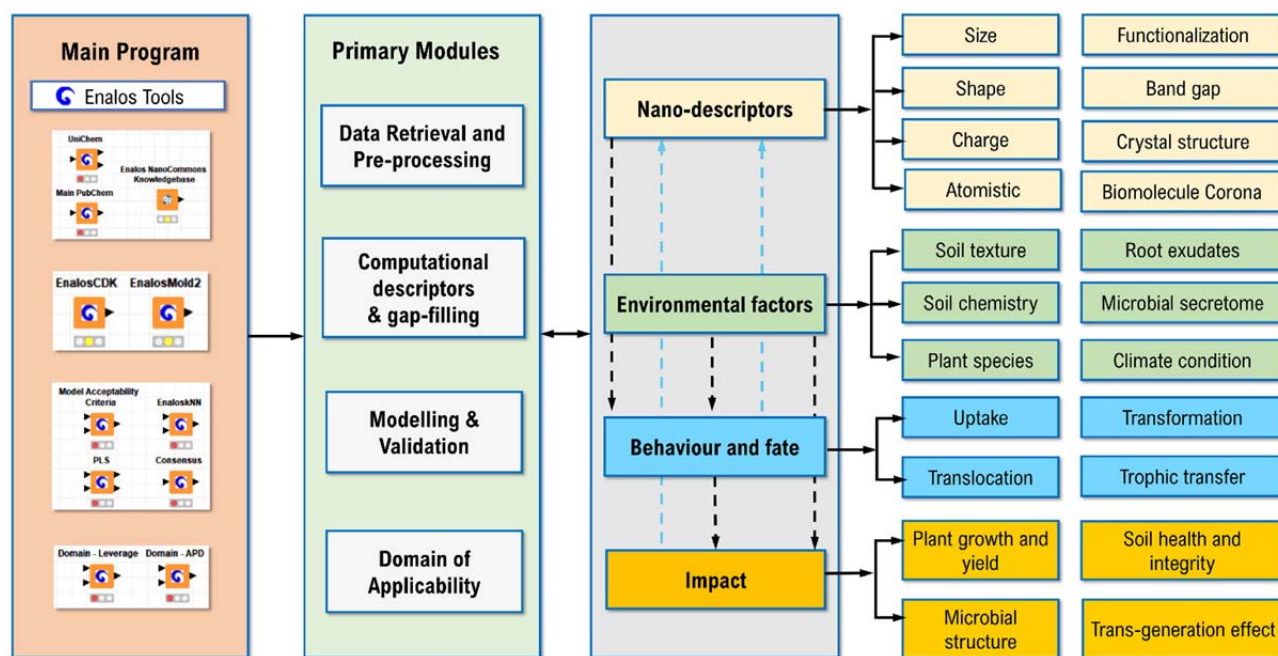
464 1) Understand the long term fate of NMs in agricultural environment including transport,
465 transformation in soil, and uptake and translocation in plant. Transformation of NMs will change their
466 original designed properties, which may defunctionalize their use as fertilizers, pesticides, carriers, or
467 sensors. The transformation could occur in soil, at plant interface (e.g., root or leaf surface) and inside
468 plant. In soil, the transformation could be driven by soil texture and chemistry, and by interaction with
469 soil microorganisms and animals. Plant interfaces, including the rhizosphere and phyllosphere (surface
470 of plant leaves and stems), are critical locations for NMs transformation. The dynamic and complex
471 composition at the these regions, including plant metabolites and microorganisms, drive the
472 transformation. NMs may also transform during their translocation in plant vascular structure by
473 interacting with plant fluids. All these area are largely unknown.

474 Another critical question is how to effectively deliver NMs to target places in plant. This
475 requires a clear understanding of the uptake and translocation of NM in plants. Both plant leaf and root
476 have physiological barriers to prevent the entry of unwanted substances, while the structure of these
477 two organs are very different. NMs that enter into leaf will translocate downward in phloem, while
478 NMs entering into roots translocate upward in the xylem. The fluid composition and flow rate in xylem
479 and phloem may greatly affect the translocation and accumulation of NMs in plant. Data and predictive
480 models for these questions are all required urgently.

481 2) Assess the long term life cycle impact of NMs in agricultural ecosystem. Given the fact that
482 repeated application of nanotechnology in agriculture is possible in the future, long term retention of
483 NMs in agriculture soil is inevitable. The majority of the current studies regarding the plant-NMs
484 interaction are phenomenological observations of NMs toxicity under short term, high dose conditions;
485 long term low dose effects of NMs on agroecosystem therefore need to be studied, addressing NM
486 impacts on plant growth, microbial acitivity and community structure, soil health (e.g., soil enzyme
487 activity, nutrient cycling), trophic transfer of NMs and transgeneration effects.

488 3) Take a systems level approach to nano-enabled agriculture. The behavior, fate and impact of
489 NMs in soil-plant system, and plant and microorganisms are all interconnected. As shown in **Figure 3**
490 and described above, change of one factor may induce a change of the whole system. Given the power
491 of A.I., and the complexity of the optimization challenges facing nano-agriculture, it is clear that their
492 convergence offers exciting new directions (**Figure 4**). Utilising extensive existing models and datasets
493 for soil quality, crop yield and NUE, for example, and combining these with models and datasets
494 related to plant and microbial secretomes, and nanomaterials physicochemical properties,
495 transformations and bioavailability, and release of active ingredients, could enable important new
496 insights into (1) the likely transformation pathways for the NMs and their resulting environmental
497 transport and bioavailability; (2) the potential impact of the NM and their associated active ingredients
498 (in cases where the NMs are carriers) on crop yield and NUE; and (3) potential identification of
499 biomarkers of crop health / diseases that can be utilized as early warning systems. Identification of data
500 gaps can also drive the design of focused experiments to gap-fill or to develop sub-models to integrate
501 into an overall model framework allowing design of NMs and active ingredient combinations that
502 optimize NUE and minimize pollution whilst enhancing crop yield and potentially even nutritional
503 (calorific) value. Integration of safe-by-design approaches, and feeding forward the emerging
504 knowledge into updating of regulatory process for advanced nano-enabled agricultural applications,
505 both in fertilization and in plant protection is essential also.

506



507

508 **Figure 4.** Approach to integration of A.I. models needed to assess ENMs behavior, fate and impact in
 509 agriculture based on the interplay between ENM and environmental factors including the crop type and
 510 soil characteristics. Integration of automated tools for harvesting data from public databases,
 511 preprocessing and curation of the data for direct input into the AI/ML models, for example via the
 512 Enalos Tools¹⁰² in KNIME, ensures that the output data from one model can serve as the input data for
 513 subsequent models, thereby facilitating model integration and development of increasingly multiplexed
 514 predictions for nano-enabled precision agriculture.

515

516 4) Utilise A.I. and machine learning to identify key nanospecific properties that initiate the
 517 adverse effects or beneficial function of NMs from large datasets obtained through use of automated
 518 data retrieval from public databases, data pre-processing and gap-filling, and data splitting into test and
 519 validation sets for modelling¹⁰² (Figure 4). There are multiple physicochemical properties of NMs
 520 such as size, shape, surface charge, surface area, surface reactivity and crystal structure that can
 521 influence their transformations and toxicity. A.I. and machine learning will enable the selection of the
 522 most critical parameters that determine the behavior and the prediction of the behavior of NMs in

523 soil and plant systems and facilitate the design of NMs that can be delivered to plants efficiently. NM
524 transformation in different soil conditions and different root rhizosphere compositions under changing
525 climate conditions, could be also predicted by integrating predictive models which allowing
526 optimization of NMs for agricultural application in a range of climatic and local conditions. Wider
527 ecosystems effects, and prediction of tripartite (NMs-soil-plant) behaviours under future climate
528 scenarios can also be predicted, utilizing for example Bayesian networks. Such models are especially
529 important as they can operate under data scarcity, yet can easily incorporate new data as it emerges.
530 Application of such models to address the broader issues of food security, and to tackling the
531 sustainable development goal of “improved nutrition and promote sustainable agriculture” (SDG2) will
532 provide important new intersectional insights and suggestions for ways forward.

533

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539

540 **Author contributions**

541 P.Z. and I.L. framed the manuscript. P.Z., Z.G., S.U. and I.L. wrote the manuscript with contributions
542 and inputs from all authors. P.Z., A.A. and G.M. produced the graphics.

