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Title	The rare earth element (REE) lanthanum (La) induces hormesis in plants
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Citation	Environmental pollution, 238, 1044-1047 https://doi.org/10.1016/j.envpol.2018.02.068
Issue Date	2018-07
Doc URL	https://hdl.handle.net/2115/78853
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Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	Manuscript2-1.pdf



The rare earth element (REE) lanthanum (La) induces hormesis in plants

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Abstract: Lanthanum is a rare earth element (REE) which has been extensively studied due to its wide application in numerous fields with a potential accumulation in the environment. It has long been known for its potential to stimulate plant growth within a hormetic-biphasic dose response framework. This article provides evidence from a series of high resolution studies published within the last two decades demonstrating a substantial and significant occurrence of lanthanum-induced hormesis in plants. These findings suggest that hormetic responses should be built into the study design of hazard assessment study protocols and included in the risk assessment process. Hormesis also offers the opportunity to substantially improve cost benefit estimates for environmental contaminants, which have the potential to induce beneficial/desirable effects at low doses.

Keywords: dose-response; hormesis; lanthanum; risk assessment; U-shape curve

Capsule: The response of plants to lanthanum is often described by hormetic model

INTRODUCTION

Lanthanum¹ (La) is the lanthanide with the largest atomic radius. Fifteen lanthanides, scandium (Sc), and yttrium (Y) are chemical elements of the periodic table which have been defined by IUPAC as rare earth elements (REEs). Despite their name, these elements are not particularly rare and can be found in well measurable concentrations in the crust of Earth. REEs do not occur naturally at high concentrations in the environment but may occur at high concentrations due to their utilization by and application within a wide spectrum of fields, including agriculture, industry and medicine (García-Jiménez et al., 2017; Hu et al., 2016; Lin et al., 2017; von Tucher and Schmidhalter, 2005).

Dose responses represent the backbone of toxicology and are necessary for assessing the effects of pollutants. Dose response relationships are established for assessing risks and deriving critical levels below which chemicals or pollutants do not pose a threat for adverse effects. Throughout the 20th century, the prevailing belief was that the response of biological organisms to chemical or environmental stressors increases linearly with increasing dose (linear-no-threshold model) or remains neutral up to a certain threshold and then increases linearly with increasing dose (threshold model) (Fig 1).

Hormesis is a biphasic dose response characterized by stimulation at low doses and inhibition at high doses (Fig 1). While hormesis has a long history (Calabrese and Baldwin, 1999; Stebbing, 1982), especially in the area of plant biology (Calabrese and Baldwin, 2000; Calabrese and Blain, 2009), it has taken on renewed focus over the past several decades (Abbas et al., 2017; Agathokleous, 2017; Belz and Piepho, 2017; Calabrese and Blain, 2011, 2009, Cedergreen et al., 2009, 2007; Agathokleous, 2018; Poschenrieder et al., 2013; Vargas-Hernandez et al., 2017). A recent paper published in *Environmental Pollution* reports the results from an experiment where the effects of La pollution are assessed in soybean seedlings under different acid rain scenarios (Zhang et al., 2017). Although this study focused

¹ From the ancient Greek word λανθάνειν (lanthanein), meaning “stay unnoticed” or “escape attention”

on the mechanisms underlying plant response, thanks to its robust experimental design, the results show hormesis induced by the earth lanthanum ion (La^{3+}) and call for re-examination of published literature dealing with the effects of La on plants.

ANALYSIS

Based on a re-examination of published literature, collective evidence for significant La-induced hormetic responses is shown for 9 species and at least 4 cultivars/varieties in 20 studies published in 12 journals over the period 2001-2017; 13 of them (65%) were published in the period 2012-2017.

Hormesis in a variety of species

Taxus yunnanensis cell cultures exposed to La^{3+} ($\leq 46.2 \mu\text{M}$, 28 d) displayed a hormetic response (MAX at $5.8 \mu\text{M}$) in average cell growth rate (Fig 2A) and taxol production (Wu et al., 2001). Desert broomrape cell cultures (*Cistanche deserticola* Ma) exposed to La^{3+} ($\leq 0.1 \text{ mmol L}^{-1}$, 30 d) showed hormetic response (MAX at 0.01 mmol L^{-1}) in dry weight (Fig 2B) and phenylethanoid glycosides content and production (Ouyang et al., 2003). Similarly, bush bean (*Phaseolus vulgaris* L.) treated with $\text{LaCl}_3 \leq 72 \mu\text{mol Kg}^{-1}$ and spinach (*Spinacea oleracea* L.) treated with $\text{LaCl}_3 \leq 360 \mu\text{mol Kg}^{-1}$ for more than a month showed MAX at $3.6 \mu\text{mol Kg}^{-1}$ (bean 110%, spinach 135%), however non-significant for bean (von Tucher and Schmidhalter, 2005). Durum wheat (*Triticum durum* Desf.) treated with La^{3+} ($\leq 10 \text{ mM}$, 9 d) showed hormesis in root length with MAX at 0.01 mM (Fig 2C), although the stimulation at 0.01 and 0.1 mM did not appear at 6 and 12 days (d'Aquino et al., 2009). Horseradish (*Armoracia rusticana* G.Gaertn.) had greater (114%) and lower (69%) average cell size of fourth true leaf 6 days after treatment (DAT) with 30 or $80 \mu\text{M}$ LaCl_3 compared with $0 \mu\text{M}$ LaCl_3 (Wang et al., 2014a). When horseradish was exposed to 13 doses ranging between 0 and 200 LaCl_3 in a field experiment conducted annually for five years, hormetic dose-response relationship appeared in yield (Fig 2D), net photosynthetic rate (P_N), chlorophyll content and peroxidase activity, with MAX at $35 \mu\text{M}$ (Wang et al., 2014a);

