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4 **1** **Mechanisms of cerium-induced stress in plants: A meta-analysis**

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7 2 Evgenios Agathokleous^{1*}, Boya Zhou^{1,2}, Caiyu Geng¹, Jianing Xu¹, Costas J. Saitanis³, Zhaozhong Feng^{1*},
8
9 3 Filip M. G. Tack⁴, Jörg Rinklebe^{5,6}

10
11
12 4 ¹ School of Applied Meteorology, Nanjing University of Information Science & Technology (NUIST),
13
14
15 5 Nanjing 210044, China.

16
17 6 ² Department of Life Sciences, Imperial College London, Silwood Park Campus, Buckhurst Road, Ascot,
18
19 7 SL5 7PY, UK.

20
21 8 ³ Lab of Ecology and Environmental Science, Agricultural University of Athens, Iera Odos 75, Athens
22
23
24 9 11855, Greece.

25
26 10 ⁴ Department of Green Chemistry and Technology, Ghent University, Ghent, Belgium.

27
28 11 ⁵ University of Wuppertal, School of Architecture and Civil Engineering, Institute of Foundation
29
30 12 Engineering, Water- and Waste-Management, Laboratory of Soil- and Groundwater-Management,
31
32
33 13 Wuppertal, Germany.

34
35 14 ⁶ Department of Environment, Energy and Geoinformatics, Sejong University, Seoul, Republic of Korea.

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37 15 • corresponding authors. Emails: evgenios@nuist.edu.cn (E.A.; ORCID: 0000-0002-0058-4857),
38
39 16 zhaozhong.feng@nuist.edu.cn (Z.F.)

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Abstract: A comprehensive evaluation of the effects of cerium on plants is lacking even though cerium is extensively applied to the environment. Here, the effects of cerium on plants were meta-analyzed using a newly developed database consisting of approximately 8,500 entries of published data. Cerium affects plants by acting as oxidative stressor causing hormesis, with positive effects at low concentrations and adverse effects at high doses. Production of reactive oxygen species and its linked induction of antioxidant enzymes (e.g. catalase and superoxide dismutase) and non-enzymatic antioxidants (e.g. glutathione) are major mechanisms driving plant response mechanisms. Cerium also affects redox signaling, as indicated by altered GSH/GSSG redox pair, and electrolyte leakage, Ca^{2+} , K^+ , and K^+/Na^+ , indicating an important role of K^+ and Na^+ homeostasis in cerium-induced stress and altered mineral (ion) balance. The responses of the plants to cerium are further extended to photosynthesis rate (A), stomatal conductance (g_s), photosynthetic efficiency of PSII, electron transport rate, and quantum yield of PSII. However, photosynthesis response is regulated not only by physiological controls (e.g. g_s), but also by biochemical controls, such as via changed Hill reaction and RuBisCO carboxylation. Cerium concentrations $<0.1-25\text{ mg L}^{-1}$ commonly enhance chlorophyll a and b , g_s , A , and plant biomass, whereas concentrations $>50\text{ mg L}^{-1}$ suppress such fitness-critical traits at trait-specific concentrations. There was no evidence that cerium enhances yields. Observations were lacking for low concentrations of cerium, whereas concentrations $>50\text{ mg Kg}^{-1}$ suppress yields, in line with the response of chlorophyll a and b . Cerium affects the uptake and tissue concentrations of several micro- and macro-nutrients, including heavy metals. This study enlightens the understanding of some mechanisms underlying plant responses to cerium and provides critical information that can pave the way to reducing the cerium load in the environment and its associated ecological and human health risks.

Keywords: Cerium effects; Environmental Pollution; Nanotechnology; Plant stress mechanisms; Rare earth elements

RESPONSE LETTER

We thank the editor and reviewers for their reviews and comments/suggestions. The comments were helpful to further improve the manuscript. We have considered them and made needed revisions (please see point-by-point responses below).

Below we reply to each comment. Changes are tracked using the Review function of MS Word in the document with changes tracked. The line numbers mentioned below in our responses refer to the document with changes tracked.

Reviewer #1:

An well conducted metanalysis/work which I enjoyed very much! An extensive work is being conducted! I think that the present manuscript could be published prior to some minor revision. It is a well-written manuscript and the authors are analytical and the tables that they are presenting indeed help the author very much. It is conscience and within the scope of the Journal. I would recommend the authors to carefully read again the manuscript and correct some mistakes regarding the articles referenced. Some references are misplaced. Also, some linguistic/grammatical mistakes could be corrected.

Reply: We are thankful to the reviewer for the positive evaluation of our study. As suggested, we carefully went through the paper again and corrected errors and typos regarding references and also minor errors in text. These are shown in track changes in the paper.

Reviewer #2:

This paper is a high-quality meta-analysis of the accumulated data concerning the effects of cerium on plants. The authors, based on a significant number of publications, provide convincing evidence of hormetic effects of cerium and some of their mechanisms. Interestingly, on the one hand, cerium causes the typical effects of strong and mild stressors of any nature (i.e., it acts non-specifically), on the other hand, this element is able to directly participate in redox reactions. The authors discussed the first point exhaustively. However, the second point (redox properties of cerium) is mentioned by the authors only in Introduction. I think it would be useful to briefly describe in the Discussion section which of the identified effects of cerium may be related to its direct participation in redox processes along with the effects of cerium through non-specific stress mechanisms.

Reply: We are grateful to the reviewer for the positive evaluation of our study as well as the many constructive suggestions. Please note that redox properties were mentioned in lines 535-603 of the Discussion. To avoid redundancy, since most mentioned along these lines affect redox biology, this is now clarified at the opening of the respective molecular section (**lines 550-551**). Then, some additional clarifications are made (**lines 564-565 and 575-578**), but we tried to be concise because of the unavoidably large size of the paper (around 9000 words excluding display elements and references).

In addition, some minor revision is required for the manuscript.

1. Graphical Abstract and Highlights. These items are made at a very good level and meet the requirements of the journal.

Reply: Thank you (no change needed).

2. Introduction.

"Rare earth elements (REEs) have been extensively introduced into the environment in the

last decades, due to their wide use in agriculture, technology (e.g. electronics)... "

Please add a comma after e.g. everywhere in the article where you give examples.

Reply: Done throughout the manuscript (changes tracked).

3. "Cerium is, with an average concentration of 62 mg Kg⁻¹, the 25th most abundant element in the Earth's crust, ranking before elements like Cu (60 mg Kg⁻¹) and Pb (13 mg Kg⁻¹) (Migaszewski and Galuszka, 2015; Tao et al., 202) "

Reply: Revised for clarity (lines 17-18).

Please replace mg Kg⁻¹ with mg kg⁻¹ everywhere in the paper.

Reply: Changed all over the manuscript (changes tracked).

4. Table S1 N (observation).

Please explain in the note to the table or in the Materials and Methods what this means. Sample size (n) or treatment numbers?

Reply: Clarified (caption of Table S1, Supplementary Materials 1).

5. 2.4 Meta-analysis

"An $rr=0$ suggests that the cerium-treated group does not differ from the control group. An $rr>0$ suggests a positive effect whereas an $rr<0$ suggests a negative effect of cerium treatment compared to control conditioning. " However, in some figures (for example, in Fig. S3 for the genus Sorghum, in the figure for the species Brassica napus) logarithm values significantly different from zero are marked as statistically insignificant (ns). In fact, the averages of cerium-treated groups, even in the absence of static significant differences relative to the control, will never completely coincide with the control average because these are sample averages. That is, the logarithms calculated in this study will never be exactly zero. Therefore, the authors should explain whether they took into account this point and statistically significant differences between treatments and the control indicated in the studies from which the data were extracted.

Reply: Please note that the quoted sentence does not refer to statistical significance. A positive or negative effect is not necessarily statistically significant (and lack of statistical significance does not mean lack of effect). The statistical significance depends on the variance (and not the average only). This is now clarified in the methods (lines 189-191).

6. Results

1. "Cerium had also a significant positive effect on 17 families and negative effect on 1 family (Supplementary Materials 2, Fig. S2)." The authors in this figure indicated either a positive or a negative effect of cerium for the families (the situation is similar in some other Figures of Supplementary Materials 2). However, some studies have certainly found both stimulating and inhibitory effects of cerium on this family/order and so on. In this case, how did the authors classify these data? Perhaps this point should be explained in Materials and methods or in the captions of the Figures.

Reply: We understand that the reviewer refers to stimulatory and inhibitory effects found within the same study (as different studies have different results, which is the point of meta-analysis). We now clarified this point in the methods (lines 140-142).

2. P. 17 L. 369 "Cerium (III) nitrate hexahydrate ($Ce(NO_3)_3 \cdot 6H_2O$) led to similar or higher effects at low doses ($\leq 0.1-1$ mg L)... " Please replace $Ce(NO_3)_3 \cdot 6H_2O$ with $Ce(NO_3)_3 \cdot 6H_2O$.

Reply: Changed accordingly (line 380).