543

544 **Conflict of interests**

545 There are no conflicts of interest to declare.

546

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1 **Nanotechnology and Artificial Intelligence to Enable Sustainable and**
2 **Precision Agriculture**

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8

9 **Abstract**

10 Climate change, increasing populations, competing demands on land for production of biofuels, and
11 declining soil quality are challenging global food security. Finding sustainable solutions requires bold
12 new approaches and integration of knowledge from diverse fields, such as materials science and
13 informatics. The convergence of precision agriculture, whereby farmers respond in real-time to changes
14 in crop growth, with nanotechnology and artificial intelligence offers exciting opportunities for
15 sustainable food production. Coupling existing models for nutrient cycling and crop productivity with
16 nanoinformatics approaches to optimize targeting, uptake, delivery nutrient capture and long term
17 impacts on soil microbial communities will allow design of nanoscale agrochemcials that combine
18 optimal safety and functionality profiles.

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25 **Introduction**

26 The Green Revolution, i.e. the 3rd Agricultural Revolution, which occurred between the 1950s and
27 1960s, dramatically increased global agriculture productions yield thereby avoiding the spread of
28 famine and malnutrition. However, the world population has also grown by more than 5 billion since
29 the beginning of the Green Revolution, entailing a continuous growth of crop production. The global
30 agriculture and food security sector is facing a wide spectrum of challenges such as low crop yields,
31 declining soil health and fertility, low use efficiency of agrochemicals due mainly to excessive use of
32 fertilizers and pesticides, shrinking arable land *per capita* and diminishing freshwater availability for
33 irrigation¹. Moreover, climate change, as arising from increasing atmospheric CO₂ concentration
34 leading to rising temperature, is likely to further affect the resilience of agricultural soils and their
35 ability to sustain productivity and ensure food security for an increasing human population².
36 Nanotechnology offers great potential to enable precision and sustainable agriculture, the opportunities
37 and challenges of which have been discussed in several recent reviews covering strategies to enhance
38 crop nutrition and smart plant sensors^{3, 4, 5}. Using nanotechnology, the delivery of fertilizer⁶ can be
39 tailored by targeting to specific tissues / organisms and stimuli-responsive release, as well as
40 potentially improving nutrient use efficiency (NUE) by releasing the nutrient slowly for plant uptake⁷.
41 Nano-enabled agriculture is expected to target pests more efficiently using lower amounts of pesticide⁸
42 thereby avoiding widespread impacts on soil health and biodiversity, and improving soil function and
43 nutrient cycling *via* soil microbiome enhancement (optimization of nitrifying/denitrifying bacterial
44 communities). Longer term applications include development of smart “sensor” plants, whereby the
45 plant itself is adapted, using targeted delivery of nanomaterials (NMs), for sensing abiotic stress⁹. As
46 with all new technologies however, the risks must be evaluated in parallel with the benefits, and indeed
47 several NMs have been identified to cause negative changes in soil community structure, e.g, TiO₂
48 NMs cascading negative effects on denitrification enzyme activity and a deep modification of the

49 bacterial community structure after just 90 days of exposure to a realistic concentration of NPs (1 mg
50 kg⁻¹ dry soil)¹⁰, while studies with Ag NMs, which are well-known for their antimicrobial activity have
51 shown that the extent of impact on soil community composition over 90 days are affected by exposure
52 time and physicochemical composition of soil as well as the type and coating of the NMs¹¹. Thus, an
53 important caveat at the outset of this review is that NMs represent a very broad spectrum of
54 chemistries, compositions and physicochemical properties, which are dynamic and evolving as the
55 NMs interact with their surroundings, and as such generalisations regarding their applications in
56 agriculture are difficult, and predictions of long-term effects are challenging currently.

57 However, as noted in the aforementioned reviews^{3, 4, 5}, the development of nanotechnology for
58 agricultural applications is still at an early stage and is moving forward quite slowly. Significant
59 differences may exist between nanotechnology-based pesticides and conventional pesticides, including
60 altered bioavailability, sensitivity, dosimetry, and pharmacokinetics^{12, 13}. Challenges and barriers
61 include limited understanding of plant-NMs interactions, limited methods for efficient delivery of NMs
62 to plants and soil, risks of potentially hazardous effects of NMs to human health from accumulation of
63 NMs and active ingredient residues in edible portions of plants⁴, and to long term soil quality and soil
64 health from accumulation of NMs and their degradation products in soil and resultant potential
65 alterations in microbial biodiversity¹⁴. There is an urgent need to address these barriers and achieve a
66 true win-win scenario, whereby improved agricultural production, reduced environmental pollution
67 from agriculture and lower costs for farmers can be achieved synergistically. A one-health approach to
68 nano-agriculture was proposed by Lombi et al., that requires interdisciplinarity and the bridging of
69 human and environmental health research¹⁵. Computational approaches including artificial intelligence
70 (A.I.) and machine learning (M.L.) modelling will undoubtedly play critical roles in the progress of
71 nano-enabled agriculture, and are already starting to gain regulatory acceptance for NMs safety
72 assessment.

73 The application of computers and artificial intelligence (A.I.) in agriculture is not new – for
74 example, articles addressing software for integrated resource management¹⁶, image digitization for soil
75 and crop science¹⁶, and light and temperature monitoring and control for plants¹⁷ were published 35
76 years ago! The rise of remote sensing and integration of remote sensing data into decision support tools
77 for contemporary farming systems is expected to improve yield production and management while
78 reducing operating costs and environmental impact¹⁸. Agricultural systems models have emerged over
79 the last 50 years, spanning field, farm, landscape, regional, and global spatial scales and engaging
80 questions in past, current, and future time periods. Integrated agricultural systems models combining
81 grasslands and cropping models, livestock models, pest and disease models and risk behaviour models
82 are also emerging, although data gaps exist across all aspects, hampering their implementation¹⁹.
83 However, the convergence of A.I. approaches and nano-enabled agriculture is in its infancy and as
84 such the current perspective aims to stimulate the development of this important area.

85 The rapid pace of the development of nanotechnologies, the enormous diversity of physico-
86 chemical properties of NMs and their dynamic interactions with, and transformations, by their
87 surroundings (e.g., corona formation, dissolution, sulfidation etc.^{20, 21}) leads to the need for *in silico*
88 approaches to predict and assess their safety²². Nanoinformatics is a powerful way of relating the
89 nanostructural features with functional properties based on data-driven A.I. and M.L. approaches^{22, 23},
90 ²⁴. Nanoinformatics emerged a decade ago in the context that development and implementation of
91 nanotechnology in the real world requires the harnessing of information at the nexus of environmental
92 and human safety, risk assessment and management, physiochemical properties and function. With A.I.
93 and M.L. enabled *in silico* risk assessment²⁵, NMs grouping and classification²⁶, and safe-by-design²⁷
94 NMs design, as well as for predictions of NMs corona formation²⁸ and consequences for cellular
95 attachment and uptake^{29, 30, 31}, nanoinformatics has played significant roles in the area of nanosafety and
96 nanomedicine, while there is also ample scope of nanoinformatics in nano-enabled agriculture that has

97 not been explored, including for prediction of NMs interactions with and impacts on rhizosphere
98 secretions, NMs transformations before and during uptake and translocation, NMs impacts on soil
99 microbial communities and for predictions up plant uptake following foliar application. Experimental
100 data are emerging in all these areas^{32, 33, 34}, and a dedicated effort to integrate and curate this data, and
101 present it in a format suitable for modelling is currently underway by the authors in the scope of their
102 nanoinformatics e-infrastructure projects NanoCommons and NanoSolveIT³⁵. Coupling these
103 approaches with existing models for nutrient cycling³⁶, NUE³⁷ and crop productivity³⁸ and the
104 aforementioned agricultural systems models into an overall Integrated Approach for Testing and
105 Assessment (IATA) will allow co-optimisation of NMs for use in agricultural systems that combine
106 safety and functionality profiles enabling precision agriculture.

107 In this perspective, emerging applications of nanotechnology and nanoinformatics in agriculture
108 and gaps in current understanding are outlined. Key research areas are identified where the application
109 of A.I. will support the effective implementation of nanotechnology in agriculture, with a view to
110 enhancing productivity and protecting or improving environmental quality. Current applications of A.I.
111 in agriculture, in nanotechnology broadly, and in nano-enabled agriculture are also outlined, along with
112 identification of key areas where their convergence and integration can accelerate the development of
113 sustainable nano-enabled precision agriculture.

