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The two faces of nanomaterials: A quantification of hormesis in algae and plants

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A B S T R A C T

The rapid progress in nanotechnology has dramatically promoted the application of engineered nanomaterials in numerous sectors. The wide application of nanomaterials and the potential accumulation in the environment sparked interest in studying the effects of nanomaterials on algae and plants. Hormesis is a dose response phenomenon characterized by a biphasic dose response with a low dose stimulation and a high dose inhibition. This paper quantifies for the first time nanomaterial-induced hormesis in algae and plants. Five hundred hormetic concentration-response relationships were mined from the published literature. The median maximum stimulatory response (MAX) was 123%, and commonly below 200%, of control response. It was also lower in algae than in plants, and occurred commonly at concentrations $< 100\,\text{mg}\,\text{L}^{-1}$. The no-observed-adverse-effect-level (NOAEL) to MAX ratio was 2.4 for algae and 1.7 for plants, and the two distributions differed significantly. Ag nanoparticles induced higher MAX than TiO_2 and ZnO nanoparticles. The MAX varied upon nanomaterial application methods, growth stage of application (seed versus vegetative), type of endpoint and time window. While nanomaterial size did not affect significantly the MAX, sizes ≤ 50 nm appeared to have lower NOAEL:MAX ratio than sizes ≥ 100 nm, suggesting higher risks from incorrect application. The mechanisms underlying nanomaterial-induced hormetic concentration responses are discussed. This paper provides a strong foundation for enhancing research protocols of studies on nanomaterial effects on algae and plants as well as for incorporating hormesis into the risk assessment practices.

1. Introduction

The wide expansion of nanotechnology and the thereby application of engineered nanomaterials in industrial and agricultural sectors lead to the accumulation of nanomaterials in the environment, stimulating the need to understand how plants and algae respond to nanomaterials, and what the implications in agriculture and ecological and human health may be (Auta et al., 2017; Carbery et al., 2018; Freixa et al., 2018; Iavicoli et al., 2017; Kabir et al., 2018; Navarro et al., 2008). For these reasons, research on plant responses to nanomaterials has received heightened interest in the recent years (Chen et al., 2018; Kumar et al., 2019; Rai et al., 2018; Verma et al., 2018, 2019). While there has been much focus on the adverse/toxic effects of high loads of engineered nanomaterials on plants, empirical data have now accumulated showing that low loads of engineered nanomaterials ($< 50\,\text{mg}\,\text{kg}^{-1}$) usually induce positive/stimulatory effects on plants (Cota-Ruiz et al., 2018; Rai et al., 2018; Reddy et al., 2016; Reddy Pullagurala et al., 2018), hinting to hormesis (Fig. 1).

Hormesis is a dose response phenomenon characterized by a biphasic dose response with a low dose stimulation and a high dose inhibition (Calabrese, 2014). Hormesis induced in plants and algae would have implications in different sectors such as research (e.g. experimental designs and study of biological mechanisms), agriculture (enhancing plant yield and productivity), environment (ecological

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Abbreviations: APX, ascorbate peroxidase; CDC2, cell-division-cycle kinase 2; ETR, electron transport rate; FBA, fructose-1,6 bisphosphate aldolase; GR, glutathione reductase; GSH, reduced glutathione; IAA, indole-3-acetic acid; IAA2, indoleacetic acid protein 8; MAX, maximum stimulatory response occurring in the low-concentration zone of a concentration-response relationship; MDA, malondialdehyde; NCED3, 9-cis-epoxycarotenoid dioxygenase; NOAEL, no-observed-adverse-effect level of a concentration-response relationship; NPQ, nonphotochemical quenching; POD, peroxidase; POR, protochlorophyllide oxidoreductase; PS, photosystem; qP, plastoquinone pool; ROS, reactive oxygen species; SOD, superoxide dismutase

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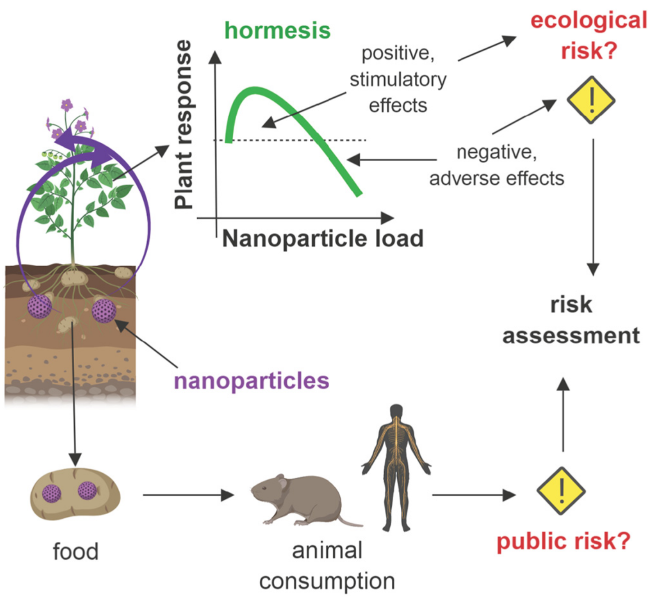

Fig. 1. Schematic diagram illustrating the issue of nanoparticles accumulation in the environment (or direct application to plants by humans), along with nanoparticles effects in a hormetic context, and the potential risks. The figure was created with the help of Biorender (credits: E. Agathokleous).

impacts), and human and ecological risk assessment (toxicological estimates) (Agathokleous et al., 2019b; Agathokleous and Calabrese, 2019; Belz and Duke, 2017; Cutler and Guedes, 2017; Cutler and Rix, 2015; Iavicoli et al., 2018; Poschenrieder et al., 2013). Hence, in the light of the continuous and increasing use and application of nanotechnology across the globe, understanding dose-response relationships induced by nanomaterials in plants and algae has emerged as an important issue in nano-toxicological research (Iavicoli et al., 2018). This is particularly important since nanomaterials may often occur at trace to low concentrations in the environment (Sanchís et al., 2012a,b), urging for advancing the understanding of the low-concentration effects.