1 1. Introduction

2 Rare earth elements (REEs) have been extensively introduced into the environment in the
3 last decades, due to their wide use in agriculture, technology (e.g., electronics), and
4 medicine (Li et al., 2016; Migaszewski and Galuszka, 2015; Srikant et al., 2021). China, as
5 the major producer of REEs worldwide, mined 140,000 tons in 2020. Another 24,700 tons
6 were produced by Australia (17,000), India (3000), Russia (2700), Brazil (1000), and
7 Vietnam (1000) (Tao et al., 2022). REE contents in the soils of mining and non-mining
8 areas in different countries were reported to range from 18 to 27,550 mg $\text{K}^{-1}\text{g}^{-1}$
9 (Mihajlovic et al., 2019; Tao et al., 2022). In sediment samples from different countries,
10 values of relative REE abundance were also reported ~~in the range of~~ to range from 11 to -
11 3,041 mg $\text{K}^{-1}\text{g}^{-1}$ (Tao et al., 2022). Hence, the levels of REEs in soils and sediments
12 display a high spatial variability and reach relatively high values. This raises
13 ecotoxicological concerns in recognition of documented effects of REEs on animals and
14 other organisms as well as potential links to human disorders and diseases, especially in
15 areas with ~~potentially~~ elevated REE pollution (González et al., 2015; Pagano et al., 2015;
16 Tao et al., 2022).

17 Cerium is, ~~with an average concentration of 62 mg $\text{K}^{-1}\text{g}^{-1}$~~ , the 25th most abundant element
18 in the Earth's crust (~~62 mg $\text{K}^{-1}\text{g}^{-1}$~~), ~~ranking before surpassing~~ elements like Cu (60 mg $\text{K}^{-1}\text{g}^{-1}$)
19 and Pb (13 mg $\text{K}^{-1}\text{g}^{-1}$) (Migaszewski and Galuszka, 2015; Tao et al., 2022). It belongs to the
20 most extensively applied REEs, leading to its widespread accumulation in the environment
21 (Liang et al., 2005). The long and extensive application of REE microfertilizers in the
22 agricultural practice, in China, considerably enhanced the yields and qualitative value of

23 many crops (Migaszewski and Galuszka, 2015). However, cerium also has a distinct property,
24 that is, its Ce^{3+} form is separated from other trivalent REEs due to its oxidation to Ce^{4+} in
25 aqueous environments with somewhat increased pH or redox potential (Eh) (Migaszewski and
26 Galuszka, 2015). ~~‡~~ The reverse conversion from Ce^{4+} to Ce^{3+} , due to valence change and
27 electron addition, also occurs in organisms (Farias, 2018). Such chemical transformations
28 suggest the possibility for unpredicted effects of cerium on non-target plants and other
29 organisms. In recent years, nano-forms of cerium have also received increased interest, not
30 only for improving ~~plants~~ plant health (Hu et al., 2020; Rodrigues et al., 2021; Sharifan et
31 al., 2020) but also for medical purposes (e.g., cerium oxide nanoparticles) because of their
32 antimicrobial activity, high oxygen buffering, and free radical-scavenging potential, among
33 other properties (Farias, 2018; Jakupec et al., 2005; Li et al., 2016). In many cases the activity
34 of nano-forms of cerium is similar to that of two key antioxidant enzymes, namely, catalase
35 (CAT) and superoxide dismutase (SOD), thus enhancing pro-oxidant activity, although
36 adverse effects, such as on respiratory tract, have also been reported (Li et al., 2016). Because
37 of the relatively high natural abundance of cerium and ~~its the~~ increased anthropogenic
38 emissions ~~of cerium~~ into the environment, there is a need to better comprehend its effects on
39 plants and other organisms.

40 A literature survey with keywords ‘cerium’, ‘plant’, and ‘review’ (PubMed; 9 July, 2022)
41 revealed ~~no that no~~ comprehensive review focusing on the overall mechanisms underlying
42 cerium effects on plants has been published (e.g. with keywords ‘cerium’, ‘plant’, and
43 ‘review’ in PubMed; 9 July, 2022). Nevertheless, the increasing interest in nano-cerium led to
44 some reviews on the effects of cerium oxide (CeO_2) nanoparticles on plants. These suggested

45 suppression of root biomass but enhancement of shoot biomass in many plants (Lizzi et al.,
46 [20182017](#)). These reviews also suggest decreased photosynthetic pigments and enhanced gas
47 exchange related to photosynthesis, as well as modified yields and nutritional quality of
48 edible plant products (Lizzi et al., [20182017](#); Prakash et al., 2021). However, the effects
49 varied among studies and plant growth conditions, indicating the degree to which the
50 mechanistic understanding remains incomplete (Lizzi et al., [20182017](#); Prakash et al., 2021).

51 Some plant species can (hyper)accumulate REEs (Tao et al., 2022); ~~H~~however,
52 hyperaccumulators represent a tiny fraction of ‘elite’ species, e.g., only approximately 0.2%
53 of the currently known vascular plant species ~~are known to have been identified as~~
54 hyperaccumulators of metals (Calabrese and Agathokleous, 2021). For ‘normal’, non-
55 (hyper)accumulator plant species, the REE contents are, generally, considerably low;
56 however, with considerable variation amongst spermatophytes (Tao et al., 2022). For
57 example, REE contents in spermatophytes can range from 0.028 to 386 mg ~~kg~~kg⁻¹ depending
58 on plant species and tissues (Tao et al., 2022). Nevertheless, such REEs still enter the food
59 chain, undergo bioaccumulation/biomagnification, and potentially affect ingesting organisms
60 (Adeel et al., 2019). Importantly, REEs, including lanthanum (La) and cerium (Ce), have also
61 been measured; in considerable levels; in human blood, hair, and sperm (Li et al., 2013;
62 Marzec-Wróblewska et al., 2015; McDonald et al., 2017). These observations further indicate
63 the widespread presence of REEs, facilitated by trophic transfer, where plants act as a major
64 primary entrance to the trophic chain. Therefore, it is profoundly important to understand
65 cerium effects on plants, not only for revealing the underlying plant mechanisms ~~for plant-soil~~
66 ~~health continuum~~ but also for understanding how plants may drive risks to the health of

67 herbivores.

68 Despite the widespread application of REEs in ~~the~~ agriculture ~~over several decades~~ to
69 increase crop productivity, there is lack of systematic assessments on positive versus negative
70 effects of REEs on living organisms, even though some literature reviews highlight the
71 occurrence of hormesis (Agathokleous et al., 2019c; Pagano, 2017; Tommasi et al., 2021,
72 [2022](#)). Such an evaluation can be facilitated by the use of meta-analytic tools that permit
73 summarizing large amounts of data. Meta-analysis is ~~such~~ an important statistical tool that can
74 give answers to questions that cannot be answered by traditional narrative literature reviews.
75 It increases the number of observations, while accounting for study-specific variance, and
76 enhances the statistical power. Meta-analysis also improves the estimated effect size of
77 experimental treatments, and can be utilized to extract quantitative conclusions from an
78 abundant scientific literature. It removes reviewer~~s~~ bias due to subjective –at least to some
79 degree– review, identifies general trends and patterns, and reduces data processing errors, thus
80 advancing theories and scientific understanding. To date, there has been no meta-analysis on
81 the effect of cerium or other REEs on any organisms (Web of Science; keywords: “cerium” or
82 “rare earth” and meta-analysis (all fields); last update on 28 April 2022), although some
83 regular reviews have examined the effects of REEs on plants and other organisms
84 (Agathokleous et al., 2019c; Cassee et al., 2011; Tao et al., 2022; Tommasi et al., 2021, [2022](#)).

85 This study aimed at identifying general impacts of cerium on plants (regardless species)
86 after collating a meta-database including approximately 8,500 entries (control-treatment
87 observations). To further partition sources of variance, the effect of cerium was examined for
88 different functional groups, crop types, orders, families, genera, and species of plants, plant

89 ontogenic stages subjected to cerium (seed, vegetative stages, or both), application route
90 (seed, foliage, root, or combinations of them), and growing media (soil or solution). This
91 study also aimed at identifying concentrations that generally produce significant positive
92 effects or toxicities across a spectrum of concentration-response ranges and exposure duration
93 intervals within the context of hormesis. ~~This can~~ provide a cost-benefit information
94 platform, to reduce the inputs of cerium into the environment and ~~to identify potential~~
95 ~~toxicities~~ optimize the benefits from cerium application. It was of further interest to examine
96 whether the effect of different concentration ranges varies with key plant traits, plant
97 ontogenic stage treated, cerium particle size (nano or bulk), cerium molecular formula,
98 exposure duration, growing medium, and application route. Finally, it was of similar interest
99 to evaluate whether application route, growing medium, cerium form, and treated plant
100 ontogenic stage modify the effect of cerium at different exposure duration intervals. This
101 meta-analysis reveals the integrated mechanisms by which cerium affects plants, advancing
102 the scientific understanding. It also provides a pathway to address the issue of cerium
103 toxicities and risks in the environment, and offers a novel perspective to tackle this issue at a
104 global scale.

105 **2. Materials and methods**

106 **2.1 Literature screening**

107 Literature screening was conducted in the Web of Science
108 (<http://apps.webofknowledge.com>), and covered the entire period with available publications;
109 the last update was conducted on 23 December, 2020. The combination of keywords (method:

110 Topic) included (cerium) AND (angiosperm OR bryophyte OR cutting OR grass OR
111 gymnosperm OR forest OR hedge OR herb OR herbaceous OR plant OR sapling OR seed OR
112 shrub OR tree OR vegetation OR woody) (Supplementary Materials 1, Fig S1). The search
113 revealed 2,275 publications in English language, and inclusion-exclusion criteria were then
114 applied (Supplementary Materials 1, Fig S2). First, publications were filtered to exclude non-
115 original research (e.g., books, editorials, reviews, and news) based on the type, title, and
116 abstract of publication. Second, articles reporting no application of cerium on plants were
117 excluded based on title and abstract, resulting in 446 [publications](#) proceeding to the next stage
118 which was duplicates checking. After excluding duplicates, 233 articles were examined in
119 detail for inclusion eligibility. At this stage, articles and observations were excluded if one or
120 more of the following conditions held true: (1) the experimental organisms were not higher
121 plants, ~~and~~ (2) measures of dispersion of data around the mean (standard error (SE) or
122 standard deviation (SD)) were not reported, and their estimation was not permitted by the
123 existing information, ~~or~~ [and](#) (3) the experimental treatments were not replicated. This
124 screening resulted in 146 articles that were finally selected for inclusion in the created
125 database (Supporting Information 1, Table S2). The screening of literature, selection of
126 articles, extraction of data, and database preparation were performed in parallel by three
127 independent reviewers under the lead author's supervision, without using workflow-
128 management software.