114

115 **Current challenges in agriculture**

116 With an ever increasing human population under a decreasing per capita agricultural land
117 globally³⁹, a key challenge is to optimize productivity whilst ensuring the conservation of soil health
118 and the protection of environmental quality. Agrochemicals (fertilizers and pesticides) enabled an
119 increase in productivity such that half of us are alive today due to the invention of industrial ammonia
120 production and its use as a fertilizer globally. However, the intensification of agriculture for enhanced

121 productivity resulted in extremely poor NUE globally (<50%)^{40, 41}. Poor NUE under an excessive
122 fertilizer use culture thus poses a serious threat to environmental quality as large amounts of nutrients
123 are lost into water and air causing eutrophication and greenhouse effects. For example, agriculture
124 contributes nearly 11% of global greenhouse gas emissions⁴². Nitrogen (N) and phosphorus (P)
125 fertilizer use in agriculture is one of the main drivers behind the breach of the safe planetary boundaries
126 for these elements that could trigger irreparable damage to the environment⁴³. Rockstrom et al.
127 recommended a reduction of reactive N use in agriculture from 150 Mt N y⁻¹ to about 35 Mt N y⁻¹
128 globally to ensure sustainability⁴³. Such a reduction can only be achieved through a combination of
129 approaches including targeted nano-enabled delivery of fertilizer to match plant demands to avoid
130 excessive losses, development and availability of low-cost in situ nutrient sensing technology to help
131 farmers plan fertilization efficiently, introduce rotations into agriculture to recover the health and
132 fertility of soils, utilize farm yard manure and slurries for meeting nutrient demands and identifying
133 crop breed that are efficient in nutrient uptake and even fixing atmospheric N₂ directly or through
134 enhance symbiosis are some of the key measures to enhance NUE, reduce excessive fertilization and
135 the subsequent losses of reactive N from cultivated soil⁴⁴. Unlike N, available terrestrial P reserves are
136 non-renewable and the current losses of available P from agriculture to water (rivers and oceans) is 10
137 times the pre-industrial and agricultural intensification era⁴³. This unsustainable use of P fertilizer in
138 agriculture is thus posing a risk to global food security⁴⁵, while causing eutrophication of fresh and
139 coastal water bodies, together with N⁴¹.

140 The grand challenge in agriculture is therefore that of optimizing usage efficiencies, timing and
141 targeting of fertilizer use to enhance and sustain crop production and while simultaneously reducing
142 amounts of fertilizers used and losses to environments external to agricultural catchments. While
143 regulatory and voluntary fertilizer use policies in Europe and USA have resulted in reduction of losses
144 to water, an overall enhancement in NUE was not achieved⁴⁶. Recent efforts to enhance NUE include

145 utilization of biofertilization to enhance microbial biodiversity⁴⁷, and application of a range of N
146 management tools across the growing season including soil testing, plant tissue testing, spectral
147 response, fertilizer placement and timing and vegetative indexes (leaf area index, and Normalized
148 Difference Vegetation Index (NDVI)) through A.I. enabled drones, handheld sensors, and satellite
149 imagery⁴⁸. Rockstrom et al. suggested that substantial N and P fertilizer use reduction can protect the
150 planet from breaching resilience thresholds, if such reductions can still ensure productivity⁴³.

151 Global agricultural yields are also impacted by crop loss due to competition from weeds, insect
152 damage and plant diseases. Weed competition causes 34% of crop loss on a global scale, while
153 microbial diseases and pest damage also cause 34% of crop loss⁴⁹. The application of synthetic
154 herbicides and pesticides thus increases yields (reduces crop loss) and, in the case of herbicides
155 containing N, P and K, improves food quality through enhanced nutrient uptake and retention⁵⁰;
156 however, these agrochemicals, which are designed to kill, also cause severe adverse impacts on the
157 health of human and non-targeted organisms and soil fertility, and result in contamination of water, soil
158 and air⁵¹. Mis-use of agrichemicals on poor quality soils, soil degradation as a result of farming
159 intensification, shrinking water availability and decreasing water quality, and globalization of diseases
160 have led to low resilience of agriculture systems.⁵² Moreover, climate changes such as elevated
161 atmospheric CO₂ levels and increasing temperatures also potentially impact the future of agriculture.⁵³

162 Nanotechnology applications in the agricultural sector have great potential to improve all
163 aspects of crop production, that is, to increase crop production yields and resource use efficiency whilst
164 reducing agriculture-related environmental pollution, thereby ensuring global food security whilst
165 ensuring future agricultural sustainability. Coupling existing models for nutrient cycling and crop
166 productivity with A.I. and machine learning to optimize targeting, uptake, delivery, nutrient capture
167 and soil microbial composition will allow design of nanoscale agrochemicals that combine optimal

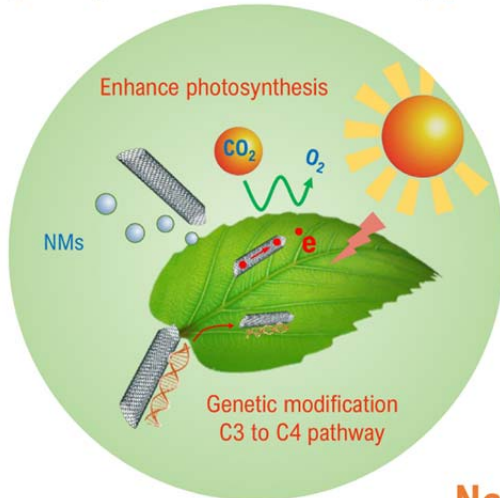
168 safety and functionality profiles and implementation of nano-agricheicals into mainstream
169 agricultural systems management.

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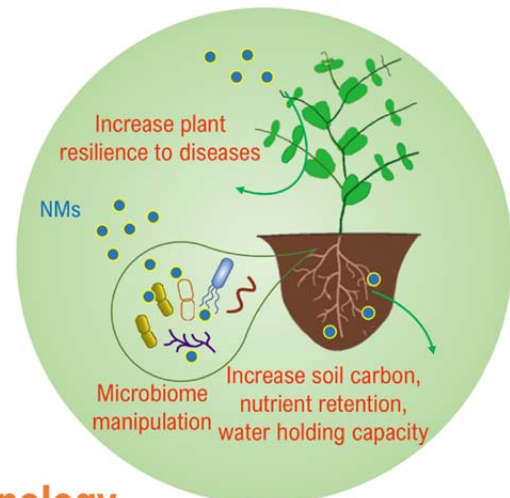
171 **Current applications of nanotechnology in agriculture**

172 Nanotechnology offers the benefit of reducing costs of fertilization at farm level directly and at global
173 level, indirectly, through reduction in environmental damage and environmental clean up costs
174 associated with agriculture-derived pollution. More importantly, enhancing NUE through
175 nanotechnology application in agriculture is a promising intervention technology that could
176 revolutionize and modernize agriculture making it precise and targeted. **Figure 1** summarises 4 key
177 areas where nanotechnology is, and will continue to, improve the precision and sustainability of
178 agriculture.

Improve production rates and crop yields

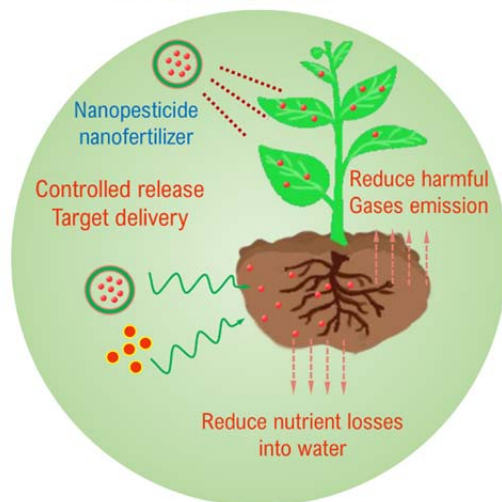


Improve soil health and plant resilience

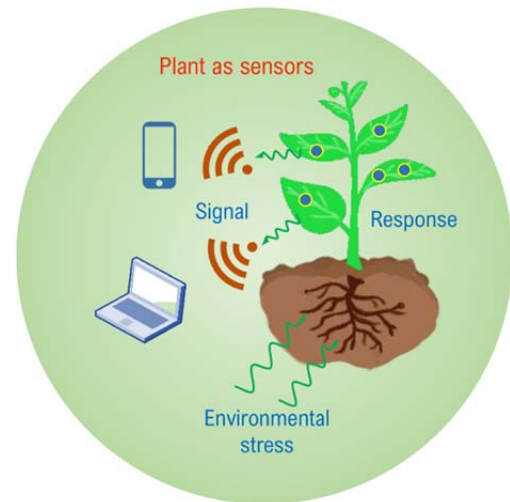


Nanotechnology In agriculture

Improve resource use efficiency
and reduce pollution



Plant as sensors



179

180 **Figure 1.** Applications of nanotechnology in agriculture, focusing specifically on crop production
181 (agronomy). Most are still at research stage, due to uncertainties regarding safety, and complex and
182 emerging regulatory processes for approval of agricultural chemicals, including plant protection
183 products, biocides and fertilizing products or plant biostimulants.