For the first time, this study documents, evaluates and discusses hormetic concentration-response relationships induced by nanomaterials in plants and algae in the context of source-exposure-health outcome continuum.

2. Documentation

Evidence for nanomaterials-induced hormesis in plants existed from the mid-2000s (Hong et al., 2005; Lin and Xing, 2007; Zheng et al., 2005). However, hormesis, with typical biphasic concentration-response relationship, was first reported in 2010, when root elongation was assessed in plants of rape (*Brassica napus* L.) after treatment with rare earth oxide nanoparticles (La_2O_3 and Yb_2O_3) (Ma et al., 2010), and for algae, when growth rate of a freshwater green alga (*Pseudokirchneriella subcapitata*) was assessed after exposure to titanium dioxide (TiO_2) particles (Hartmann et al., 2010). The first review study focusing on nanoparticle-induced hormesis in different biological models revealed limited evidence for hormesis, and this was notable for both plants and algae (Iavicoli et al., 2010). This was also the case for a later review study, but with more evidence for green algae (Iavicoli et al., 2014); however, the increase in the interest in the research field and the improved research protocols noted in the recent years revealed more studies ($n = 8$ for plants, $n = 2$ for algae) with evidence for hormesis induced by nanoparticles (Iavicoli et al., 2018).

The studies cited in the previous reviews (Iavicoli et al., 2010, 2014, 2018) were re-evaluated for the existence of hormetic concentration-response relationships. A concentration-response relationship was

Table 1
Journals that published papers with data showing hormetic dose-response relationships. The superscript numbers indicate the references as follow: 1: (Antonoglou et al., 2018); 2: (Alidoust and Isoda, 2013); 3: (Tiwari et al., 2014); 4: (Morelli et al., 2012); 5: (Salama et al., 2019); 6: (Hong et al., 2005; Zheng et al., 2005); 7: (Morelli et al., 2013); 8: (Ji et al., 2011); 9: (Gong et al., 2011; Ma et al., 2010); 10: (Bello-Bello et al., 2017); 11: (Alidoust and Isoda, 2014); 12: (Tombuloglu et al., 2019); 13: (Lin and Xing, 2007; Miao et al., 2009; Tombuloglu et al., 2018; Wang et al., 2019; Xie et al., 2019); 14: (López-Moreno et al., 2010a; Wang et al., 2013); 15: (Zhu et al., 2017); 16: (Boykov et al., 2019); 17: (Jhanzab et al., 2015); 18: (Choudhary et al., 2019; Li et al., 2019); 19: (Salama, 2012); 20: (López-Moreno et al., 2010b); 21: (Razzaq et al., 2016); 22: (Chutipaijit and Sutjaritvorakul, 2017); 23: (Mykhaylenko and Zolotareva, 2017; Taran et al., 2016); 24: (Spinoso-Castillo et al., 2017); 25: (Alsaeedi et al., 2019; Syu et al., 2014; Venkatachalam et al., 2017); 26: (López-Moreno et al., 2016); 27: (Manickavasagam et al., 2019); 28: (Hartmann et al., 2010); 29: (Warheit et al., 2007).

ACS Applied Materials & Interfaces[1]	Acta Physiologiae Plantarum[2]	Applied Nanoscience[3]	Aquatic Toxicology[4]	Biocatalysis and Agricultural Biotechnology[5]
Biological Trace Element Research[6]	Biophysical Chemistry[7]	Chemical Engineering Journal[8]	Chemosphere[9]	Dose-Response[10]
Environmental Earth Sciences[11]	Environmental Nanotechnology, Monitoring & Management[12]	Environmental Pollution[13]	Environmental Science and Technology[14]	Environmental Toxicology and Pharmacology[15]
Genomics[16]	International Journal of Agronomy and Agricultural Research[17]	International Journal of Biological Macromolecules[18]	International Research Journal of Biotechnology[19]	Journal of Agricultural and Food Chemistry[20]
Journal of Nanoscience and Technology[21]	Materials Today: Proceedings[22]	Nanoscale Research Letters[23]	Plant Cell, Tissue and Organ Culture[24]	Plant Physiology and Biochemistry[25]
Science of the Total Environment[26]	Scientific Reports[27]	Toxicology[28]	Toxicology Letters[29]	

classified hormetic if there was a stimulatory response to at least one exposure level (> 100% of control) followed by a decline in the response, thus, presenting a biphasic concentration-response relationship. This literature sample was significantly enriched by surveying additional studies, after reviewing the published literature for existence of hormetic concentration-response relationships in plants and algae based on the aforementioned criterion. This effort resulted to the identification of a sample of 9 papers with algae and 31 papers with plants (tracheophytes) reporting data documenting hormetic concentration-response relationships. These studies often incorporated multi-factorial experimental designs including different species or different types or sizes of nanoparticles. The 40 papers were published from 2005 to 2019, in 29 journals with a broad range of scopes and aims; 50% of these papers were published in the last 3 years (post 2015), indicating an increased interest and more robust experimental designs permitting the detection of hormesis (Table 1).

3. Evaluation

To evaluate nanomaterials-induced hormetic concentration-response relationships quantitatively, data were extracted from tables or figures (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA, USA) of the 40 papers. The response to nanomaterial treatment (% of control response; control is commonly a null exposure) was calculated as $Response = \mu_C/\mu_\chi \times 100$, where μ_c is the arithmetic mean of the control group and μ_χ is the arithmetic mean of a group treated with a nanomaterial concentration level of χ.[1] For endpoints where a decrease in the response can have biologically positive effect (e.g. reduction of reactive oxygen species, ROS, and malondialdehyde, MDA), the response was calculated as $Response = \mu_\chi/\mu_c \times 100$.