129 **2.2 Data preparation**

130 The values of means of experimental conditions/groups, the values of given measure of
131 dispersion around the mean (SE or SD), sample size (N), and number of replicates for both

132 the control group (typically zero cerium added) and cerium treatments were gathered in a
133 database. Qualitative information was also collected and recorded in the database in order to
134 study sources of variation (see next section). Data presented in the text or in tables of the
135 reviewed articles were extracted directly. Data that were presented only in graphs were mined
136 with GetData Graph Digitizer v. 2.26 (<http://getdata-graph-digitizer.com>), with an accuracy of
137 $\pm 1\%$ compared to the actual values (Xie et al., 2014). Multiple observations reported in a
138 single article/study were considered to come from independent studies if concerning different
139 genotypes, cultivars, species, cerium concentrations, application techniques, or measurement
140 periods (Feng et al., 2010; Wittig et al., 2009). Therefore, all relevant data from studies
141 reporting both stimulatory and inhibitory effects were included in the database and meta-
142 analysis, regardless of the direction of the effect. Regarding dependent observations in studies
143 reporting traits with multiple treatments data and a common control, the mean values of
144 treatment or control groups were used, according to Lajeunesse (2016). Moreover, if different
145 levels of a stressor were applied to plants in a study, the average value was calculated. The
146 information of plants considered in the meta-analysis is provided in Supplementary Materials
147 1 (Table S1).

148 **2.3 Sources of variation**

149 To clarify variation in cerium effects and reduce potential confounding of factors other
150 than cerium treatment with uneven distribution across datasets, a plethora of sources of
151 variation were considered. These included functional groups (eudicots or monocots and crops,
152 shrubs, or trees), crop types (cereals, fruit trees, legumes, medicinal, oilseed crops, pasture,
153 vegetable, and wild herbs), orders, families, genera, and species of plants with eligible (see

154 previous section) and sufficient number (see next section) of entries. Furthermore, variation
155 was partitioned into plant traits, plant ontogenic stages subjected to cerium (seed, vegetative
156 stages, or both), cerium concentration ranges and treatment duration, cerium particle size
157 (nano or bulk), cerium molecular form, application route (seed, foliage, root, or combinations
158 of them), and growing medium (soil or solution). In plant ontogenic stages, seed represents
159 cerium application to germinating or non-germinated seeds whereas vegetative stage
160 represents cerium application to plants at any stage after completion of germination.
161 Regarding the effect of cerium concentration, the majority of studies reported concentrations
162 in mg L^{-1} . Therefore, wherever they could be converted accurately with the reported
163 information, the units were ~~converted~~changed into mg L^{-1} for harmonization. For a
164 considerable number of entries (about 2700), the concentration unit was mg Kg^{-1} . Hence,
165 entries of the two units were analyzed separately. To cover the entire continuum of dose-
166 response relationship in order not to preclude the identification of both subtoxic and toxic
167 effects widely occurring in biphasic dose responses, arbitrary concentration ranges were
168 created based on the abundance of entries to provide ranges with logical arrangement of
169 spacing. Given the abundant literature with considerably high number of entries, 17 and 15
170 segments were created ranging from $\leq 0.1 \text{ mg L}^{-1}$ to $4,000 \text{ mg L}^{-1}$ and from $>1 \text{ mg Kg}^{-1}$ to
171 $2,000 \text{ mg Kg}^{-1}$, thus permitting the evaluation of potentially antithetic effects between low
172 and high concentrations. Exogenously applied chemicals exhibit important variation in their
173 effects depending on the treatment period~~Exogenously applied chemicals exhibit important~~
174 ~~temporal variation in their effects~~ (Agathokleous et al., 2021). Hence, various arbitrary
175 segments of treatment duration were created ~~depending on the data availability~~. Specifically,

176 11 segments were created, ranging from few hours (<1 day) to 210 days, in order to account
177 for homeostatic controls as well as long-term effects.

178 2.4 Meta-analysis

179 Natural log response ratio (rrX) was used to estimate the ~~effect-effect size~~ of cerium as

$$180 \quad rr = \ln\left(\frac{X_t}{X_c}\right)$$

181 where rr is the natural logarithm (ln) of the average of cerium-treated group (Xt) divided by
182 the average of the control group (Xc) (Feng et al., 2010; Hedges et al., 1999; Wittig et al.,
183 2009). The control group is theoretically cerium-free, e.g., a water-based solution with no
184 added cerium. An rr=0 suggests that the cerium-treated group does not differ from the control
185 group. An rr>0 suggests a positive effect, whereas an rr<0 suggests a negative effect of
186 cerium treatment compared to control condition. The positive or negative rr values are
187 interpreted as biologically positive or negative effects, depending on plant trait under
188 consideration~~However, both negative and positive values may indicate biologically negative~~
189 ~~or positive effects, depending on plant trait~~ (see results and discussion). Whether an effect is
190 statistically significant or not depends on the variance around the mean, and is determined by
191 the statistical model of meta-analysis.

192 To pool effect sizes and conduct analyses, a random-effects model was applied, based on
193 the hypothesis that inter-group differences (among studies and groups of comparisons) come
194 from sampling errors as well as from true random variation (Xie et al., 2014). To reduce the
195 uncertainty underlying the estimation, 64,999 bootstrap iterations (maximum number of
196 iterations -permitted by the software) were applied to re-sample data and construct confidence

197 limits around the size of effect and effect size variance (Rosenberg et al., 2000). The
198 estimates of effect size were classified significant when zero (0) was outside the confidence
199 interval (CI) of 95% (Wittig et al., 2009). The total heterogeneity (Q_T) was partitioned to
200 within-group heterogeneity (Q_W) and between-group heterogeneity (Q_B) in order to compare
201 differences between and within categories. ~~Randomized-A randomized~~ p value <0.05 derived
202 from the resampling technique indicates that ≥ 2 levels significantly differed ~~between them-~~
203 ~~suggesting no random group variance~~. In order ~~for~~ a categorical level (group) to be included
204 in the meta-analysis, it should be composed of ≥ 10 observations regardless the number of
205 independent studies or of >5 observations obtained from ≥ 3 independent studies (Feng et al.,
206 2010; Wittig et al., 2009). The mean effect size and the bootstrapped 95% CIs of each
207 categorical level were calculated for each variable. ~~The~~ meta-analysis was performed with
208 ~~the~~ MetaWin v. 2.1.3.4 (Sinauer Associates, inc., Sunderland, MA, USA) ~~software~~.

209 **3. Results**

210 **3.1 Plant taxonomic groups (order, family, genus, species)**

211 The pooled effect of cerium ~~application~~ on different plant taxonomic groups was examined
212 across all studies with random-effects model, independently of other conditions; sources of
213 variance are analyzed in succeeding sections.

214 Cerium application had a significant positive effect on 17 orders of plants, representing many
215 thousands of species and covering a vast array of food crops as well as plants used for
216 domestic animal feed (Supplementary Materials 2, Fig. S1). The average effect was
217 commonly up to approximately 50% of the control, except for two orders, Apiales (81%) and

218 Dioscoreales (214%), which also had a greater variance and were composed of a relatively
219 small sample size (Supplementary Materials 2, Fig. S1). This increased effect of cerium on
220 Apiales and Dioscoreales (applied at 63-500 and 100-1000 mg $\text{K}_2\text{Ce}(\text{SO}_4)_4 \cdot \text{H}_2\text{O} \cdot \text{L}^{-1}$, respectively) was also
221 contributed by the high number of entries regarding Ce in plant tissues (22.2 and 54.5 % of all
222 entries, respectively), of which response is multi-fold greater (see also section 3.3).

223 Cerium also had ~~also~~ a significant positive effect on 17 families and a negative effect on 1
224 family (Supplementary Materials 2, Fig. S2). The negatively affected Liliaceae was
225 comprised of only 13 observations, 2 studies, and 1 species, and the effects included
226 statistically significant inhibitions of individual-level endpoints based on the original studies
227 too. In these studies either Ce^{3+} (2-50 mg L^{-1}) (Kotelnikova et al., 2019) or nano-cerium oxide
228 (CeO_2 ; 250-1000 mg L^{-1}) (Andersen et al., 2016) was applied, but with more super-NOAEL
229 (no-observed-adverse-effect-level) concentrations, thus leading to an overall negative pooled
230 effect. Similarly to the effect on orders, the average effect on families was commonly up to
231 approximately 54% of the control, except for two families, Apiaceae (81%) and
232 Dioscoreaceae (214%), with enlarged effect and variance (Supplementary Materials 2, Fig.
233 S2).