184

185 *Increasing crop yields and production rates*

186 The Green Revolution relied highly on the traditional agronomic factors including use of synthetic
187 fertilizer and pesticide coupled to rainfall patterns or irrigation, and breeding technology. Instead of

188 increasing intensity and doses of those activities, improving the “efficiency” in agriculture is a more
189 realistic strategy to realise significant enhancement of crop yield and production rates whilst avoiding
190 overuse of natural resources and reducing agricultural pollution, ensuring a win-win-win future.
191 Nanotechnology is undoubtedly one of the most promising approaches that can achieve this goal.

192 One promising way to enhance crop yield is using ‘plant nanobionics’, a recently coined term
193 referring to the approach of designing NMs to interact with plants in order to enhance native functions
194 or to give the plant non-native functions⁹. A key focus is to improve the efficiency of photosynthesis,
195 an essential process occurring in plant leaves which uses solar energy to produce sugar from CO₂ and
196 water for plant growth. Photosynthesis efficiency can be enhanced by improving the efficiency of the
197 photosynthetic enzyme ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO). A pioneering
198 study found that TiO₂ NMs promote the photosynthesis rate by activating the RuBisCO carboxylation
199 process, potentially the result of the photocatalytic activity of TiO₂ NMs⁵⁴. More recently, root
200 application of carbon dots (CDs) was found to enhance RuBisCO activity thus improving the
201 photosynthesis efficiency and carbohydrate production in *Arabidopsis thaliana*⁵⁵, leading to 20%
202 increase of plant yield; this enhancement of plant growth was also demonstrated for several other plant
203 species such as soybean, tomato and eggplant. The overlapping adsorption of CDs with chloroplasts at
204 420 ~ 700 nm and the photo-induced electron donating and accepting properties of CDs are considered
205 to contribute to the enhanced photosynthesis efficiency. Other NMs, such as multiwalled carbon
206 nanotubes (MWCNTs)⁵⁶ and CeO₂ NMs have also shown potential for improving plant photosynthesis
207 under stress conditions^{57, 58}. CeO₂ NMs can scavenge free radicals such as hydroxyls in mesophyll cells
208 thereby improving plant tolerance to stress and photosynthesis.

209 Enhanced photosynthesis can also be achieved by broadening the range of solar light that can be
210 absorbed by plant leaves. Plants can naturally only absorb visible light in the range 400 ~ 700 nm with
211 energy conversion efficiency less than 4%. Single walled carbon nanotubes (SWCNTs) are capable of

212 capturing a broad range of solar light covering ultraviolet, green and near-infrared. Seminal work by
213 Giraldo et al. found that SWCNTs can insert into the thylakoid membrane, and that the formed
214 assemblies enabled a higher rate of electron transport and augmentation of photosynthesis in leaves due
215 to the semi-conductive nature and wide light absorption ability of SWCNTs⁹. Using SWCNTs as a
216 carrier also enabled gene-delivery into chloroplast, a structure that is hard to target using current (often
217 liposome-based) methods⁵⁹, to improve light capture efficiency. The nanotubes also prevented the non-
218 native DNA from integrating into the plant genome thus avoiding consumer concerns over genetically
219 modified crops. Importantly, the delivery efficiency is plant species independent and may help with
220 high-throughput screening of plants to identify phenotypes with desired functions, e.g., optimised
221 photosynthesis efficiency. For example, it could facilitate the engineering of C3 crops (e.g., rice, wheat)
222 to use the C4 pathway (e.g., maize), which have nearly 50% higher light use efficiency and higher N
223 and water use efficiency than C3 pathway plants.

224

225 ***Improving resource use efficiency and soil health***

226 **As discussed by Lowry et al.⁴**, NMs and nanotechnology could also improve the use efficiency of natural
227 resources whilst reducing agricultural derived environmental pollution, which is one of the main pillars
228 of the sustainable vision. Crop yield is highly dependent on external inputs of N, P and potassium (K)
229 and micronutrients (e.g., B, Fe, Mn, Cu, Zn) into the agricultural land. The overall NUE by plants
230 currently stands at less than 50% globally⁴⁰, with the rest retained in soil, leached into water, or emitted
231 into air, causing detrimental environmental impacts. Engineered NMs offers great opportunity to
232 improve NUE *via* nano-based smart delivery platforms, i.e. so-called controlled release and targeted
233 delivery for efficient plant uptake⁶⁰, or through NM influence on microbial communities and their
234 nitrogen fixing abilities⁵⁵. For example, using hydroxyapatite nanoneedles as carriers of urea can
235 remarkably slow the release rate of urea from the nanohybrid surface, which can lead to better yields at

236 50% lower application rate and reduced hydrolysis of urea and hence lower emission of ammonia into
237 the air.⁶ Such a system could also deliver pesticide active ingredients more efficiently thus reducing the
238 amount of pesticides needed. For example, nano copper pesticides show four orders higher efficacy
239 against bacterial blight on pomegranate at 10⁴ times lower concentrations than that recommended for
240 copper oxychloride⁶¹. Nanotechnology also allows the nutrients or pesticides to be delivered only at the
241 target position, such as the plant rhizosphere. These strategies reduce the use of fertilizers and
242 pesticides which would reduce the waste of natural resources and synthetic agrochemicals whilst also
243 protecting soil health by lowering the input of contaminants. In addition to avoiding emissions from
244 agrochemicals, Lowry et al.⁴ also pointed out that selective removal or recovery of nutrients from
245 contaminant water and waste streams using nanotechnology provide additional opportunities for
246 improving NUE. NMs applied to soil have been shown to alter the microbiome activity and
247 abundance⁶², thus could potentially be used to intentionally alter the signaling and community structure
248 of microbiome (e.g., N fixing bacteria) to enhance the availability of nutrients to plants. It is also
249 possible to increase the population of beneficial symbiotic bacteria (endophyte) to enhance crop
250 productivity; however, as noted by Lowry et al., achieving this requires better understanding of the
251 connection of soil and plant microbiome and the plant physiology involved⁶³. One promising approach
252 to address these knowledge gaps, and facilitate development of initial A.I. models, could be soilless
253 growth systems such as hydroponics⁶⁴, where introduction plant growth-promoting rhizobacteria and
254 use of multi-element sensors and interpretation algorithms based on machine learning logic to monitor
255 the availability of nutrients/elements in the hydroponic solution and to modify its composition in
256 *realtime*⁶⁵, are feasible in the near term and the lessons learned can then be translated to more complex
257 soil systems.