This evaluation yielded 499 concentration responses (46 with algae and 453 with plants) with maximum stimulatory response (MAX). These were induced by 29 unique nanomaterials (Supplementary materials, Section 1) in at least 5 algae taxa (one species unidentified) and 20 plant taxa. A qualitative assessment of the experiments to depict hormesis revealed a low score for strength (3.0 for algae and 7.5 for plants; Supplementary materials, Section 2), which is however higher than other hormesis databases with plants (Agathokleous et al., 2019a). Concentration-response relationships were developed, and the no-observed-adverse-effect level (NOAEL) was estimated. Since not all the concentration responses crossed the zero equivalent point (ZEP), the distance from MAX to NOAEL (NOAEL:MAX ratio) could be estimated (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA, USA) for 269 entries (of which 39 were from algae).

The median MAX for all the concentration responses was 122.8% (geometric mean = 137.3%) and lower in algae than in plants (Table 2). The NOAEL:MAX ratio (median = 1.8, geometric mean = 2.2), was 1.4 times higher in algae than in plants (Table 2). Although the sample size for algae is small for drawing robust conclusions (given the complexity of nanomaterial effects), these results may suggest that algae may have a lower MAX response but with a wider stimulatory zone than plants. The 487 concentration responses displayed a MAX commonly (90.0%) below 200% of the control response: 41.1% showed a MAX in the range [110%–150%) while 22.2% showed a MAX in the range [150%–200%); excluding algae, the percentages were 91.4% (< 200%), 39.1% [110%–150%) and 23.4% [150%–200%). The frequency of MAX occurrence below 200% of control response is similar to previous analyses where a variety of stress inducing agents induced hormesis in plants (Agathokleous et al., 2019a; Calabrese and Blain, 2009).

Table 2
Hormesis characteristics for algae and plants. Analysis of the median maximum stimulatory response (MAX) and the median distance from MAX to no-observed-adverse-effect level (NOAEL) (NOAEL:MAX ratio). The level of significance was set a priori to $\alpha = 0.05$. All the analyses in this study were conducted with MS EXCEL 2010 (Microsoft©) and STATISTICA v.10 (StatSoft Inc.©).

	MAX	NOAEL:MAX ratio
Algae	119.7% ($n = 46$)	2.4 ($n = 39$)
Plants	125.2% ($n = 453$)	1.7 ($n = 229$)
Kruskal-Wallis test	$H = 4.00$, $P = 0.046$	$H = 6.32$, $P = 0.012$

Excluding algae (and 20 entries concerning calli), the plant entries were grouped into those where treatment was done only at the stage of seed (seed soaking, $n = 64$) and those where treatment was classically done during plant growth (vegetative stage, $n = 369$). An analysis revealed a significant difference in the MAX (Kruskal-Wallis, $H = 4.48$, $P = 0.34$) between seed soaking (median = 147.1%, geometric mean = 150.3%) and vegetative stage (median = 122.6%, geometric mean = 137.0%). Although the sample size for seed soaking is not large, these findings suggest that: a) seed soaking with nanoparticles can effectively induce MAX; b) treatment of seed with nanoparticles may be seen as a potential medium for seed priming; and c) combination of seed soaking and application during vegetative stages may offer an optimum stimulation.

Plant entries were also categorized as to the tissue from which nanoparticles are taken up, i.e. roots ($n = 267$) versus foliage ($n = 144$)[2] (excluding calli-regenerated plants). The median for roots was 127.3% (geometric mean = 140.4%) whereas for foliage was 114.9% (geometric mean = 126.7%), and the two distributions differed significantly (Kruskal-Wallis, $H = 11.79$, $P < 0.001$). While nanoparticles may enter the tree stem faster when applied to leaves than when applied to roots (Cocozza et al., 2019), this analysis revealed that applying nanoparticles onto leaves does not necessarily yield higher MAX. Further, the root entries were grouped into two categories: a) those with plants grown in a liquid growing medium (hydroponic system, $n = 88$) and b) those with plants grown in soil substrate (no hydroponic system, $n = 179$). The median MAX values were 125.5 and 128.8% for hydroponic and no hydroponic systems (geometric means of 132.9 and 144.2%). The similar distribution of the two groups (Kruskal-Wallis, $H = 0.05$, $P = 0.832$) suggests that application of nanoparticles into a soilless growing medium can induce similar MAX as when applied onto soil. This suggestion is supported by an experiment where phosfon-induced hormesis in peppermint (*Mentha piperita*) plants was similar either in a soil medium or a mineral nutrient solution (Calabrese and Howe, 1976). Hence, nanoparticles can be used within a hormetic context in greenhouse hydroponic cultures too (Venkatachalam et al., 2017). This finding also suggests that soil-particles interaction is not a major driver of hormesis.

The size of the nanomaterials did not appear to influence significantly the MAX (Table 3A). However, the NOAEL:MAX increased considerably when the particles increased in size from ≤50 nm to > 100 nm (Table 3B). These results suggest that ultrafine particles (< 50 nm) are less "safe" than fine particles (> 100 nm)[3] because they may generate higher environmental/ecological risk due to the smaller concentration range separating MAX from NOAEL (after which adverse effects are expected to begin). While this analysis does not incorporate bulk particles and the entries with particle size > 300 nm are limited, some difference may exist between fine and bulk particles. For instance, when tested at the same concentrations, ultra-fine particles (< 150 nm) seem to have a higher capacity to induce hormesis with low-

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[1] Note: For several concentration-response relationships in (Zheng et al., 2005), the units of the endpoints were not given and thus the response could not be calculated (those data are excluded from this analysis).

[2] In some studies the application method was not given.

[3] Particles are classified ultrafine, fine and coarse when their size is 1–100, 100–2500 and 2500–10,000 nm, respectively.

Table 3

Hormesis dependence on nanoparticle size in algae and plants. Analysis of the median maximum stimulatory response (MAX) and the median distance from MAX to no-observed-adverse-effect level (NOAEL) (NOAEL:MAX ratio). Different lowercase letters above medians indicate significant differences for groups with one or more samples stochastically dominating another sample after applying a Bonferroni correction against inflation of Type I error. Different uppercase letters above medians indicate significant differences with no applying a Bonferroni correction against inflation of Type I error ($\alpha = 0.05$).