234 Overall, 27 genera were positively affected, 3 genera were negatively affected, and 8 genera
235 were non-significantly affected by cerium application (Supplementary Materials 2, Fig. S3).
236 The average positive effect was commonly up to approximately 75% relative to control,
237 except for *Dioscorea* ~~which~~ that exceeded 200% as aforementioned for its family and order
238 (Supplementary Materials 2, Fig. S3). The negative effect was below 20% (Supplementary
239 Materials 2, Fig. S3). Similarly to the aforementioned studies with negative effects on

240 Liliaceae family (Andersen et al., 2016; Kotelnikova et al., 2019), the negative effect on
241 *Nicotiana*, *Pisum*, and *Spirodela* genera stems from more decreases in elements and/or more
242 doses ≥above NOAEL, with even biphasic dose responses observed, and includes significant
243 inhibition of growth too (Skiba et al., 2020; Skiba and Wolf, 2019; Song et al., 2018; Xu et
244 al., 2017). The overall numerically positive effect can also be regarded biologically positive
245 effect for the plants because the vast majority of plant traits covered represent traits of which
246 increase reflects a biologically positive outcome of the plants, such as increased pigments and
247 yields (see section 3.3). That is, the number of observations of traits of which increase can
248 lead to biologically negative effects (e.g., reactive chemical species) is considerably limited in
249 the overall analyses (see section 3.3).

250 Across all studies, cerium treatment positively affected 30 species, negatively affected 4
251 species, and had no significant effect on 11 species (Supplementary Materials 2, Fig. S4; see
252 Fig. S5 for an analysis per plant common name). It should also be noted that this represents an
253 overall effect, and the non-significant effect on 11 species does not imply absence of effect on
254 each one of-these species. This is because the effect depends upon the traits studied
255 (including also the number of negatively affected versus the number of positively affected)
256 and treatment concentrations as shown in other meta-analyses too (Agathokleous et al., 2021).

257 The negative effect on the 4 species (*Allium cepa*, *Nicotiana tabacum*, *Pisum sativum*,
258 *Spirodela polyrrhiza*) is attributed to the reasons explained earlier-previously for families and
259 genera, and was below 20% relative to control except for *Allium cepa* that reached 45%
260 (Supplementary Materials 2, Fig. S4). The degree of average positive effect varied widely
261 with species, but was commonly up to ≈50% except for *Capsicum annuum* (68%),

262 *Coriandrum sativum* (55%), *Cucumis sativus* (78%), *Dioscorea esculenta* (207%),
263 *Lycopersicon esculentum* (184%), and *Medicago sativa* (61%).

264 **3.2 Plant type groups**

265 Across studies, cerium had a significant positive effect on cereals (18%), fruit trees
266 (18%), legumes (22%), medicinal plants (23%), oilseed crops (10%), pastures (17%),
267 vegetables (10%), and wild herds (7%) (Supplementary Materials 2, Fig. S6). The effect of
268 cerium was smaller on vegetables and wild herbs than on cereals, legumes, medicinal plants,
269 and pasture.

270 A further grouping of plant functional types across studies revealed that cerium
271 positively affected plants regardless [the functional groups](#) (Supplementary Materials 2, Fig.
272 S7). Specifically, a similar average effect was observed among crops (16%), shrubs (14%),
273 and trees (16%), as well as between eudicots (14%) and monocots (17%) (Supplementary
274 Materials 2, Fig. S7).

275 **3.3 Plant traits (mechanisms)**

276 **3.3.1. Trait groups**

277 Cerium significantly enhanced chlorophyll fluorescence (6%), defense system (15%),
278 development (11%), and gas exchange (17%) (Fig. 1; Supplementary Materials 2, Fig. S8). It
279 also positively affected mineral (ion) balance (10%) and increased non-essential elements
280 (305%), which were mainly comprised of cerium and heavy metals (Fig. 1). Conversely,
281 cerium application decreased essential micro- (7%) and macronutrients (4%) as well as
282 photosynthetic pigments (8%), whereas the overall effect on growth, productivity and yields
283 was insignificant (Fig. 1). Hereafter, the results are analyzed for different traits per trait

284 category.

285 3.3.2. Photosynthesis-related traits

286 Regarding chlorophyll fluorescence-related traits, cerium increased the actual
287 photosynthetic efficiency of PSII (14%), the coefficient of photochemical quantum yield in
288 dark (2%), the PSII effective quantum yield (4%), the electron transport rate (11%), and the
289 maximal quantum yield (1%) (Fig. 2A; Supplementary Materials 2, Fig. S9).

290 Gas exchange analysis revealed that photosynthetic rate (22%) and stomatal conductance
291 (13%) were also significantly increased by cerium (Fig. 2B).

292 Chlorophyll *a* (12%), chlorophyll *b* (13%), and carotenoids (12%) were significantly
293 decreased; however, total chlorophylls (*a+b*) and chlorophyll *a* to chlorophyll *b* ratio were not
294 significantly affected (Fig. 2C). It should be clarified that the total chlorophylls (above zero
295 but CI overlapping zero) consisted of nearly twice the number of observations, and was
296 this trait represented a more robust group compared to the individual chlorophyll
297 pigments.

298 3.3.3. Biochemical (stress-related) traits

299 Cerium affected the plant defense system in diverse ways (Fig. 3A). It increased CAT
300 (17%), dehydroascorbate reductase (DHAR; 54%), glutathione (GSH; 12%), reduced GSH to
301 oxidized glutathione ratio (GSH/GSSG; 20%), malondialdehyde (MDA; 33%), reactive
302 oxygen species (ROS; 38%), and SOD (7%) (Fig. 3A; Supplementary Materials 2, Fig. S10).
303 Conversely, it decreased lycopene (7%), membrane permeability (35%), and polyphenol
304 oxidase (28%) (Fig. 3A; Supplementary Materials 2, Fig. S10). Similarly, cerium decreased
305 starch (13%) but increased free thiols (24%), hill reaction (18%), photophosphorylation rate

306 (17%), and RuBisCO carboxylation (23%) (Fig. 3B; Supplementary Materials 2, Fig. S10).

307 **3.3.4. Elemental/mineral traits**

308 Regarding essential elements, cerium decreased B uptake (13%) and its levels in tissues
309 (10%) and the ratio of carbon to nitrogen (C/N; 8%) (Fig. 4A; Supplementary Materials 2,
310 Fig. S11). It also decreased the levels of Ca (12%), Fe (11%), K (5%), and Mo (31%) in
311 tissues, but increased the uptake of Cu (19%), Fe (58%), Mn (20%), and Ni (76%), although
312 the latter increases are based on [a](#) considerably small number of observations (Fig. 4A).

313 As to non-essential elements, cerium application led to significantly decreased Cd (23%)
314 and Se (13%) levels in tissues and increased Ce (624% and 623%) and Al (67% and 77%)
315 uptake and their levels in tissues (Fig. 4C; Supplementary Materials 2, Fig. S11).

316 Cerium also altered mineral (ion) balance, with significant increases in Ca^{2+} (9%),
317 electrolyte leakage (15%), K^+ (20%), K^+/Na^+ (19%), and Mg^{2+} -ATP_{ase} (20%) (Fig. 4B;
318 Supplementary Materials 2, Fig. S11).

319 **3.3.5. Growth, productivity, and yields**

320 Cerium significantly increased the total plant biomass (7%), number of root tips (23%),
321 root volume (15%), stem biomass (6%), and stem diameter (11%), and decreased root length
322 (11%) and yields (6%) (Fig. 5; Supplementary Materials 2, Fig. S12). Traits [that were overall](#)
323 negatively affected [by cerium](#) are further analyzed by concentration ranges (see section 3.4.6).

324 **3.4. Applied cerium concentration**

325 **3.4.1. Overall concentration ranges**

326 As explained before, the majority of observations, specifically 5,313 observations, [were](#)
327 [for](#) [concerned the](#) concentration units of mg L^{-1} , representing approximately 62% of the total

328 number of observations in the entire database. An additional 2,648 observations ~~were~~
329 ~~for~~concerned the concentration units of mg $\text{K}\text{e}\text{g}\text{k}\text{g}^{-1}$, that is approximately 31% of the total
330 number of observations in the entire database. Therefore, emphasis was ~~given~~ placed on
331 ~~to~~ the analysis of data given in concentration units of mg L^{-1} .

332 Across studies, cerium had either a positive or a non-significant effect on plants (Fig. 6).
333 Importantly, the significant positive effect occurred from concentrations as low as ≤ 0.1 mg L^{-1}
334 ¹, which was kept at similar levels up to 50 mg L^{-1} (%). The concentration of 100 mg L^{-1} also
335 had a positive effect similar to that of concentrations ≤ 0.1 mg L^{-1} (Fig. 6). For concentrations
336 ≥ 125 -800 mg L^{-1} , only concentrations > 210 -300 mg L^{-1} and 500 mg L^{-1} had a positive effect.
337 Cerium concentrations of 1000 and ≥ 1600 -2000 mg L^{-1} also led to a positive effect. All these
338 effects were similar to that of concentrations ≤ 0.1 mg L^{-1} (Fig. 6). Similar results were
339 revealed for the observations with cerium concentrations in mg $\text{K}\text{e}\text{g}\text{k}\text{g}^{-1}$, with significant
340 positive effects of different ranges from as low as > 1 -5 mg $\text{K}\text{e}\text{g}\text{k}\text{g}^{-1}$ ~~through to~~ 1000 mg $\text{K}\text{e}\text{g}\text{k}\text{g}^{-1}$
341 and negative effect at 600 mg $\text{K}\text{e}\text{g}\text{k}\text{g}^{-1}$ (Supplementary Materials 2, Fig. S13).