258

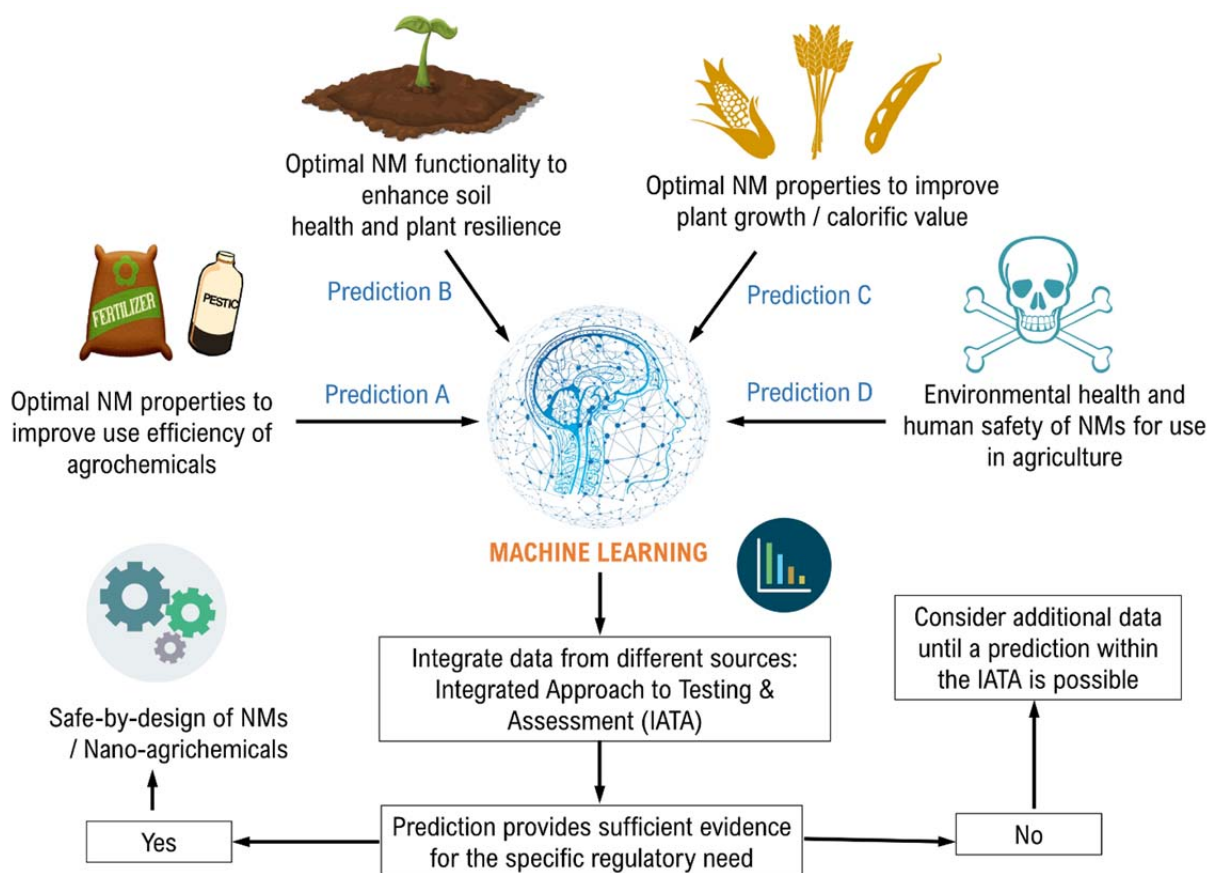
259 ***Improving management of soil health and plant growth***

260 Nanotechnology can also enable smart sensing of undesirable ambient biotic (plant pathogens, weed
261 competition, insect damage) and abiotic (drought or flooding, high salinity, extreme climate) stressors,
262 thus improving management effectiveness to reduce crop loss, which is a major challenge in global
263 agronomy. Nanotechnology based approaches for monitoring plant stress and resource deficiencies has
264 been recently reviewed by Giraldo et al⁵. For example, the secretome of microbes, fungi, rhizosphere
265 and plants are rich in information about the organisms adaption to their environment, and offer a means
266 to probe changes in the environment, or stress responses *via* secretion of biomarkers^{63, 66}. Developed
267 inventories of secreted proteins under normal, biotic and abiotic stress conditions revealed several
268 different types of novel secreted proteins, such as leaderless secretory proteins potentially involved in
269 the defense/stress responses, which could be explored (including computationally, see later sections for
270 details) for use as biomarkers⁶³. Molecule specific NMs-based sensors could be designed to detect
271 metabolites and root exudates to monitor crop growth status. Remote and real time detection of plant
272 pathogens or pests is also possible using NMs sensors, which could greatly reduce the use of pesticides,
273 especially if coupled with stimuli-responsive release^{67, 68}. Stimuli responsive sensing systems can
274 deliver agrochemicals only when it is necessary in response to environmental changes such as shortage
275 of nutrients, extreme pH conditions, elevated temperature or CO₂. These strategies will greatly improve
276 agronomic management and resilience of agroecosystems to stress, especially under changing climate
277 conditions.

278 In order to maximise the use of NMs in agriculture and agronomy, however, there are some
279 concerns that need to be addressed, including the potential toxicity of the NMs to non-target organisms
280 and adverse impacts on ecosystems^{69, 70}, their persistence and mobility in the environment and that of
281 their break-down or transformation products. As with all agrochemicals, concerns about potential
282 residues in edible portions of plants also need to be addressed, as part of an overall risk assessment of
283 nano-enabled agrochemicals⁶⁸. Since the use of NMs in farmland will require large quantities of NMs,

284 the synthesis of which requires high energy input, evaluating the cost of NMs production and the
285 benefit trade-offs should be considered in the development of NMs for application in agriculture.

286 While in terms of both risk and application of NMs, current studies in the lab, mesocosms and
287 field are expensive, time-consuming and complicated, limiting the range of conditions that can be
288 varied systematically. Results are often hard to conclude because the interpretation of the results is
289 influenced by factors such as experimental procedures, protocols, duration, NMs types, doses, soil
290 types and plant species. Integrating of the existing data, albeit with gaps and limitations, and
291 supplementation with predictive modelling and machine learning approaches, including Bayesian
292 networks^{71, 72}, for example, which can be dynamically updated as new knowledge emerges, into IATA
293 offer exciting new directions; development of a nano-agriculture IATA case study utilising the OECD
294 IATA case study approach⁷³ to seems like a logical next step (**Figure 2**).



295

296 **Figure 2.** Application of machine learning in risk assessment and safe-by-design of NMs and their
297 extension to support nano-enabled agriculture, building on advances in both nanoinformatics and
298 agricultural systems modelling. Integrating different modelling and experimental approaches, *via* an
299 IATA, will lead to enhanced prediction power and faster and safer implementation of precision nano-
300 enabled agriculture.

301

302 **A.I. and machine learning for agronomy**

303 *A.I. and machine learning approaches*

304 As computer power increases, and the value of data as knowledge to be exploited is realized more and
305 more, A.I. and machine or deep learning approaches are emerging as means to identify patterns in large
306 datasets that are predictive of future outcomes. One of the most widely used approaches involves neural
307 networks algorithms, which use an unbiased subset of the total available data as the training set to
308 develop a model that makes predictions using the rest of the data and the validity of the predictions are
309 evaluated to ensure that they could not arise randomly. The size and range of the dataset used to train
310 the model provides the limits to its predictive power, or its domain of applicability – models cannot
311 predict reliably outside their range of data. Box 1 describes the various types of data-driven machine
312 learning models, among which are models that link structure or properties (e.g. of a chemical) to
313 specific effects or impacts on the environment, so called Quantitative Structure Activity (or Property)
314 Relationship models (QSARs / QPARs)⁷⁴, and Bayesian Networks (BNs) which are a powerful tool for
315 incorporating uncertainty into decision support systems⁷⁵, by providing a basis for probabilistic
316 inference and facilitating assessment of changes in probabilistic belief as new evidence is entered into
317 the model. The larger the dataset available to train a machine learning model, the more powerful it will
318 be – typically in drug discovery or chemoinformatics for example, models will utilize data from
319 thousands of different chemicals to develop a prediction. Similarly, genomics and related approaches,

320 where hundreds of thousands of datapoints are available, allow generation of strong gene interaction
321 networks and assessment of effects of specific genetic perturbations, for example used to understand
322 gene regulation networks in plants⁷⁶.

Box 1. The main types of Machine Learning algorithms, and examples of their application in agriculture and/or nanomaterials design and safety assessment⁷⁷