Particle size	Median (%)	Geometric mean (%)	Sample size (number of concentration responses)
A) MAX			
≤10	122.2	133.4	121
> 10 ≤ 20	121.2	135.4	260
> 20 ≤ 50	138.9	142.0	55
≥100 ≤ 380	121.9	138.2	35
Kruskal-Wallis test	$H = 5.31$, $P = 0.150$		
B) NOAEL:MAX			
≤10	1.7^{aAB}	2.1	46
> 10 ≤ 20	1.6^{aA}	1.9	149
> 20 ≤ 50	1.9^{abBC}	2,6	43
≥100 ≤ 380	3.0^{bC}	4.0	19
Kruskal-Wallis test	$H = 22.93$, $P < 0.001$		

Note: the size of the nanoparticles was not reported in all the papers.

concentration stimulation and higher toxicity at high concentrations than bulk/fine particles (> 300 nm) (Ji et al., 2011; Warheit et al., 2007). This may be because nanoparticles may have a higher potential to adsorb onto soil colloids, than bulk particles of the same material, because of their high large surface area to mass ratio (Alidoust and Isoda, 2014).

Other factors may influence the concentration-response relationships such as particle aggregation, heteroaggregation, aggregate structure, shape, surface functionalization, crystallinity, metal concentration and stabilizer (Supplementary materials, Section 3) (Hartmann et al., 2010; Ma et al., 2010; Syu et al., 2014; Wang et al., 2013; Bello-Bello et al., 2018). However, presently the available literature does not permit such an evaluation.

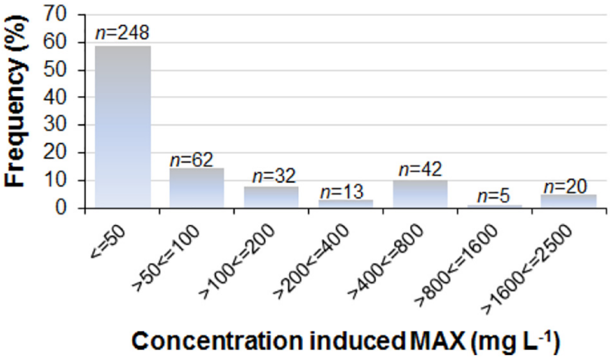

Fig. 2. Concentrations induced maximum stimulatory response (MAX) in algae ($n = 14$) and plants ($n = 408$). The frequency indicates the percentage of 422 dose responses. High concentrations > 400 $mg\,L^{-1}$ where commonly from experiments with seed soaking (see Table 5).

Table 4

Dependence of the maximum stimulatory response (MAX) on the inducing concentration in algae and plants. Different lower case letters above medians indicate significant differences for groups with one or more samples stochastically dominating another sample after applying a Bonferroni correction against inflation of Type I error. Different uppercase letters above medians indicate significant differences with no applying a Bonferroni correction against inflation of Type I error ($\alpha = 0.05$).

Concentrations induced MAX ($mg\,L^{-1}$)	Number of concentration responses	Median MAX (%)
≤10	88	119.7^{aAB}
≥15 ≤ 25	74	113.0^{aA}
≥30 ≤ 50	86	155.5^{bC}
≥60 ≤ 125	72	$130.4b^{abBC}$
≥200	102	124.9^{abAB}
Kruskal-Wallis test	$H = 27.21$, $P < 0.001$	

From the 478 entries, 422 (of which only 14 for algae) reported concentrations in mg L^{-1} or in units that permitted conversion to mg L^{-1}. The median concentration inducing MAX was 30.0 $mg\,L^{-1}$ (geometric mean = 40.3 $mg\,L^{-1}$). A breakdown of the concentrations induced MAX reveals that 58.8 or 73.5% of these entries displayed MAX at concentrations ≤50 or ≤100 $mg\,L^{-1}$, suggesting that MAX appears commonly at concentrations ≤100 $mg\,L^{-1}$ (Fig. 2). To test whether MAX depends on the inducing concentration, the 422 entries were grouped based on the range of concentrations, such that the groups provide a sufficient sample size of concentration responses and independent studies (Table 4). This analysis revealed that the maximum median MAX (across any other experimental conditions) increased when the MAX-induced concentrations increased up to 30–50 $mg\,L^{-1}$, suggesting that concentrations below 30 $mg\,L^{-1}$ may be inadequate to induce a MAX closer to the real one; concentrations above 50 $mg\,L^{-1}$ may also underestimate the real MAX which may be due to chemical engineering factors (e.g. chemical aggregation).

The plant entries with concentration in mg L^{-1} were further analyzed (20 entries with calli were excluded) between those where treatment was done only at the stage of seed (seed soaking) and those where treatment was classically done during plant growth (vegetative stage). The distributions of the two groups differed significantly (Table 5), with the median MAX-inducing concentration being 21.7 times higher at seed stage than at vegetative stage. Given that the NOAEL:MAX ratio for plants is < 2, it seems that seed stage has multifold plastic limits than vegetative stages. However, seed size may define how seeds respond to nanomaterials. For instance, small seeds have higher surface to volume ratio than large seeds, thus, higher responses at lower concentrations may occur in small seeds (Ma et al., 2010), something that should be considered in the future.