342 3.4.2. Concentration ranges as a function of application route

343 The overall effect of cerium, regardless of other factors, showed no clear pattern of
344 variation due to the application route, with only few differences (Supplementary Materials 2,
345 Fig. S14-S15). For instance, root and foliage+root applications had a significant positive
346 effect at concentrations > 0.1 -1 mg L^{-1} , but ~~not~~ foliage and seed applications had not. This
347 distinction was no longer present at concentrations > 1 -5 mg L^{-1} , where all application routes
348 led to a significant positive effect on plants. At concentrations > 5 -10 mg L^{-1} , foliage
349 application did not significantly affect, root and foliage+seed application positively affected,

350 and seed application negatively affected [plants](#). At >10-25 mg L⁻¹, foliage and root application
351 positively affected and seed application negatively affected. The only significant effect
352 at >50-80 mg L⁻¹ was a positive influence of seed application. However, at 100 mg L⁻¹ the
353 only significant effect was a positive influence of root application (Supplementary Materials
354 2, Fig. S14-S15). For concentrations ≥125-160 mg L⁻¹, foliage and seed applications but not
355 root application positively affected plants. Regarding concentrations from 200 to 421 mg L⁻¹,
356 no specific application route had positive effects. Then, 1000, ≥1600-2000, and ≥3000-4000
357 mg L⁻¹ significantly positively affected [plants](#) when applied to root (Supplementary Materials
358 2, Fig. S14-S15). For all the significant positive effects, the effects were similar among the
359 different concentration ranges. Since, the unit of mg [K₂CO₃](#)⁻¹ does not include foliage
360 application, data given in mg [K₂CO₃](#)⁻¹ were not considered worth of more detailed analysis.

361 **3.4.3. Concentration ranges as a function of cerium particle size**

362 The effect of cerium (mg L⁻¹) on plants differed between the nano-form and bulk cerium,
363 with half of the concentration ranges showing superiority of nano-cerium (Supplementary
364 Materials 2, Fig. S16). Specifically, nano-cerium had an ~~improved~~increased effect at
365 [concentrations](#) ≤0.1, >1-5, >10-25, >25-50, 100, and >210-300 mg L⁻¹ relative to bulk cerium
366 (Supplementary Materials 2, Fig. S16). Less clear was the difference for the analysis of the
367 effect of cerium concentrations in mg [K₂CO₃](#)⁻¹ (Supplementary Materials 2, Fig. S17).
368 Specifically, nano-cerium had a better effect at >25-50 mg [K₂CO₃](#)⁻¹ but bulk cerium had a
369 significant positive effect at ≥125-500 mg L⁻¹ when nano-cerium had either negative or non-
370 significant effect (Supplementary Materials 2, Fig. S17).

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371 **3.4.4. Concentration ranges as a function of cerium molecular formula**

372 Approximately 10 molecular formulas of cerium were analyzed across different
373 concentrations ranges, depending on the availability of observations and sample size
374 (Supplementary Materials 2, Figs. S18-S19). However, the most extensively applied form is
375 cerium dioxide (CeO_2), which widely produced positive effects at various concentrations, e.g.,
376 at ≤ 0.1 , $>0.1-1$, $>5-10$, $>10-25$, $>25-50$, and $>210-300$ mg L^{-1} and at $>25-50$, $>210-300$, and
377 500 mg kg^{-1} . The lowest concentrations (≤ 0.1 mg L^{-1}) produced equal or greater effects
378 than higher concentrations.

379 Diammonium cerium (IV) nitrate ($\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$) had smaller effects at ≤ 0.1 mg L^{-1}
380 and similar effects at higher concentrations compared to CeO_2 . Cerium (III) nitrate
381 hexahydrate ($\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$) led to similar or higher effects at low doses ($\leq 0.1-1$ mg L^{-1}),
382 but there were indications toward negative effects at concentrations $>5-10$ mg L^{-1} . This was
383 also the case for cerium (III) chloride (CeCl_3) for similar significant positive effects up to 25
384 mg L^{-1} , followed by a trend toward negative effects at $>25-50$ and $\geq 125-160$ mg L^{-1} .
385 Compared to CeO_2 , $\text{Ce}(\text{NO}_3)_3$ had smaller positive effects at concentrations ≤ 0.1 mg L^{-1} ,
386 similar effects at concentrations $>0.1-10$ mg L^{-1} , and greater positive effects at
387 concentrations >10 mg L^{-1} (Figs. S18-S19). Then, the effect of $\text{Ce}(\text{NO}_3)_3$ became non-
388 significant or negative at higher concentrations. The observations were insufficient for other
389 molecular formulas for an insightful assessment of the concentration-response spectrum.
390 Furthermore, the number of studies for molecular formulas other than CeO_2 ~~is~~ was extremely
391 small for concentrations in mg kg^{-1} , and thus ~~not considered further~~ such formulas were not
392 analyzed further.

393 **3.4.5. Concentration ranges as a function of growing medium**

394 The effect of cerium (mg L^{-1}) had little differences between soil and solution growing
395 media (Supplementary Materials 2, Fig. S20). Soil application had no significant effect
396 at $>10-25$, $>25-50$, $\geq 1600-2000$, and $\geq 3000-4000 \text{ mg L}^{-1}$, concentrations at which application
397 to solution positively affected plants. Conversely, application of cerium to solution did not
398 significantly affect plants at 100 , $\geq 125-160$, 200 , $>210-300 \text{ mg L}^{-1}$, while these concentrations
399 had a positive effect in soil medium (Supplementary Materials 2, Fig. S20).

400 **3.4.6. Concentration ranges as a function of ontogenic stage treated**

401 This analysis revealed that at several concentration ranges within which seed treatment
402 had no significant effect ($>5-10$, $>10-25$, $>210-300$, 1000 , and $\geq 1600-2000 \text{ mg L}^{-1}$), treatment
403 at vegetative stages or at both seed and vegetative stages produced significant positive effects
404 (Supplementary Materials 2, Fig. S21). Conversely, at $>50-80$ and $\geq 125-160 \text{ mg L}^{-1}$ seed
405 treatment, but not treatment at vegetative stages, significantly positively affected plants
406 (Supplementary Materials 2, Fig. S21). For the observations in mg Kg^{-1} , the effects were
407 more variable and included both negative and positive effects for seed treatment
408 (Supplementary Materials 2, Fig. S22). Overall, seed treatment showed less significant effects;
409 however, the number of observations and studies for seed treatment are limited and such
410 results should be interpreted with caution.

411 **3.4.7. Concentration ranges as a function of plant trait**

412 The effect of different cerium concentration ranges was analyzed also as a function of
413 selected traits that are key to individual level fitness, namely photosynthetic pigments,
414 photosynthetic rate and stomatal conductance, plant biomass, and yields, some of which were
415 negatively affected in the overall analyses per plant trait (see section 3.3).

416 Chlorophyll *a* and chlorophyll *b*, ~~which were negatively affected in the overall analyses~~
417 ~~per trait~~, were significantly increased by concentrations >1-5 mg L⁻¹ and decreased by >50-80
418 and ≥125-160 mg L⁻¹ and ~~by~~ ≥320-421 mg K_gkg⁻¹; chlorophyll *b* was also decreased by 100
419 mg K_gkg⁻¹ (Supplementary Materials 2, Fig. S23). Total chlorophylls (*a+b*) were significantly
420 increased by concentrations >0.1-1, >10-25, and 100 mg L⁻¹ and ~~by~~ >25-50 and >210-300 mg
421 K_gkg⁻¹, with no negative effects occurring at any concentration range. No significant effect
422 was observed for carotenoids at the analyzed concentration ranges (Supplementary Materials
423 2, Fig. S23).

424 Photosynthetic rate was enhanced by concentrations >10-25 mg L⁻¹ and ~~by~~ >5-10, 100,
425 and 1000 mg K_gkg⁻¹, with no negative effects occurring at the partitioned concentration
426 ranges (Supplementary Materials 2, Fig. S23). Stomatal conductance was significantly
427 affected by >5-10 and 100 mg K_gkg⁻¹ only, effects that were positive (Supplementary
428 Materials 2, Fig. S23).

429 Plant biomass was increased by concentrations ≤0.1, >0.1-1, >1-5, and 100 mg L⁻¹ and
430 ~~by~~ 100 mg K_gkg⁻¹, whereas it was decreased by ≥125-160 and 500 mg L⁻¹ (Supplementary
431 Materials 2, Fig. S23). However, the only significant effect on yields was suppression by >50-
432 80 and ≥320-421 mg K_gkg⁻¹ (Supplementary Materials 2, Fig. S23).

433 3.4.8. Concentration ranges as a function of exposure duration

434 A common pattern observed in all the five intervals of low concentrations from ≤0.1 to
435 10 mg L⁻¹ (a 100-fold concentration range) is the common maximization of the positive effect
436 within three days of exposure (Supplementary Materials 2, Figs. S24-S25). This outcome was
437 followed by a decline in response over the course of exposure, but often maintained at

438 significantly positive levels for up to approximately 13 weeks, depending on the
439 concentrations (Supplementary Materials 2, Figs. S24-S25). No clear time-dependent pattern
440 was observed for concentrations $>10\text{-}100\text{ mg L}^{-1}$, where significant positive effects were
441 observed at different times depending on the concentration (Supplementary Materials 2, Figs.
442 S24-S25). Lack of a specific time-dependent pattern was also observed for concentrations
443 $\geq 125\text{ mg L}^{-1}$, where positive effects occurred early and/or late during the exposure, depending
444 on the cerium concentration (Supplementary Materials 2, Figs. S26-S27). Regarding analysis
445 of meta-data in $\text{mg K}_{\text{ekg}}^{-1}$ ($>5\text{-}1000\text{ mg K}_{\text{ekg}}^{-1}$), observations were considerably less
446 abundant and available only for $>7\text{-}210$ days. No specific time-dependent trend was revealed;
447 however, both low and high concentrations induced significant effects early and/or late in the
448 exposure, depending on the concentration range (Supplementary Materials 2, Figs. S28-S29).