- **Supervised Learning.** This algorithm consists of a target outcome (dependent variable) to be predicted from a given set of predictors (independent variables), generating a function that maps inputs to desired outputs. The training process continues until the model achieves the desired level of accuracy on the training dataset, and is then tested on the test dataset that was not involved in the training procedure.
Examples of Supervised Learning: Regression, Decision Tree, Random Forest, K nearest neighbours (KNN), Logistic Regression
Applications in agriculture and agronomy: A KNN algorithm was used to predict water retention at -33- and -1500-kPa matric potentials, using a hierarchical set of inputs (soil texture, bulk density, and organic matter content).
*Applications in NMs design, safety and interactions*⁷⁸: KNN algorithms have been applied to develop a predictive QSAR model for NMs cellular association based on their physico-chemical properties and adsorbed protein corona, as a means to understand the drivers of NMs toxicity⁷⁹.
Potential applications in nano-enabled agriculture: could be applied to prediction of acquired biomolecule coronas (rhizosphere secretions, foliar sections and biont) and their evolution during NMs uptake into plants; for prediction of NMs transformations and impacts on soil or foliar bionts. As part of IATA could be integrated with water retention models to predict NMs mobility in soil.
- **Unsupervised Learning.** In this algorithm, there is no target or outcome variable to predict. It is used for clustering data into different groups.
Examples of Unsupervised Learning: A priori algorithm, K-means.
Applications in agriculture and agronomy: A segmentation algorithm, inspired from an image-processing region-merging algorithm, for delineation of discrete contiguous management zones has been developed that is applicable to high- or low-density irregular data sets, such as yield data⁸⁰, and can identify coherent management units to facilitate differential crop management.
Applications in NMs design, safety and interactions: K-means clustering has been applied to signal processing of spICP-MS raw data (used for characterisation of NMs size and to distinguish particulate versus ionic fractions for quantification of NMs dissolution, uptake etc.) to discriminate particle signals from background signals, leading to a sophisticated, statistically based method to quantitatively resolve different size groups contained within a NM suspension⁸¹.
Potential applications in nano-enabled agriculture: could be applied to prediction of NMs transformations under different soil and climate conditions; for prediction and clustering of efficacy of nano-enabled agrichemicals and NUE of fertilisers. Integration with crop management approaches could be applied to determine optimal nano-agrchemical application strategies.
- **Reinforcement Learning.** The machine is trained to make specific decisions. Using trial and error, the machine learns from past experience and tries to capture the best possible knowledge to make accurate decisions.
Example of Reinforcement Learning: Markov Decision Process.
Applications in agriculture and agronomy: A smart agriculture Internet of Things system based on deep reinforcement learning has been developed to increase food production using deep reinforcement learning in the cloud layer to make immediate smart decisions such as determining the amount of water needed for irrigation to improve the crop growth environment⁸².
Applications in NMs design, safety and interactions: A recent example used Kohonen networks⁸³, or self-organising maps (SOMs), to visualise sets of silver and platinum NMs based on structural similarity and overlay functional properties to reveal hidden patterns and structure/property relationships. Visual inspection of the SOMs revealed a strong structure/property relationship between the shape of silver NMs and the energy of their Fermi level, and a weaker relationship between shapes with a high fraction of (111) surface area and the ionisation potential, electron affinity and electronic band gap. Both energy levels and crystal structure or exposed crystal face are linked to NMs reactivity and toxicity⁸⁴.
Potential applications in nano-enabled agriculture: initial applications in hydroponics as part of realtime responsiveness to changes in nutrient and microbial compositions and integration with NMs structure-property relationships under different environmental and local conditions to optimize release rates and

323

324 ***Current A.I. and machine learning in agriculture***

325 A 2018 review of the use of machine learning in agriculture has classified the application areas into (a)
326 crop management, including applications on yield prediction, disease detection, weed detection crop
327 quality, and species recognition; (b) livestock management, including applications on animal welfare
328 and livestock production; (c) water management (daily, weekly, or monthly evapotranspiration rates);
329 and (d) soil management such as prediction-identification of agricultural soil properties⁸⁵. Application
330 of Bayesian Networks to agricultural systems has been a challenge to date however, as there is often
331 insufficient data for computing the prior and conditional probabilities required for the network⁷⁵.

332 In terms of the key areas identified for improvements in crop production, process based
333 machine learning models (e.g., the SPACSYS model⁸⁶) for plant growth, incorporating assimilation,
334 respiration, water and N uptake, partitioning of photosynthate and N, N-fixation for legume plants and
335 root growth⁸⁷, are emerging and being constantly improved. With increased understanding of the
336 processes, and the availability of intervention strategies such as precision nanoagrochemicals, the
337 potential of machine learning for optimisation of agroecosystems has never been higher; integrating
338 machine learning, simulation, and portfolio optimization can inform decisions and support selection of
339 optimal seed (e.g., soybean) varieties to grow with resolution at the level of a specific farm with its
340 individual crop rotation history rather than at regional scale based on soil type and quality⁸⁸. Indeed, a
341 very recent review of the potential impacts of A.I. on the achievement of the UN sustainable
342 development goals (SDGs) suggested that A.I. will be an enabler for SDG2 on sustainable agriculture,
343 but highlights generally that the pace of development of A.I. may have implications in terms of a lack
344 of regulatory oversight and insight, which could potentially result in gaps in transparency, safety, and
345 ethical standards⁸⁹.

346 *Nanoinformatics models applicable to nano-enabled agriculture*

347 The application of machine learning in NM risk assessment, and for design of “safe” and
348 environmentally friendly NMs, is also an area of intensive research in the last few years. For example,
349 nanoQSAR models linking specific NMs properties to uptake by, and impacts on, cells or organisms
350 are emerging, as well as models that allow determination of surface functionalizations that enhance (or
351 decrease), for example, protein binding and/or cellular association (as a pre-requisite for
352 internalization⁷⁹), and can be applied for design of targeting strategies in precision nano-agriculture.
353 Similarly, extending advances in nanomedicine to precision nanoagriculture will facilitate the design of
354 optimized controlled release agrochemicals^{90, 91}. For example, deep learning employing an automatic
355 data splitting algorithm and the evaluation criteria suitable for pharmaceutical formulation data was
356 developed for the prediction of optimal pharmaceutical formulations and doses⁹². From an agricultural
357 perspective, understanding the factors (NM, plant, soil, climate etc.) that control the release rate of
358 active ingredients, and the factors driving transport of the carrier can influence selection of formulation
359 parameters. Such data-driven models require significant amounts of data to train and validate them,
360 which is certainly a barrier to their current development, although significant work is underway in the
361 nanosafety arena broadly to develop optimized workflows for data and metadata generation (e.g.
362 utilizing Electronic Laboratory Notebooks), annotation with relevant ontological terms mapped to the
363 data schema of the receiving databases and automated upload to nanosafety knowledgebases⁹³, which
364 in the medium term will facilitate the aggregation, integration and re-use of nanosafety and nano-
365 agriculture related datasets.

366 As noted above however, there are significant concerns regarding the safety and risk of NMs
367 that must be addressed before their widespread intentional application to the environment can be
368 sanctioned, and there are tight regulatory processes for approval of agrochemicals⁹⁴. A recent review
369 has assessed the regulation of pesticides for risk assessment and the potential use of *in silico* computer-

370 based chemical modeling technologies to facilitate risk assessment of nano-enabled pesticides⁹². This
371 review concluded that while quantum chemistry is an appropriate tool to characterize the structure and
372 relative stabilities of organic compounds isomers, for studying degradation processes pathways, and *via*
373 use of quantum descriptors for QSAR development, a reevaluation for their suitability for nano-enabled
374 agriculture is needed.

375

376 **Challenges and barriers to precision nano-agriculture**

377 Although nanotechnology demonstrates high potential in a wide range of applications in agriculture, it
378 is still primarily at the research stage. There are many challenges to be overcome to move this area
379 forward from basic research to full commercial scale application. This includes lack of mechanistic
380 understanding of the interaction at NM-plant-soil interface and NM uptake and translocation in plant
381 vascular structure and organelles; insufficient understanding of the environmental safety and human
382 health risks of intentional NM application; lack of soil and large scale field study to demonstrate the
383 efficacy of NMs under realistic scenarios; and an unclear balance between adoption of a new
384 technology and the low profit margin in agriculture, **and the aforementioned challenges regarding**
385 **collection and harmonization of the datasets needed for development of A.I models.**

386 Long term studies at ecosystem level under environmentally relevant conditions are currently
387 lacking. For example, silver-, zinc- and copper-based NMs show the potential to be applied as efficient
388 pesticides or fungicide; however, the potential impact on non-target organisms (e.g., beneficial plant
389 rhizosphere bacteria, worms) and long term impacts on soil quality are not known. Although
390 nanofertilizers may enhance the NUE, effects (e.g., alteration of the content of carbohydrates, macro-
391 or micro- nutrient) of NMs on the nutritional quality of food have been reported⁹⁵ and need to be
392 assessed systematically and predictive models need to be established. NMs might accumulate in seeds
393 and the potential to cause transgenerational effects^{96,97} are largely unknown. The presence of NMs may