Among the nanomaterials used, only three groups could be created to provide a robust sample size for analysis, i.e. Ag (excluding 16 entries with carbon- and PEG-coated Ag), TiO_2, ZnO. Ag induced higher median MAX than TiO_2 and ZnO, although at a less strict alpha level ($P = 0.044$) for TiO_2 (Table 6), suggesting that the elemental release from particles is not the major reason for stimulation or that silver may simultaneously suppress fungi with these plants showing a higher MAX. In a further analysis, the dose responses were grouped into those induced by nanomaterials containing essential elements (N, P, K, Ca, Mg, S, B, Cl, Fe, Mn, Zn, Cu, Mo, Ni, H, O and C) and those containing only non-essential elements. Interestingly, the median MAX was higher for the group of non-essential elements than the group of the essential elements, and the two distributions differed significantly (Table 6). These findings suggest that the MAX is not upon essential elements of the nanoparticles but also that incorporation of essential elements in the nanomaterials may yield lower MAX (e.g. it may reduce the "xenobiotic effect").

Hormesis seems to depend on the type of nanomaterials, with different nanomaterials displaying different responses at the same concentrations, when tested under same experimental conditions (Alidoust and Isoda, 2014; Chutipaijit and Sutjaritvorakul, 2017; Huang et al., 2018; López-Moreno et al., 2010a; Ma et al., 2010), and our analysis may support this hypothesis. Mixtures of nanoparticles can also induce hormesis (Taran et al., 2016), and more experiments are needed to provide insights important for risk assessment in the future.

The concentration responses, for which the time window from

Table 5
Analysis of the median maximum stimulatory response (MAX) as per the plant growth stage. The level of significance was set a priori to $\alpha = 0.05$.

Concentrations induced MAX ($mg\,L^{-1}$)	Number of concentration responses	Median MAX-inducing concentration ($mg\,L^{-1}$)
Seed stage	64	650.0
Vegetative stage	324	30.0
Kruskal-Wallis test	$H = 19.98$, $P < 0.001$	

Table 6
Dependence of the maximum stimulatory response (MAX) on the type of nanomaterial. Different lower case letters above medians indicate significant differences for groups with one or more samples stochastically dominating another sample after applying a Bonferroni correction against inflation of Type I error. Different uppercase letters above medians indicate significant differences with no applying a Bonferroni correction against inflation of Type I error ($\alpha = 0.05$).

Nanomaterial	Number of concentration responses	Median MAX (%)
Ag	79	161.0^{bB}
TiO_2	42	135.1^{abA}
ZnO	100	123.5^{aA}
Kruskal-Wallis test	$H = 18.80$, $P < 0.001$	
Including essential elements	338	117.1^{aA}
Including only non-essential elements	161	146.1^{bB}
Kruskal-Wallis test	$H = 38.44$, $P < 0.001$	

Table 7
Dependence of the maximum stimulatory response (MAX) on the time window. Different letters above medians for NOAEL:MAX indicate significant differences for groups with one or more samples stochastically dominating another sample (after applying a Bonferroni correction against inflation of Type I error). The level of significance was set a priori to $\alpha = 0.05$.

Time (days)	Number of concentration responses	Median MAX (%)
≤ 14	206	116.0^{a}
$> 14 \leq 30$	138	151.3^{c}
$> 30 \leq 90$	153	125.7^{b}
Kruskal-Wallis test	$H = 30.46$, $P < 0.001$	

treatment to response measurement was given or could be calculated, could be grouped into three robust groups, i.e. ≤ 14, $> 14 \leq 30$ and > 30 days. Interestingly, it seems that MAX was maximized in 15–30 days and then dropped to a lower level again (Table 7). A recent analysis of lanthanum effects on plants also suggested that MAX may decline over time but can still remain at a biologically important level (i.e. > 120%) to offer a net benefit (Agathokleous et al., 2019c). This is the case for nanomaterials where even if the median MAX declines after 1 month it still remains at a biologically important level (126%).

The major types of endpoints for the 499 concentration responses were biochemical (34.1%), growth (16.4%), physiological (11.4%) and production (20.6%). The lowest median MAX appeared for physiological endpoints (Table 8), and this might be explained by the high temporal variation of physiological endpoints (in addition to the small sample size) which is commonly not accounted for in the experiments (i.e. MAX may be measured at a time where response is not at the maximum). The distribution of production endpoints (including yields and biomasses) was significantly different for those of growth and physiological but not that of chemical endpoints. The higher medians for production and biochemical endpoints might be due to the possibility that they are less influenced by the temporal component than physiological endpoints.

4. Mechanisms

The herein evaluation suggests that nanomaterial-induced hormesis is not an outlier phenomenon but rather a widely occurring and well documented one. Hence, these understandings should be supported by a mechanistic basis.

Table 8
The maximum stimulatory response (MAX) as per the major types of endpoints. Different lowercase letters above medians indicate significant differences for groups with one or more samples stochastically dominating another sample after applying a Bonferroni correction against inflation of Type I error. Different uppercase letters above medians indicate significant differences with no applying a Bonferroni correction against inflation of Type I error ($\alpha = 0.05$).

Type of endpoint	Number of concentration responses	Median MAX (%)
Biochemical	170	123.0^{bcBC}
Growth	82	121.8^{abB}
Physiological	57	110.3^{aA}
Production	103	141.2^{cC}
Kruskal-Wallis test	$H = 37.13$, $P < 0.001$	

4.1. *Preconditioning or not?*

Nanomaterials can change the response of plants and algae to other stressors, such as heavy metals (Hartmann et al., 2010; Huang et al., 2018), indicating that nanomaterials can induce preconditioning within a hormetic framework. For example, an extensive field experiment also revealed that low concentrations of engineered Si nanoparticles alleviated negative effects of reduced watering on plant growth and leaf greenness, and increased yields in a hormetic manner (Alsaeedi et al., 2019). Nanomaterials may reduce or increase the accumulation of heavy metals by suppressing or enhancing the expression of transporter genes involved in heavy metal uptake and translocation (Yang et al., 2019).

Seed treatment and germination with nanoparticles/nanotubes can also induce hormesis in the emerged seedlings with priming/preconditioning (Savvides et al., 2016) at low concentrations persisting during the post-emergence seedling growth (Choudhary et al., 2019; Hong et al., 2005; Li et al., 2019; López-Moreno et al., 2010a,b; Ma et al., 2010; Razzaq et al., 2016; Taran et al., 2016; Tiwari et al., 2014). A statistical analysis conducted in this study indicated that seed soaking can induce as large or larger MAX than root or foliage treatment but optimum stimulation may be achieved when combined with vegetative treatments (root and foliage) (Taran et al., 2016); however, this may depend on the duration the seed preconditioning effect can persist.