Supporting Information, Table S1). Rangpur lime plants (*Citrus limonia* Osbeck) also showed significant stimulation in wet weight by 50 mg La chloride heptahydrate ($\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$) in contrast to significant inhibition by 100, 200 and 400 mg $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, three weeks after the treatments application (Turra et al., 2015).

Hormesis in rice

Hormesis was found multiple times in rice (*Oryza sativa* L.). Seedlings grown in red soil and exposed to LaCl_3 (≤ 1200 mg Kg^{-1}) displayed hormesis with MAX at 30 mg Kg^{-1} in plant height and tillers (Fig 2E) at 30 DAT, but not at 80 DAT, however MAX was non-significant for tillers (Zeng et al., 2006). In other studies, hormesis was found in fresh root weight (Fig 2F), length of total nodal root, number of nodal roots and number of total lateral roots of nodal roots (Liu et al., 2013), and in soluble protein content and activity of peroxidase (Fig 2G) and catalase in the roots (Liu et al., 2016) of seedlings exposed to La^{3+} (≤ 1.5 mM, 13 d) with MAX at 0.05 or 0.1 mmol L^{-1} . When exposed to 0, 81.6, 1224.5 and 2449 μM LaCl_3 , rice displayed hormesis in P_N , stomatal conductance, Hill reaction rate, apparent quantum yield (AQY) and carboxylation efficiency (CE) at different growth stages and at different pH; stimulation occurred only at 81.6 μM (Wang et al., 2014b). Hormesis appeared in the content of Mg, P, K, Ca, Mn, Fe and Ni, transcription of several chloroplast ATPase subunit genes, activity of Mg^{2+} –ATPase, P_n , dry and fresh weight of leaves, leaf area and relative growth rate in rice exposed to 0, 0.08, 1.2, and 2.4 mM La ($\text{LaCl}_3 \cdot 6\text{H}_2\text{O}$) for 15 d; MAX commonly occurred at 0.08 mM (Hu et al., 2016).

Hormesis in soybean

Hormesis was also frequently found in soybean (*Glycine max* L.). Seedlings treated with La^{3+} (≤ 1.2 mM, 7 d) and simulated acid rain with pH 7.0, 4.5 or 3.5 showed hormesis in chlorophyll content and main root length at all pH levels; in plant height, leaf area, photochemical yield of photosystem II (Φ_{PSII}) and Hill reaction rate (Fig 2H) only at pH 7.0; in initial fluorescence (F_0), dry weight of leaves and stem and dry weight of root at pH 7.0

and 4.5; and in P_n at pH 7.0 and 3.5 (Wen et al., 2011). In the same experimental design, hormesis was found in Mg at pH 4.5; in nitrate reductase transcriptional level at pH 7.0 (Fig 2J); in K and Fe content at pH 7.0 and 4.5; and in nitrate reductase activity at all pH levels (Xia et al., 2017). Under the same conditions, hormesis was found in multiple root endpoints: amino acid content at pH 7.0; glutamine synthetase activity at pH 7.0 and 4.5; NO^{-3} content at pH 7.0 and 3.5; glutamate dehydrogenase (DGH) activity at pH 4.5 and 3.5; nitrate reductase activity and NH^{+4} content; and glutamine-oxoglutarate amino transferase (GOGAT) activity (Fig 2J) and soluble protein content at all pH levels (Zhang et al., 2017). In the latter three studies stimulation occurred at 0.08 mM. Hormesis was also found in P_N (Fig 2K), content of Cu in roots, and content of Cu, Fe and Zn in shoots of seedlings treated with $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (160 μM , 28 d), with significant stimulation at 5 and/or 10 μM (de Oliveira et al., 2015).