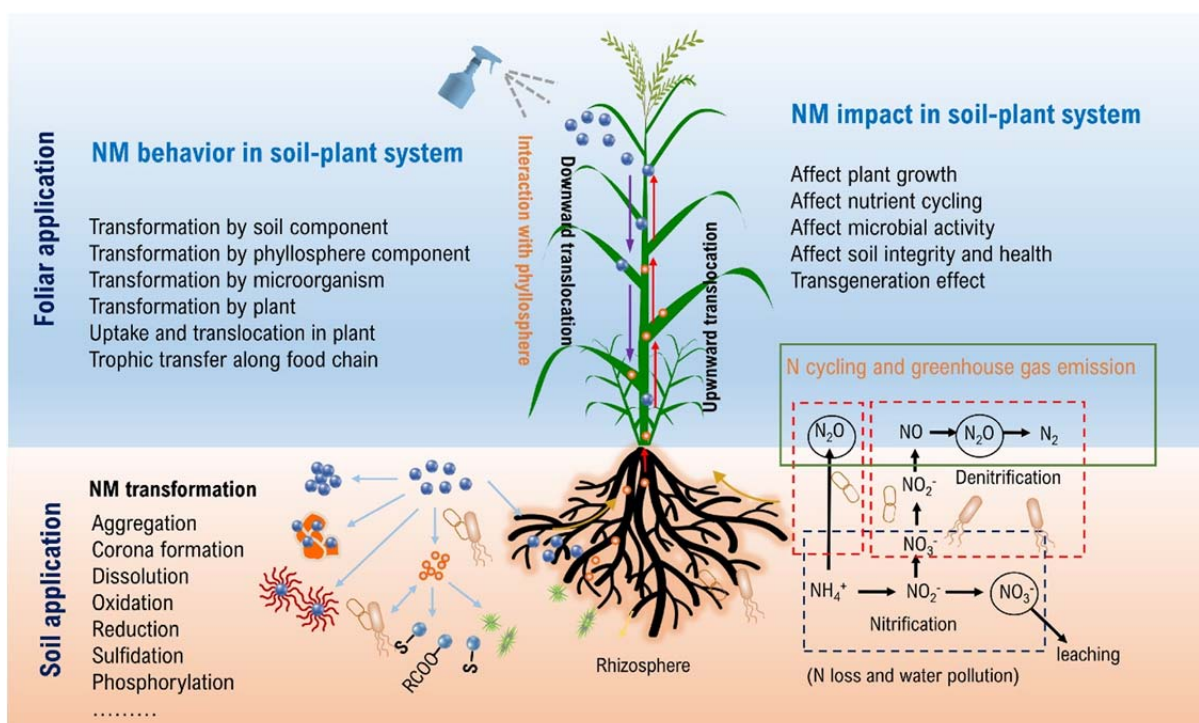
394 cause enhanced uptake of contaminants by plants, e.g. by binding to the NM surface and co-transport,
395 and may amplify their adverse effects^{98, 99}. Such co-effects need to be fully understood.

396 NMs undergo numerous transformations (physically, chemically or biologically) in soils and
397 plants. For example, many metal based NMs such as ZnO, Cu and Ag tend to dissolve and release
398 metal ions, which can further react with soil and plant components such as phosphate, sulfur, chloride
399 *etc.* The original NM properties that are designed for specific application purpose might not be
400 maintained due to these processes. For example, antifungal NMs such as Ag NMs can be oxidized,
401 dissolve and sulfidized in soil environments either by interaction with the soil microbiome or within
402 plants, and the antifungal property of the Ag NMs could be reduced or diminished¹⁰⁰. Some
403 transformations might release toxic components, for example, graphene oxide was reported to degrade
404 under sunlight and release PAH (polycyclic aromatic hydrocarbon) -like compounds which are likely to
405 exhibit toxic properties and persist in the environment¹⁰¹.

406 Computational tools that can predict NM transformation processes will favour the design to
407 manipulate or even simulate directly the transformation in order to maintain the NM function or modify
408 their impacts. However, the complexity of soil chemistry and the high responsiveness of plants and their
409 secretions into the rhizosphere increase the variability and diversity of potential NM transformations
410 (**Figure 3**). Many factors are interlinked. For example, NM transformations are affected by the soil and
411 plant microbiome and the excreted extracellular polymeric substances (EPS) and plant root exudates
412 around the rhizosphere. However, plant root exudate composition and microbiome can affect each
413 other and both may be altered due to NM exposure, which can in-turn affect the NM transformation
414 processes. Changes to the microbiome will affect the N cycling processes in soil. Foliar applied NMs
415 can translocate downwards to root and interact with phyllosphere components such as microorganism
416 and leaf exudates. All of the above are also subject to further change and disruption as a result of
417 climate changes, *e.g.*, altered CO₂ and temperatures can shift nutrient cycling, alter rates of reactions /

418 transformations, change plant susceptibility to NMs and more. Therefore, the dynamic nature of the
419 whole system needs to be considered making this a perfect candidate for A.I. and machine learning
420 solutions.

421 Compared to small molecules toxicity prediction, nanoinformaticians are used to working with
422 smaller datasets (sometimes just a few NM variants), and use exposure concentrations and timepoints
423 as a means to expand the dataset. Thus, evaluation of the impact of NMs on NUE in a hydroponic
424 system for example could evaluate a panel of 8-10 NMs and evaluate their effect alone and in
425 combination with fertilizer at different ratios and over different timescales, and determine the N
426 concentrations in the water, plant mass and emitted to air under controlled temperatures and CO₂
427 levels, which would provide a multi-factorial dataset for establishment of machine learning models to
428 predict the NUE of a new NM, as long as its physicochemical characteristics fell within the domain of
429 applicability of the model, i.e. at least one of the NMs in the training and test set had some overlap with
430 the properties of the “new” NM. If the NMs were characterised over time under the different
431 conditions, e.g., in terms of their size, dissolution, acquired corona composition, further models
432 predicting corona composition and NMs fate and behaviour could be build, identifying the key NMs
433 properties and environmental factors driving the specific effect. If data on plant growth (roots, shoots)
434 or localization of the NMs in the plants were determined, increasingly complete models of NUE versus
435 localisation in plants could be developed. System complexity can then be build by moving to soils for
436 example, where the NM characterization challenges increase, but where models for the NMs
437 environmental fate already exist, such as the NanoFASE soil-water-organism model, which predict the
438 fate of NMs in the environment²¹. Thus, the steps will be small initially, but as the datasets and models
439 emerge, their integration with other models and tools into overall IATA and agricultural systems
440 models will become feasible and achievable.



441

442 **Figure 3.** Schematic illustration of the complexity of NM behavior in the soil-plant environment and
 443 the potential impacts in soil-plant systems. Understanding and predicting these translocation,
 444 transformations, and identifying the optimal NMs forms to retain bioavailable N species in the soil will
 445 facilitate design of sustainably functional NMs for agriculture, enhancing NUE while simultaneously
 446 reducing pollution and the need for fertilizers. Coupling this with enhanced targeting and sustained,
 447 controlled release of pesticides can be facilitated using A.I. to design optimal nano-agricheicals.

448

449 **A roadmap for progress**

450 Smart and nano-enabled agriculture, combined with A.I. and machine learning capability offer an
 451 exciting convergence of technologies with the unique capability to address the overarching UN SDGs,
 452 the “improved nutrition and promotion of sustainable agriculture”. The impetus for smart agriculture is
 453 thus multi-pronged: from enhancing and sustaining productivity through nano-enabled (responsive)
 454 delivery of agrochemicals to crops, through to reduction in environmental pollution and negative
 455 human health impacts from agriculture. Agriculture’s grand challenges can only be solved if the power

456 of NMs can be harnessed safely, responsibly and sustainably. Nanoinformatics will play a vital role in
457 probing the design parameters, the plant and ecosystem responses, and their co-optimising for safe and
458 sustainable agriculture. For example, A.I. may predict NM impacts on the agricultural ecosystem and
459 their performance in improving agricultural production (NUE, reduction in air and water pollution
460 forms of key elements), by integrating experimental data from across different soil conditions and
461 different plant species/climate change conditions and NM physicochemical properties, which enables
462 safer-by-design development of nanoagricultural chemicals. Future reseach directions are outlined here
463 to address these challenges – a summary of the future research needs is given in Box 2.

Box 2 Future research needs

- Determine the long term fate of NMs including transformation, transport in soil, uptake and translocation in plants, curate this data and its accompanying metadata into NMs-KnowledgeBases and enrich it with global soil and weather characteristics, plant biology knowledge and microbial community characteristics to facilitate development of deep learning models tailored to specific NMs being developed for nano-agriculture and the local environmental conditions.
- Assess the long term life cycle impacts of NMs in agricultural ecosystems including the trophic transfer of NMs along food chains and the potential for transgenerational impacts. Integration of these datasets into the aforementioned KnowledgeBases will enable further iteration of the models, including development of Integrated Approaches to Testing and Assessment (IATA) and integrated agricultural systems models.
- Take a systems levels approach (as illustrated in **Figure 3**) since the whole ecosystem is interlinked with numerous co-variances, and feed this enhanced understanding into emerging regulatory frameworks.
- Utilise A.I. and machine learning to identify key nanospecific properties that initiate the adverse effects or beneficial function of NMs from large dataset obtained, thereby facilitating design of optimised (safe-by-design) nano-agrochemicals that are fully compliant with emerging regulations.
- Integrate models addressing different aspects of the overall challenge (physics-based, process based and data driven) through alignment of input and output parameters and development of an IATA, as shown

schematically in **Figure 2**.