Plants and algae can transform nanoparticles, thus, changing bioavailability and the thereby effects (López-Moreno et al., 2010a). This organismic property, and the direct effects of nanomaterials on the growing media and surfaces, highlight the need to understand if the preconditioning by low concentrations is due to real organismic stress response or a stimulation resulting indirectly, such as due to changes in the bioavailability of nutrients in the growing media.

When a type of 300 nm TiO_2 nanoparticles (surface area = $11.5\,m^2\,g^{-1}$) was tested in algae, it decreased toxicity of dissolved Cd(II) species, which was due to decreased bioavailability of Cd as a result of sorption/complexation of Cd^{2+} ions to the TiO_2 surface. However, one type of 30 nm TiO_2 nanoparticles (surface area = $47\,m^2\,g^{-1}$) increased toxicity of dissolved Cd(II) species, suggesting a combined effect of Cd and TiO_2 nanoparticles and/or that TiO_2 increased the bioavailability of Cd, i.e. carrier effect (Hartmann et al., 2010). The carrier effect depends on the cell wall. For instance, a study showed that carboxyl-CdSe/ZnS quantum dots decreased Pb and Cu intracellular content in walled strains, whose main cell wall component is glycoproteins, but highly increased Pb and Cu intracellular content in wall-less strains of green microalgae (Worms et al., 2012). These suggest that nanoparticles-induced protection against other stressors is not only due to classical biological preconditioning but also due to chemical engineering phenomena (e.g. chemical aggregation, metal corrosion, sorption of ions).

Studies with plant preconditioning also showed changes in the nutrient availability, uptake or accumulation. For instance, low concentrations of nanomaterials reduced arsenic-induced toxicity in two varieties of rice, but Fe_3O_4 and Fe nanomaterials prevented better the transportation of arsenic to the aboveground parts than $CxO(H_2O)y$ and $Ca_{10}(PO_4)_6(OH)_2$ nanomaterials (Huang et al., 2018). In another experiment, Si nanoparticles increased N, K, and Si uptake in all plant tissues and decreased Na uptake in root, stem, and leaves of cucumber plants; all the nutrient contents and K/Na ratio displayed a hormetic-like dose-response relationship (Alsaeedi et al., 2019). Similarly, experiments with barley seeds soaked with $MnFe_2O_4$ or $NiFe_2O_4$ nanoparticles and then grown in an $MnFe_2O_4$ or $NiFe_2O_4$ nanoparticle-containing hydroponic system revealed that low concentrations inducing stimulatory effects increased the leaf Mn or Ni and Fe contents too (Tombuloglu et al., 2018). Furthermore, in an experiment with soybean germinated seeds, the low concentration of ZnO nanoparticles that stimulated root elongation showed also lower agglomeration (and higher Zn concentration in the tissues) than higher concentrations with inhibitory effects, accompanied with higher availability of nanoparticles and Zn ions (López-Moreno et al., 2010a). These suggest that at least some of the response can be induced by elemental changes in both algae and plants. Changes in the elemental content in the tissues may be due to changes in the ionome which result from released ions from the nanomaterials. To this end, the recently expanding field of ionomics, and especially study of ionome-genome interactions, can provide further insights in the future (Watanabe et al., 2015, 2016). Hormesis-based applications of nanoparticles, with slow release of ions, on plants may be optimized based on preceding tests with major plant diseases at certain environments (Choudhary et al., 2019).

4.2. *Hormesis mechanisms*

As explained, one possible mechanism for hormesis could be changes in nutrient status. Low concentrations of nanomaterials can increase or decrease the content of micro- and macro-nutrients in plant tissues (Bello-Bello et al., 2017; López-Moreno et al., 2016; Spinoso-Castillo et al., 2017; Tiwari et al., 2014; Tombuloglu et al., 2018, 2019; Wang et al., 2019; Xie et al., 2019). Elemental release from the nanomaterials can lead to accumulation of the released elements in the plant tissues (Tombuloglu et al., 2018, 2019; Wang et al., 2013). In fact, metal corrosion from the nanomaterials can increase the release of metals/ions, which may act as a main driver for the nanoparticles-induced toxicities (indirect effect) (Miao et al., 2009; Zhu et al., 2017; Bello-Bello et al., 2018). The amount of metal leaching from the nanoparticles should be considered because high release of ions may induce conversion of cellular O_2 metabolic products (e.g. H_2O_2 and $O-_2$) into $\cdot OH$ and thus cause genotoxicity (López-Moreno et al., 2010a; Singh et al., 2009). However, studies showed that this is not commonly the case as for example when magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) types of iron oxide nanoparticles at low concentrations enhanced muskmelon fruit fresh mass and fruit vitamin C without increasing significantly the Fe content in leaves, stem, root and fruit (Wang et al., 2019). Toxicological testing of the effects of dissolved ions, at amounts equal to the ions dissolved from applied high nanoparticles concentrations that caused inhibitory effects in wheat (*Triticum aestivum* L.) and rape (*B. napus* L.), also revealed no significant effect of released ions per se (Ma et al., 2010). These suggest that elements/ions released from nanomaterials are not a major driver of hormesis, although there can be potential ion exchange (e.g. via Ca—Fe interactions) in the cell wall matrix (Tiwari et al., 2014).