Hormesis in broad bean

Finally, several hormetic dose responses were found in and claimed for broad bean (*Vicia faba* L.) too. Clear U-shape dose-responses were found in guaiacol peroxidase (GPX) activity, heat shock protein 70 (HSP 70) level and endoprotease isozymes (Fig 2L) in roots of seedlings exposed to $\text{La}(\text{NO}_3)_3$ (0-12 mg/L = 10.2-433 μg La/g root dry weight, 15 d) with MAX at 0.5 or 1 mg/L (=74.9 or 108 $\mu\text{g/g}$), although with high variance (Wang et al., 2011). In a further study, seedlings hydroponically cultured under 6 μmol cadmium chloride (CdCl_2) L^{-1} and a range of $\text{La}(\text{NO}_3)_3$ levels (0-480 mg/L, 15 d) showed hormesis in Cd content, superoxide dismutase (SOD) activity, GPX activity, catalase activity, ascorbate peroxidase (APX) isozyme activity and HSP 70 production (Fig 2M) in the roots; stimulation occurred between 2 and 120 for all endpoints and was significant for all endpoints except APX activity (Wang et al., 2012a). Under the same experimental conditions, leaf K and Mo content and APX activity (Fig 2N) showed clear hormetic responses with significant effects in the low dose region being observed in the range 8-120 mg/L; catalase activity also showed U-shaped dose response but with no any significant effects (Wang et al., 2012c). Root HSP 70

production showed also a *U*-shaped dose-response (Fig 2O) when seedlings were exposed to 9 doses of $\text{La}(\text{NO}_3)_3$ (0-16 mg L^{-1} , 10 d), with MAX at 0.5 mg L^{-1} albeit non-statistically significant (Wang et al., 2012b). In a different study, seedlings exposed to 5 low doses of $\text{La}(\text{NO}_3)_3$ (0-8 mg L^{-1} , 20 d), showed significant effects, only at 2 or 4 mg L^{-1} , that would contrast the expected effects by high doses in root Cu content, tail length of root tips (Fig 2P) and apical leaves nuclei, and tail moment of root tips and apical leaves nuclei (Wang et al., 2012d).

CONCLUSIONS

This study provides evidence from a series of recent papers showing that hormesis commonly occurs in a variety of plants in response to La. These findings build upon a strong historical research foundation demonstrating La-induced hormesis in plants during the last three decades of the 20th century (Hu et al., 2004).

The effects at low La doses may be driven by micro-interference to the molecular structure of vitronectin-like protein (VN), whereas the effects of high La doses may be upon binding to VN with a formation of stable La-VN complexes that leads to damage in the VN molecular structure (Wang et al., 2017).

The collective evidence presented here challenges the research community to assess the nature of the dose response over the full dose-response continuum and with appropriate dose spacing especially in the low dose zone. It also suggests the need to investigate whether a prior exposure to low doses of La, which induce biological stimulation, can protect against a subsequent exposure to higher doses of La, so called preconditioning (Calabrese, 2016a, 2016b).

La-induced hormesis in plants, as well as the broader hormetic literature, indicate that hormesis should be incorporated within the hazard and risk assessment process for deriving environmental quality standards. REEs, including La, can be utilized in agricultural practice

(Ozaki et al., 2000; Tommasi and D'Aquino, 2017; Xu et al., 2002; Zhang et al., 2015), and, thus, hormesis should be incorporated into the agricultural practice as well for the optimum beneficial effects within an optimized cost benefit framework.

Acknowledgements: The authors of the original articles are acknowledged for the fundamental contribution in developing this understanding. EA is an International Research Fellow (ID No: P17102) of the Japan Society for the Promotion of Science (JSPS). This research was supported by JSPS KAKENHI Grant Number JP17F17102 (EA and MK). JSPS is a non-profit, independent administrative institution. EJC acknowledges longtime support from the US Air Force (AFOSR FA9550-13-1-0047) and ExxonMobil Foundation (S18200000000256). The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

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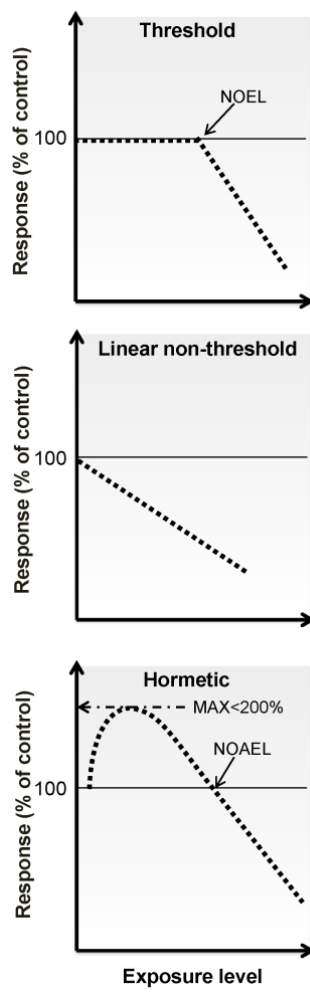
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Captions

Fig 1. Hypothetical threshold, linear non-threshold (LNT), and hormetic dose-response models. The maximum stimulatory response (MAX) in the hormetic model is commonly below 200%. The toxicological thresholds above which adverse effects appear in the threshold and hormetic models are indicated by no-observed-effects-level (NOEL) and no-observed-adverse-effects-level (NOAEL).

Fig 2. Typical examples of hormetic dose responses from published literature. When needed, response data were estimated from figures of reviewed articles using image analysis software (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA, USA).

330 **Fig 1.**



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