449 3.5. Exposure duration

450 In accordance with the common time-dependent pattern of low concentrations of cerium
451 (see preceding section), cerium overall effect (regardless other factors) maximized within the
452 first 24 h of exposure, and then declined but remained at significant positive levels up to 60
453 days, and neutralized $>60\text{-}210$ days after exposure (Fig. 7).

454 No clear time-dependent pattern among cerium application routes was observed,
455 although treatment of seed had significant overall negative effects at $>1\text{-}3$ and >60 days of
456 exposure (Supplementary Materials 2, Fig. S30).

457 No clear time-dependent pattern was observed between soil and solution treatment either.
458 (Supplementary Materials 2, Fig. S31). However, treatment of plants grown in solution led to
459 more significant positive effects ~~that~~ than treatment of soil-grown plants. Specifically, cerium

460 application to soil-grown plants had no significant overall effect at >1-3 and >60-90 days.

461 Regarding the influence of ontogenic stage treated, when analyzed per the different
462 exposure duration intervals, cerium had fewer significant positive effects or more significant
463 negative effects when applied to seed only than when applied to vegetative growth stages
464 (Supplementary Materials 2, Fig. S32). The number of observations for application at both
465 seed and vegetative stages was limited in this analysis.

466 The time-dependent pattern was generally similar between nano-cerium and bulk cerium
467 (Supplementary Materials 2, Fig. S33).

468 **3.6. Other effects (sources of variation)**

469 Regarding cerium application routes, the overall effect of seed treatment was non-
470 significant, with the majority of values negative (Supplementary Materials 2, Fig. S34).
471 Foliage, root, and seed+foliage application produced a similar positive effect. Moreover, there
472 was no evidence that combined root and foliage application offers an improved effect
473 compared to foliage or root application individually (Supplementary Materials 2, Fig. S34).

474 As to the plant growing medium, application of cerium into soil substrate produced
475 a significant overall average effect of +12% (Supplementary Materials 2, Fig. S35). However,
476 the effect was significantly higher (19%) when cerium was applied into solution
477 (Supplementary Materials 2, Fig. S35).

478 Regarding the ontogenic stage treated, ~~seed treatment the~~ average overall effect of [of](#)
479 [seed treatment](#) was non-significant (Supplementary Materials 2, Fig. S36). There was also no
480 significant difference between the significant positive effects of cerium application at
481 vegetative growth stages or at both seed and vegetative growth stages; however, the number

482 of observations for the latter category was considerably small (Supplementary Materials 2,
483 Fig. S36).

484 **4. Discussion**

485 Across all studies, cerium application had an overall positive effect on a plethora of plant
486 orders, representative of over 161,000 species (based on data from www.britannica.com;
487 accessed 11 May 2022), regardless traits and other factors. This is further substantiated by the
488 many families, genera, and species significantly affected by cerium application. The finding
489 that cerium application had an overall positive effect on cereals, fruit trees, legumes,
490 medicinal plants, oilseed crops, pastures, vegetables, and wild herbs shows the potential of
491 cerium to widely affect numerous plants used as main food and dietary supplements of
492 humans and other animals as well as for the production of herbal extracts and
493 pharmaceuticals. Nevertheless, the effect of cerium depends on the type of plants, with a
494 smaller effect on vegetables and wild herbs. These suggest that vegetables and wild herbs
495 may be less responsive to cerium than cereals, fruit trees, and pastures; however, these results
496 should be interpreted with caution due to the considerably small number of studies for cereals,
497 fruit trees, and pastures. The effect of cerium did not differ among crops, shrubs, and trees or
498 between eudicots and monocots, indicating a more homogenous effect of cerium at higher
499 levels of plant functional groups.

500 Cerium overall enhanced chlorophyll fluorescence and gas exchange. Specifically, the
501 actual photosynthetic efficiency of PSII, the coefficient of photochemical quantum yield in
502 dark, the electron transport rate, the PSII effective quantum yield, and the maximal quantum

503 yield were overall increased, mechanisms that are tightly linked to diverse reaction processes
504 in photosynthesis (Moustakas et al., 2022; Peng et al., 2021). The enhancement of these traits
505 indicates increased efficiency of the PSII electron transfer chain, higher internal efficiency in
506 converting light energy, improved efficiency in capturing primary light energy when PSII is
507 partially closed, and thus, higher photosynthesis potential of plants under stress (Moustakas
508 et al., 2022; Peng et al., 2021). This is further supported by the overall increased
509 photosynthetic rate and its linked stomatal conductance that this meta-analysis revealed,
510 indicating higher CO₂ uptake by plants and increased photosynthetic rate. Hill reaction
511 reflects the O₂ evolution during the illumination-dependent steps in the process of
512 photosynthesis, which along with the ‘Mehler reaction’ can contribute to photoprotection in
513 photosynthesizing organisms (Shevela et al., 2012). The effect on Hill reaction activity may
514 also imply analogous effects on CO₂ assimilation, NADP reduction, and phosphorylation
515 inactivation during stress conditions. Cerium also increased the photophosphorylation rate, a
516 stress-indicating status, suggesting the possibility of enhanced needs of ion uptake and
517 management of ion export in stressed cells (Fork and Herbert, 1993). RuBisCO carboxylation
518 capacity is fundamental for improving photosynthesis and yield (Iñiguez et al., 2021), and
519 the overall increased RuBisCO carboxylation by cerium indicates that the enhancement of
520 photosynthesis by cerium is not only due to physiological driving mechanisms (e.g., stomatal
521 conductance) but also due to a biochemical mode of action of cerium. However, this meta-
522 analysis revealed no evidence that the overall enhanced photosynthetic rate is due to increased
523 chlorophylls. Conversely, chlorophyll *a*, chlorophyll *b*, and carotenoids were overall
524 decreased by cerium application, suggesting that cerium causes oxidative stress in plants. As

525 to carotenoids, lycopene in fruit was also decreased by cerium, which further suggests that
526 cerium can affect the nutraceutical value of plant products routinely used for enhancing
527 human health (Imran et al., 2020). Further partitioning the variance into different cerium
528 concentration ranges revealed that total chlorophylls were increased by various concentration
529 ranges from as ~~little-small~~ as $>0.1-1$ mg L⁻¹. Moreover, chlorophyll *a* and chlorophyll *b* were
530 increased by low concentrations ($>1-5$ mg L⁻¹) but decreased by higher concentrations (>50
531 mg L⁻¹). These findings suggest that cerium causes a biphasic-hormetic dose response, with
532 low concentrations increasing ~~chlorophylls~~ and higher concentrations decreasing
533 ~~chlorophylls~~. This hormetic pattern of photosynthetic pigments (and photosynthetic rate)
534 was found in numerous photosynthesizing organisms exposed to a wide array of pollutants
535 and other xenobiotics, reflecting an improved defense capacity against environmental
536 challenges (Agathokleous, 2021). Apart from the leaf level, this biphasic-hormetic pattern
537 was also revealed for total plant biomass, which was increased by concentrations $\leq 0.1-5$ and
538 100 mg L⁻¹ (and 100 mg ~~kg~~ kg⁻¹) and decreased by concentrations ≥ 125 mg L⁻¹. These
539 findings demonstrate the hormetic function of cerium as a xenobiotic inducing oxidative
540 stress, a hypothesis that is further supported by a different perspective. Specifically, the
541 cerium effect was commonly up to 50% relative to control, across all analyses, indicating that
542 it ~~commonly~~ is commonly rather modest. These findings further demonstrate that the positive
543 effect of cerium on plants is not due to a ‘fertilizer effect’. Instead, this effect is similar with
544 that induced by xenobiotics within the framework of hormesis, with a maximum low-dose
545 positive effect of typically 30-60%, which is constrained by the biological plasticity bounds
546 (Calabrese et al., 2019; Calabrese and Blain, 2009), even if Ce uptake and its levels in tissues

547 increase by approximately 620% as this meta-analysis revealed.