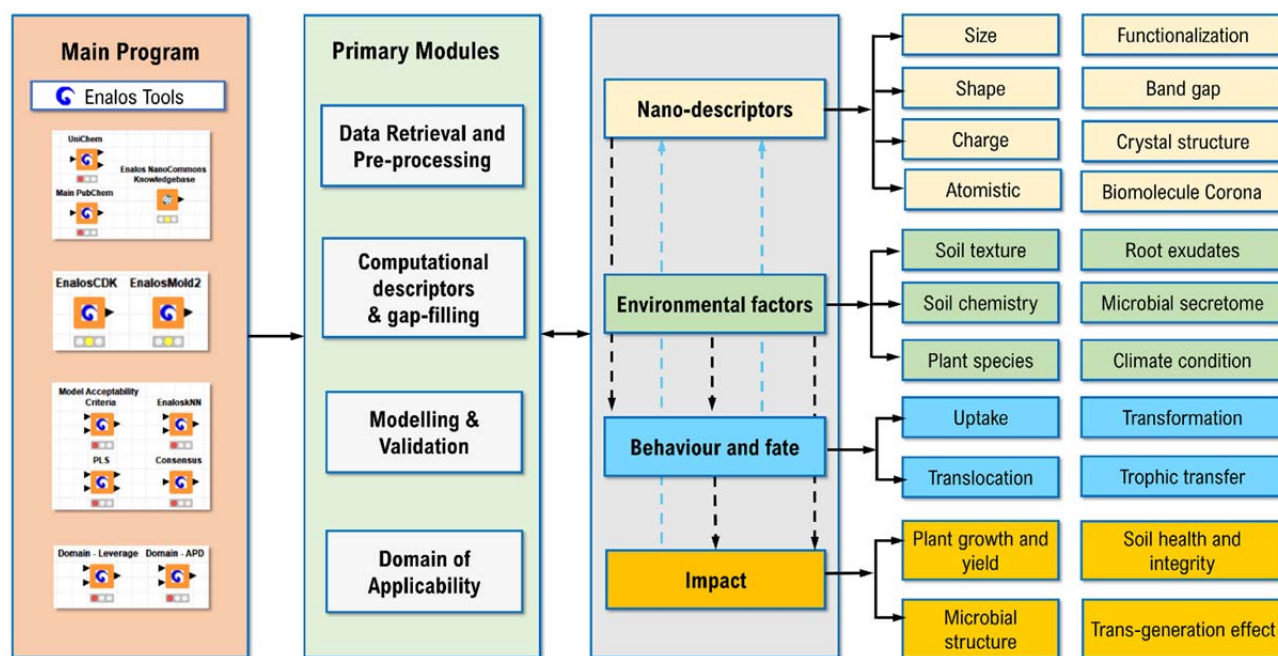
464 1) Understand the long term fate of NMs in agricultural environment including transport,
465 transformation in soil, and uptake and translocation in plant. Transformation of NMs will change their
466 original designed properties, which may defunctionalize their use as fertilizers, pesticides, carriers, or
467 sensors. The transformation could occur in soil, at plant interface (e.g., root or leaf surface) and inside
468 plant. In soil, the transformation could be driven by soil texture and chemistry, and by interaction with
469 soil microorganisms and animals. Plant interfaces, including the rhizosphere and phyllosphere (surface
470 of plant leaves and stems), are critical locations for NMs transformation. The dynamic and complex
471 composition at the these regions, including plant metabolites and microorganisms, drive the
472 transformation. NMs may also transform during their translocation in plant vascular structure by
473 interacting with plant fluids. All these area are largely unknown.

474 Another critical question is how to effectively deliver NMs to target places in plant. This
475 requires a clear understanding of the uptake and translocation of NM in plants. Both plant leaf and root
476 have physiological barriers to prevent the entry of unwanted substances, while the structure of these
477 two organs are very different. NMs that enter into leaf will translocate downward in phloem, while
478 NMs entering into roots translocate upward in the xylem. The fluid composition and flow rate in xylem
479 and phloem may greatly affect the translocation and accumulation of NMs in plant. Data and predictive
480 models for these questions are all required urgently.

481 2) Assess the long term life cycle impact of NMs in agricultural ecosystem. Given the fact that
482 repeated application of nanotechnology in agriculture is possible in the future, long term retention of
483 NMs in agriculture soil is inevitable. The majority of the current studies regarding the plant-NMs
484 interaction are phenomenological observations of NMs toxicity under short term, high dose conditions;
485 long term low dose effects of NMs on agroecosystem therefore need to be studied, addressing NM
486 impacts on plant growth, microbial acitivity and community structure, soil health (e.g., soil enzyme
487 activity, nutrient cycling), trophic transfer of NMs and transgeneration effects.

488 3) Take a systems level approach to nano-enabled agriculture. The behavior, fate and impact of
489 NMs in soil-plant system, and plant and microorganisms are all interconnected. As shown in **Figure 3**
490 and described above, change of one factor may induce a change of the whole system. Given the power
491 of A.I., and the complexity of the optimization challenges facing nano-agriculture, it is clear that their
492 convergence offers exciting new directions (**Figure 4**). Utilising extensive existing models and datasets
493 for soil quality, crop yield and NUE, for example, and combining these with models and datasets
494 related to plant and microbial secretomes, and nanomaterials physicochemical properties,
495 transformations and bioavailability, and release of active ingredients, could enable important new
496 insights into (1) the likely transformation pathways for the NMs and their resulting environmental
497 transport and bioavailability; (2) the potential impact of the NM and their associated active ingredients
498 (in cases where the NMs are carriers) on crop yield and NUE; and (3) potential identification of
499 biomarkers of crop health / diseases that can be utilized as early warning systems. Identification of data
500 gaps can also drive the design of focused experiments to gap-fill or to develop sub-models to integrate
501 into an overall model framework allowing design of NMs and active ingredient combinations that
502 optimize NUE and minimize pollution whilst enhancing crop yield and potentially even nutritional
503 (calorific) value. Integration of safe-by-design approaches, and feeding forward the emerging
504 knowledge into updating of regulatory process for advanced nano-enabled agricultural applications,
505 both in fertilization and in plant protection is essential also.

506



507

508 **Figure 4.** Approach to integration of A.I. models needed to assess ENMs behavior, fate and impact in
 509 agriculture based on the interplay between ENM and environmental factors including the crop type and
 510 soil characteristics. Integration of automated tools for harvesting data from public databases,
 511 preprocessing and curation of the data for direct input into the AI/ML models, for example via the
 512 Enalos Tools¹⁰² in KNIME, ensures that the output data from one model can serve as the input data for
 513 subsequent models, thereby facilitating model integration and development of increasingly multiplexed
 514 predictions for nano-enabled precision agriculture.

515

516 4) Utilise A.I. and machine learning to identify key nanospecific properties that initiate the
 517 adverse effects or beneficial function of NMs from large datasets obtained through use of automated
 518 data retrieval from public databases, data pre-processing and gap-filling, and data splitting into test and
 519 validation sets for modelling¹⁰² (Figure 4). There are multiple physicochemical properties of NMs
 520 such as size, shape, surface charge, surface area, surface reactivity and crystal structure that can
 521 influence their transformations and toxicity. A.I. and machine learning will enable the selection of the
 522 most critical parameters that determine the behavior and the prediction of the behavior of NMs in

523 soil and plant systems and facilitate the design of NMs that can be delivered to plants efficiently. NM
524 transformation in different soil conditions and different root rhizosphere compositions under changing
525 climate conditions, could be also predicted by integrating predictive models which allowing
526 optimization of NMs for agricultural application in a range of climatic and local conditions. Wider
527 ecosystems effects, and prediction of tripartite (NMs-soil-plant) behaviours under future climate
528 scenarios can also be predicted, utilizing for example Bayesian networks. Such models are especially
529 important as they can operate under data scarcity, yet can easily incorporate new data as it emerges.
530 Application of such models to address the broader issues of food security, and to tackling thhe
531 sustainable development goal of “improved nutrition and promote sustainable agriculture” (SDG2) will
532 provide important new intersectional insights and suggestions for ways forward.

533

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539

540 **Author contributions**

541 P.Z. and I.L. framed the manuscript. P.Z., Z.G., S.U. and I.L. wrote the masnucrypt with contributions
542 and inputs from all authors. P.Z., A.A. and G.M. produced the graphics.

543

544 **Conflict of interests**

545 There are no conflicts of interest to declare.

546

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