The low-concentration enhancement can improve the photochemical reactions of photosystem II and induce notable changes in the nonphotochemical quenching (NPQ) in a time-concentration-response continuum (Mykhaylenko and Zolotareva, 2017; Malea et al., 2019). For example, CuZn bimetallic nanoparticles induced hormetic responses in the photosystem II (PSII) functionality of tomato plants, under high light (900 μmol photons $m^{-2} s^{-1}$), where reduction status of the plastoquinone pool (qP), relative PSII electron transport rate (ETR) and NPQ showed similar spatiotemporal responses (Antonoglou et al., 2018; see also Malea et al., 2019). Nanoparticles were also found to promote photophosphorylation activity of chloroplasts, related to both PSII and PSI, in a hormetic manner (Hong et al., 2005). Low concentrations of nanoparticles can enhance the chloroplast Hill reaction activity, accelerating FeCy reduction and O_2 evolution (might enter the chloroplasts). Nanoparticles may have a direct effect on the O_2-evolving complex, by increasing the permeability of the thylakoid membranes, hence enabling Ca^{2+} and Cl^- enter the O_2-evolving complex center easier, as well as by changing the combining position and state of Ca^{2+} and Cl^- and protein structure in the O_2-evolving complex (Hong et al., 2005). In addition to these light-related responses, research with algae revealed a potential direct shading effect by encapsulation of the cells (Hartmann et al., 2010); shading can also reduce the amount of light reaching the tissue surface (Hjorth et al., 2016), suggesting some potential protection against photoinhibition in environments with excess light (Kitao et al., 2000; Moustaka et al., 2018). Possible mechanisms for shading include adhesion of particles/aggregates to algal cell surface, physical effects (e.g. disruption of the cell membranes), and reduction of cellular nutrient uptake (Gong et al., 2011; Hartmann et al., 2010).

Hormetic response of photosynthetic pigments and carbohydrate and protein levels were found in different plants and for different nanomaterials (Choudhary et al., 2019; Razzaq et al., 2016; Salama, 2012; Tombuloglu et al., 2019). For example, increased biomass production by low concentrations of nanoparticles was accompanied with alike increases in the catalase activity and chlorophyll content in the leaf (Tombuloglu et al., 2018). Similarly, hormetic response was found in H_2O_2 content, and antioxidant (superoxide dismutase (SOD) and peroxidase (POD)) and defense (phenylalanine ammonia lyase and polyphenol oxidase) enzymes activities (Choudhary et al., 2019), as well as for total phenolic content and antioxidant capacity (Bello-Bello et al., 2017; Spinoso-Castillo et al., 2017). However, the latter hormetic responses were accompanied by linear response of ROS, which suggests that increase in ROS (and perhaps lipid peroxidation) up to a certain level stimulates while further increase inhibits plant functions (Bello-Bello et al., 2017; Spinoso-Castillo et al., 2017). Low concentrations of nanoparticles that can significantly increase photosynthetic pigments levels, protein contents, plant growth rate and biomass, may simultaneously decrease MDA production (Venkatachalam et al., 2017). MDA, proline and H_2O_2 contents displayed U-shape dose-response relationships in other studies with nanoparticles too (Manickavasagam et al., 2019), indicating a mechanism for reducing oxidative lipid injury. Furthermore, the low-concentration enhancement seems to relate to glutathione reductase (GR) and ascorbate peroxidase (APX) activities (anticorrelation), which are associated in the Halliwell-Asada cycle, where NAPDH and reduced glutathione (GSH) aid in restoring the reduced ascorbate pool (Morelli et al., 2012). APX and GR activities seem to also associate with catalase activity in the low-concentration zone (Morelli et al., 2012)

Although assessments of the physiological mechanisms underpinning nanomaterials-induced hormesis are becoming increasingly available, their links to genes are too limited. Among several miRNAs analyzed in switchgrass plants (*Panicum virgatum* L.), only some showed hormetic-like responses whose low-concentration responses were quantitatively similar to those of growth and production traits (Boykov et al., 2019). A research with *Arabidopsis* also revealed that low concentrations of Ag nanoparticles could alter the expression of genes regulating cellular pathways, such as proliferation, photosynthesis and hormone signaling, including auxin, abscisic acid, and ethylene (Syu et al., 2014). Accumulation of ROS and the proteins cell-division-cycle kinase 2 (CDC2), protochlorophyllide oxidoreductase (POR), and fructose-1,6 bisphosphate aldolase (FBA) and expression of the genes indoleacetic acid protein 8 (IAA8), 9-cis-epoxycarotenoid dioxygenase (NCED3), and dehydration-responsive RD22, were major mechanisms underpinning the low-concentration stimulation in *Arabidopsis* (Syu et al., 2014). Furthermore, chitosan nanoparticles induced hormesis in chlorophyll and soluble protein content, biomasses, R/S ratio, seeds germination of wheat (Li et al., 2019). This stimulation was upon upregulation of indole-3-acetic acid (IAA) synthetic genes and downregulation of metabolic genes (Li et al., 2019). In a recent study, Ag nanoparticles induced inverse U-shape concentration-response relationships in callus induction frequency, regeneration frequency, root length and number of roots and U-shape concentration-response relationships in MDA, H_2O_2 and proline content of regenerating calli of indica rice (*Oryza sativa* L.), with significant responses at both low and high concentrations along the full concentration-response spectrum (Manickavasagam et al., 2019). Similar U-shape concentration-response relationships were revealed for *ERF063*, *OsRab16*, *OsIAA1*, *RR2*, and *PBZ1*, which are ethylene, abscisic acid, auxin, cytokinin, and gibberellic acid responsive genes, respectively. Although the responses to low concentrations were statistically non-significant, our analysis suggests that the responses of these genes are significantly correlated with the responses of root length across the concentration-response spectrum (Supplementary materials, Section 4), suggesting they associate with hormesis via decreasing or increasing expression levels. Regarding algae, the data of an extensive study with *Phaeodactylum tricornutum* Bohlin suggest that there were no apparent hormetic-like biphasic concentration-response relationships in the mRNA level of 10 genes (*cox*3, *atp*A, *nad*5, *suf*S, *Isc*U, *psa*B, *pet*F, *rbc*L, *psb*D, and *fts*H) 48 h after the exposure (Zhu et al., 2017). However, *cox*3, *atp*A, *nad*5, *psa*B, and *pet*F showed a hormetic-like response with increased mRNA levels at 10 μM Cu nanoparticles, which was significantly different compared to the control particularly for *nad*5, 96 h after exposure. For cox3 (encodes the cytochrome *c* oxidase subunit), nad5 (encodes the NADH dehydrogenase subunit), and *pet*F (encodes in the photosystem reaction centers), there was a significant decline in the mRNA level around or below the control levels at 40 μM Cu nanoparticles (Zhu et al., 2017). *cox*3, *atp*A and *nad*5 encode proteins associated with the respiratory electron transport chain, whereas *psa*B and *pet*F encode proteins associated with photosynthesis electron transport chain, and such responses associated with hormetic-like responses observed in photosynthetic pigments as well. The different responses of these genes to lower and higher concentrations of nanoparticles suggest that they may be target for further research for hormesis drivers, this should be studied as a function of time as the responses differed over time. However, other genes (or the same but earlier) showed linear increases or decreases in the mRNA levels (Zhu et al., 2017), indicating that small increases or decreases may associate with low-level stimulation whereas high increase or decrease may associate with high-level inhibition. Further omic studies are need.