548 The mechanisms underlying the observed effects caused by cerium are similar to those
549 induced by various biotic and abiotic stressors, from viruses to pollutants (Awasthi, 2020;
550 Carvalho et al., 2020; Moustakas et al., 2022; Poschenrieder et al., 2013). Cerium also had
551 further multiple overall effects on different traits related to the defense system [and redox](#)
552 [homeostasis](#). It increased CAT, DHAR, GSH, GSH/GSSG, ROS, and SOD. These effects
553 further support the conclusion that cerium acts as a xenobiotic, with its positive effects
554 attributed to stimulation via adaptive responses activated by low doses of oxidative stress.
555 CAT is an antioxidant enzyme of profound importance in the mitigation of oxidative stress,
556 and its increase indicates an enhanced capacity to eliminate cellular H₂O₂, a ROS, to produce
557 O₂ and H₂O (Nandi et al., 2019). Therefore, [an increase of in](#) CAT indicates the existence of
558 oxidative stress. This is also the case of SOD, an enzyme catalyzing the O₂^{·-} into H₂O₂, and
559 providing a first-line defense against ROS-induced damage (Poschenrieder et al., 2013; Zhao
560 et al., 2021). In addition to these enhanced antioxidant enzymes (SOD and CAT), cerium
561 increased also non-enzymatic antioxidants. Specifically, it increased GSH, a thiol molecule
562 playing a central role in stress signaling and antioxidant defense system, which also alters the
563 GSH/GSSG redox state (Hasanuzzaman et al., 2017; Poschenrieder et al., 2013). Free thiols
564 were also enriched, indicating the overall involvement of thiols in enhancing stress tolerance
565 (Tausz et al., 2003; Zagorchev et al., 2013). [Thiol-based redox regulation is important for a](#)
566 [swift response of chloroplast metabolism to light intensity \(Cejudo et al., 2019\)](#). Similarly,
567 DHAR is important to couple the GSH and ascorbate pools with the metabolism of H₂O₂, and
568 is involved in plant defense, development, and growth (Ding et al., 2020; Hasanuzzaman et

569 al., 2017). GSH/GSSG ratio reflects homeostasis (redox state) and can serve as an indicator of
570 oxidative stress, which is often increased together with increased CAT, SOD, and GSH
571 (Hasanuzzaman et al., 2017). The GSH/GSSG redox pair plays a major role in controlling
572 redox signaling (Hasanuzzaman et al., 2017; Szalai et al., 2009). As such, increased cellular
573 GSH level and GSH/GSSG ratio are essential for maintaining plant health under oxidative
574 stress (Hasanuzzaman et al., 2017; Szalai et al., 2009). These increases in CAT, DHAR, GSH,
575 GSH/GSSG, ROS, and SOD suggest that the overall increase of ROS by cerium application
576 did not exceed the threshold level for adverse effects. [ROS and associated antioxidant](#)
577 [molecules act as signaling agents modulating cellular metabolism, in accordance to](#)
578 [endogenous and exogenous stimuli, and affect cellular redox homeostasis \(De Gara et al.,](#)
579 [2010\)](#). Polyphenol oxidase is also an antioxidant enzyme driving the conversion of phenols
580 into quinones, and is linked to detoxification and elimination of ROS (Taranto et al., 2017).
581 Their overall significant response to cerium revealed by the meta-analysis (including leaves
582 and roots) indicates their involvement in plant response to cerium-induced stress. A basal
583 level of ROS is beneficial for health and optimal growth, and a mild increase in ROS triggers
584 a hormetic defense response, followed by inhibitory effects at levels above specific thresholds
585 (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). Because excessive ROS
586 inhibit chlorophyll synthesis and accumulation (Moustakas et al., 2022; Ruban, 2015), it can
587 be postulated that decreased chlorophylls by higher doses of cerium stems, at least partly,
588 from excessive ROS. Since ETR should also be [restricted](#) below some levels to avoid ROS
589 accumulation (Moustakas et al., 2022), it can also be argued that ETR and ROS are involved
590 in the high-dose inhibition of chlorophylls, although the overall effect on non-photochemical

591 quenching was non-significant in the two studies that included it. The stressor mode of action
592 of cerium is further illustrated by the significant alteration of membrane permeability and
593 starch (in leaf and fruit) revealed by the meta-analysis. Starch metabolism plays a key role in
594 the plant response to stress, and its decrease has been shown in numerous plants under various
595 abiotic stresses (Thalmann and Santelia, 2017). Starch reserve remobilization is important to
596 make energy, sugars, and metabolites available to facilitate stress mitigation (Thalmann and
597 Santelia, 2017). Also, decreased membrane permeability, expected at low cerium doses, may
598 protect against increased ion leakage as the stress progresses, whereas high cerium doses
599 would increase it, thus changing the ion balance and promoting ion leakage in damaged
600 tissues (Filek et al., 2012; Mansour, 2013; Niu and Xiang, 2018). The significant stress-
601 related role of cerium is also extended to increased electrolyte leakage, Ca^{2+} , K^+ , K^+/Na^+ ,
602 which indicates that K^+ and Na^+ homeostasis plays a significant role in the response of plants
603 to cerium and that cerium further alters mineral (ion) balance. Increased electrolyte leakage is
604 usually linked to increased ROS, with potentially activated K^+ efflux, and can promote
605 programmed cell death under severe stress (Demidchik et al., 2014). However, under lower
606 doses of stress, K^+ efflux can stimulate catabolic processes and save metabolic energy that is
607 needed for the processes of damage repair and adaptation (Demidchik et al., 2014).
608 Furthermore, higher cytosolic K^+/Na^+ ratio is regarded an important mechanism for higher
609 tolerance to stress (Almeida et al., 2017). Overall, these mechanisms underlying the effects of
610 cerium on plants indicate the presence of oxidative stress and the existence of dual biological
611 responses with positive biological effects up to some stress level followed by adverse effects
612 (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). These mechanisms are

613 similar to those found for various air and soil contaminants, such as heavy metals and toxic
614 anions, ground-level ozone, pesticides, nanomaterials, and pharmaceuticals (Agathokleous et
615 al., 2019a, 2019b, 2018; Carvalho et al., 2020; Jalal et al., 2021; Moustakas et al., 2022;
616 Poschenrieder et al., 2013; Shahid et al., 2020).

617 This meta-analysis also revealed various alterations in essential and non-essential
618 elements as well as in the mineral (ion) balance in plants. The decreased C/N ratio may be
619 partly attributed to the increased allocation of C to C-based metabolites that increase under
620 cerium-induced stress. Coordination of the metabolism of C and N is essential for optimal
621 development and growth, and disrupted signaling driven by C/N balance may have further
622 implications within ecosystems, such as changing the interaction of plants with pests, the
623 quality of plant litter and its decomposition, and altering the ecosystem response to other
624 environmental conditions such as atmospheric CO₂ (Chen et al., 2015; Zheng, 2009). As to
625 essential elements, cerium treatment decreased the uptake of B and increased the uptake of Cu,
626 Fe, Mn, and Ni. It also decreased B, Ca, Fe, K, and Mo levels in tissues. The observation that
627 cerium overall increased the uptake of Fe while decreasing its levels in tissues may suggest its
628 key role in cerium stress as Fe homeostasis must remain under control in stressed plants.
629 Accumulation of Fe within cells can lead to toxicities, and its decreased levels due to cerium
630 treatment may indicate a mechanism to reduce potential Fe-induced toxicity and/or that more
631 Fe is used for photosynthesis and respiration electron-transport chains, to produce electron
632 transport chain components and/or enzyme cofactors (Connolly and Guerinot, 2002;
633 Connorton et al., 2017). The decrease of several essential elements (B, Ca, Fe, K, and Mo) in
634 tissues due to cerium indicates altered elemental homeostasis with unknown implications to

635 plant health in the long term. These alterations extend to non-essential elements too, as
636 cerium treatment decreased Cd and Se in tissues and increased Al uptake and its levels in
637 tissues, although for Al uptake ~~this~~ is weakly supported because it is based on only one
638 ~~independent~~ study (Trujillo-Reyes et al., 2013). Some of these elements typically do not have
639 beneficial effects on plants but widely induce phytotoxicities at high concentrations (Schmitt
640 et al., 2016; Watanabe, 2022). The mechanisms of the increased uptake by plants and their
641 levels in tissues are not understood; however, the possibility of their binding with cerium (e.g.,
642 attached on cerium particles) and subsequent release into plant tissues cannot be excluded.
643 The mechanisms of decreasing other non-essential elements in tissues are unknown,
644 warranting further studies.

645 ~~Unlike-While~~ Ce uptake and plant tissue levels ~~were that~~ increased ~~by~~ approximately 620%
646 due to cerium treatment, the average effect of cerium on other ~~chemical~~ elements ranged from
647 10% to 77%. However, these effects are significant and raise ecological and human health
648 concerns rising from the arbitrary application of cerium within the agricultural practice. ~~This~~
649 ~~is~~ because it is now shown that cerium extensively alters the chemical composition of plant
650 tissues decreasing several micronutrients that are important for human health while increasing
651 some heavy metals and decreasing others. Similar to the hormetic effects of cerium on plants
652 at ~~the~~ individual level, cerium changes mineral nutrient concentrations in a dose-dependent
653 fashion too (Ramírez-Olvera et al., 2018). Therefore, the applied concentration of cerium is ~~a~~
654 key ~~to-for~~ minimizing ecological and human health risks.

655 Besides the physiological and biochemical responses, this meta-analysis revealed ~~an~~
656 overall negative effect of cerium on root length and yields, which demonstrates ~~s~~ that cerium-

657 induced oxidative stress suppressed growth and reproduction traits that are critical to plant
658 fitness. The yield suppression occurred at concentrations $>50 \text{ mg K}_{\text{eg}}\text{g}^{-1}$, in line with the
659 inhibition of chlorophylls *a* and *b* by concentrations $>50 \text{ mg K}_{\text{eg}}\text{g}^{-1}$, as shown by the meta-
660 analysis results. However, total plant biomass was decreased by concentrations $>125 \text{ mg L}^{-1}$.
661 Hence, there was no evidence that cerium enhances yields (often decreases them), and yields
662 appear to be more sensitive than plant biomass. These findings indicate that cerium pollution
663 can cause adverse effects to vegetation. Importantly, concentrations that were revealed here to
664 cause various adverse effects on plants widely occur in the environment and specifically in
665 agroecosystems, indicating the potentially hazardous nature of cerium (Moreira et al., 2019;
666 Wiseman et al., 2016). However, numerous factors affect the REE bioavailability to plants
667 including soil physicochemical traits (cation exchange capacity, humic acid, metal oxides,
668 organic and inorganic ligands, pH, redox potential), REE valence, REEs interacting with
669 compounds, Casparian strip in plant root exudates (organic acids), and rhizospheric microbes
670 (Liang et al., 2005; Tao et al., 2022). Thus, the real outcomes can be hardly predicted based
671 on the ‘dose’ only, and new studies that incorporate such factors in addition to the ‘dose’
672 component are needed.