Nanoparticles may also affect plants indirectly by effecting the microbial community in the rhizo- or phyllo-sphere, something which remains to be studied.

4.3. Relevance to humans

Zn-chitosan nanoparticles increased the Zn content in maize (*Zea mays* L.) grain linearly with increasing Zn-chitosan nanoparticles concentration, protected against disease, and caused significant enhancement of grain yields at low concentrations (Choudhary et al., 2019). Other studies showed that Ag nanoparticles induced hormesis in the yields of wheat, with significant increases at low concentrations and inhibition at high concentrations; in one of the studies this was accompanied with enhanced N, P and K use efficiency (Jhanzab et al., 2015; Razzaq et al., 2016). ZnO nanoparticles given as foliar sprays also induced hormesis in field-cultivated dry bean (*Phaseolus vulgaris* L.) (Salama et al., 2019). Low concentrations enhanced plant growth, seed yields, shoot residues, the total energy for seeds, amino acids content, and micro- and macro-elements content in leaves and seeds; unique proteins at molecular weight 78 KDa were found in response to the concentration at which the maximum stimulatory responses commonly occurred (Salama et al., 2019). These suggest that nanomaterials can induce hormesis in yields, with a potential for increasing agricultural products for human and animal consumption (Choudhary et al., 2019; Razzaq et al., 2016; Salama et al., 2019; Wang et al., 2019). However, low concentrations of nanomaterials can also increase or decrease the content of minerals that are important for human nutrition (e.g. increase fruit vitamin C (Wang et al., 2019)), depending on the plant tissue and element, which may change the ratio between elements (Alsaeedi et al., 2019; López-Moreno et al., 2016; Xie et al., 2019). This would entail implications to human nutrition and health. For this reason, the stoichiometry of agricultural products should be studied after applications of low concentrated nanomaterials.

The tissue-specific accumulation of elements released from nanoparticles in plant tissues, when nanoparticles applied at low concentrations for phytostimulation, should be further studied and understood in relation with humans and animals who potentially consume such agricultural products (Iavicoli et al., 2014; Wang et al., 2013). As nanomaterials induce hormesis in pathogens too, consumption of agricultural products with low concentration or content of nanomaterials may stimulate infectious pathogens, such as some strains of *Escherichia coli*, increasing the public risk, especially for sensitive populations facing heightened risks from infectious pathogens (Iavicoli et al., 2018; Xiu et al., 2012). Therefore, future studies should address potential risk within a nanomaterial-plant/environment-animal framework.

The World Health Organization (WHO) International Program on Chemical Safety (IPCS), the United Nations Environment Program (UNEP) and the International Labor Organization (ILO) publish jointly the Concise International Chemical Assessment Documents (CICADS), primarily concerned with the characterization of chemical hazard and dose-response. Future revisions of the CICADS should consider nanoparticle-induced hormetic dose responses in relation to human health and the environment (e.g. for Ag; World Health Organization, 2002).

5. Conclusions

Hormesis was widely induced by nanomaterials in plants and animals. Although hormesis appeared to vary among experimental conditions, MAX commonly constrained below two-fold the control response, indicating that nanomaterial-induced hormesis is constrained by the limits of biological plasticity.

This study suggests that seed soaking with nanomaterials may be utilized as a potential medium for seed priming with effective induction of maximum stimulatory responses. Seed soaking with nanomaterials may provide an important perspective for agricultural applicability to precondition plants before field cultivation. This practice may reduce the nanomaterials residuals in the environment if less field applications would be needed at vegetative stages.

The herein analysis also suggests that foliar application is not more effective than root application in inducing MAX, and that particles ≥ 100 nm may be safer for application into the environment than particles ≤ 50 nm. Furthermore, it indicates that application of nanoparticles into a soilless growing medium, such as hydroponic culture, can induce similar MAX as when applied onto soil. While this provides a perspective for application to hydroponic cultures, chemical composition of resulting agricultural products should be assessed to account for potential risks from consumption.

The elemental release from particles does not seem to be the major mechanism for stimulation by low concentrations of nanomaterials. The understandings of the physiological mechanisms underlying hormesis are increasing; however, omic analyses within a concentration-time-response continuum are lacking. Future studies should examine how other factors may influence the concentration-response relationships such as particle size, aggregation, heteroaggregation, aggregate structure, shape, surface functionalization, crystallinity, metal concentration and stabilizer.

Hormesis should be considered in the nanomaterials risk assessment procedures, and potential risks by low-concentration responses should be taken into account.

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Author contributions

Design of the study, literature survey and review, data extraction and handling, and initial drafting of the manuscript were done by E.A. Critical revisions of the manuscript for important intellectual content were performed by ZZ.F., I.I. and E.J.C. Each author has read and approved the final manuscript.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105044.

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