673 Given that fitness critical traits (photosynthesis rate, photosynthetic pigments, and plant
674 biomass) were enhanced by cerium concentrations as small as $\leq 0.1\text{-}25 \text{ mg L}^{-1}$ (or $>5\text{-}100 \text{ mg}$
675 $\text{K}_{\text{eg}}\text{g}^{-1}$), depending on the trait, new studies should focus the shift to lower concentrations in
676 the range of $\leq 0.1\text{-}25 \text{ mg L}^{-1}$ (or $>5\text{-}100 \text{ mg K}_{\text{eg}}\text{g}^{-1}$). This is especially important since the
677 number of observations of yield response was extremely limited at concentrations $\leq 25 \text{ mg L}^{-1}$
678 (and studies typically lacking a proper ‘dose-response’ component), which underlines that the

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679 notion that the higher dose is always the best for enhancing yields is invalid. These results can
680 provide the basis to highly reduce the load of cerium into the environment, which can be
681 further promoted by turning into nano-cerium as this meta-analysis showed it is equally or
682 even more effective than its bulk counterpart. Cerium-carrying nanoparticles can have
683 positive effects on humans too (Li et al., 2016), and thus nano-cerium effects deserve more
684 attention.

685 Making a further step, this meta-analysis provides insightful information regarding the
686 role of cerium molecular formula within a concentration-response spectrum. Based on this
687 information, molecular formulas with lower potency for toxic effects on organisms but with
688 adequate positive effects (e.g., CeO₂) can be selected over more potentially toxic formulas
689 (e.g., CeCl₃, Ce(NO₃)₃·6H₂O, Ce(NO₃)₃). However, there is a gap of knowledge about the
690 effect of several molecular formulas of cerium within the full concentration-response
691 continuum.

692 More research is also needed into combinations of seed treatment and application of
693 cerium at vegetative stages to potentially maximize the positive effect of cerium by
694 appropriately treating seeds under controlled conditions and reducing the load on the field.
695 Besides, the results of meta-analysis call for cost-benefit evaluations to conclude whether
696 cerium should be actively applied ~~within-in~~ agriculture, considering the potentially limited
697 positive effects and the large uncertainties about long-term environmental implications of this
698 agricultural practice.

699 5. Conclusion

700 This meta-analysis revealed major physiological mechanisms underlying the response of
701 plants to exogenous application of cerium. It is demonstrated that cerium application leads to
702 up to ~~≈approximately~~ 620% increase in Ce uptake and its levels in tissues, on average,
703 offering various positive effects of commonly up to ~~≈approximately~~ 60% relative to control.
704 At concentrations as low as ≤ 0.1 to 25 mg L^{-1} cerium commonly enhances chlorophylls, g_s , A ,
705 and plant biomass; however, at concentrations $> 50 \text{ mg L}^{-1}$ cerium causes various negative
706 effects on plants at trait-specific concentrations. This hormetic pattern is driven by the
707 oxidative stress mode of action of cerium, increasing ROS and their tightly linked antioxidant
708 enzymes and non-enzymatic antioxidants.

709 Cerium further alters the redox signaling and mineral (ion) balance, including changes in
710 K^+ and Na^+ homeostasis. Various chlorophyll fluorescence traits can be improved by cerium,
711 enhancing photosynthetic efficiency and quantum yield of PSII, while the increase in A is also
712 linked to biochemical drivers, namely Hill reaction and RuBisCO carboxylation. However,
713 the potential of cerium application to benefit plant yields remains blurred due to lack of data
714 for low concentrations of cerium and negative effects at concentrations $> 50 \text{ mg kg}^{-1}$.

715 Cerium changes the uptake and level in tissues of several micro- and macro-nutrients,
716 including heavy metals that can pose risks to ingesting organisms. As cerium can decrease the
717 levels of several micronutrients, its arbitrary application in agriculture further suggests that
718 cerium pollution may have further implications for disease risk.

719 To reduce ecological and human health risks associated to cerium pollution, a shift is
720 needed from very high concentrations of cerium to considerably small concentrations (≤ 0.1 to

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721 25 mg L⁻¹), often a 1000-fold or higher decrease. ~~Finally,~~†This study also offers further
722 ~~further~~ technical information about the application of cerium that can help to maximize
723 cerium positive effects while minimizing its load in the environment and its associated risks.

724

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728

729 **Conflict of Interest** E.A. is the Managing Editor of the Virtual Special Issue in which this
730 article is published; however, he was not involved in the peer-review process of this article.

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731 The authors declare that they have no conflict of interest.

732

733 **Author contributions** E.A. conceived the idea, and all authors participated in the study
734 design. E.A. had a leading role and supervised the production of the manuscript. B.Z., C.G.,
735 and J.X. surveyed literature, extracted data, and created the data bases with inputs from E.A.,
736 C.J.S., and Z.F. B.Z. analyzed data and created display elements with inputs from G.C., J.X.,
737 E.A., and Z.F. E.A. drafted the paper, and all coauthors reviewed the draft and contributed
738 intellectual input. All authors approved the final version of manuscript for publication.

739

740 **Supplementary Materials (for online publication only)**

Filename	Description
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- Supplementary Materials 1 Display elements illustrating the keyword combination (Fig. S1), the procedure of literature survey and selection (Fig. S2), description of plants considered in the meta-analysis (Table S1), as well as the complete list of references finally included in the meta-analysis database (Table S2).
- Supplementary Materials 2 Figures reporting effect sizes of additional results of further meta-analyses as well as supplementary figures with calculated arithmetic per cent for aiding interpretation by readers (Figs. S1-S36).

741

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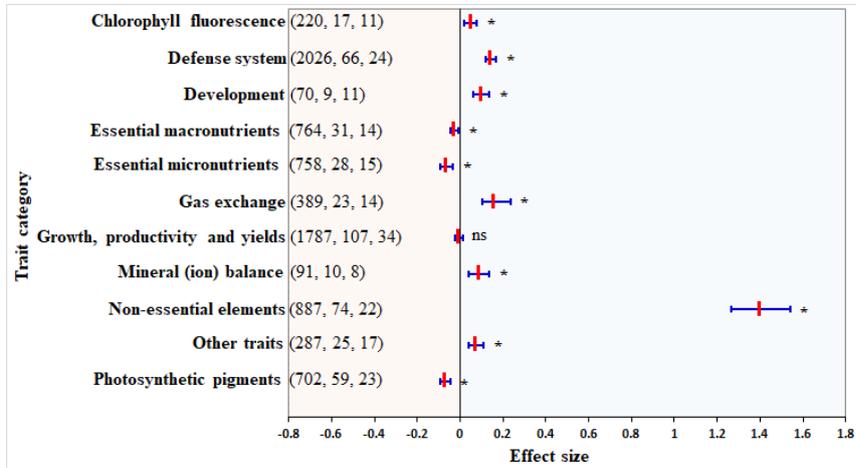
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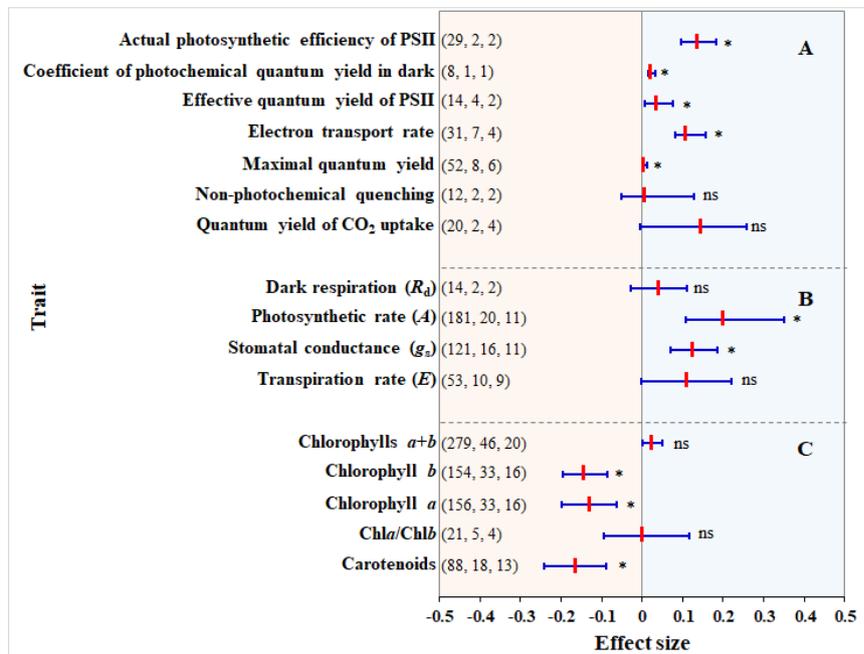
1007 **Figures**



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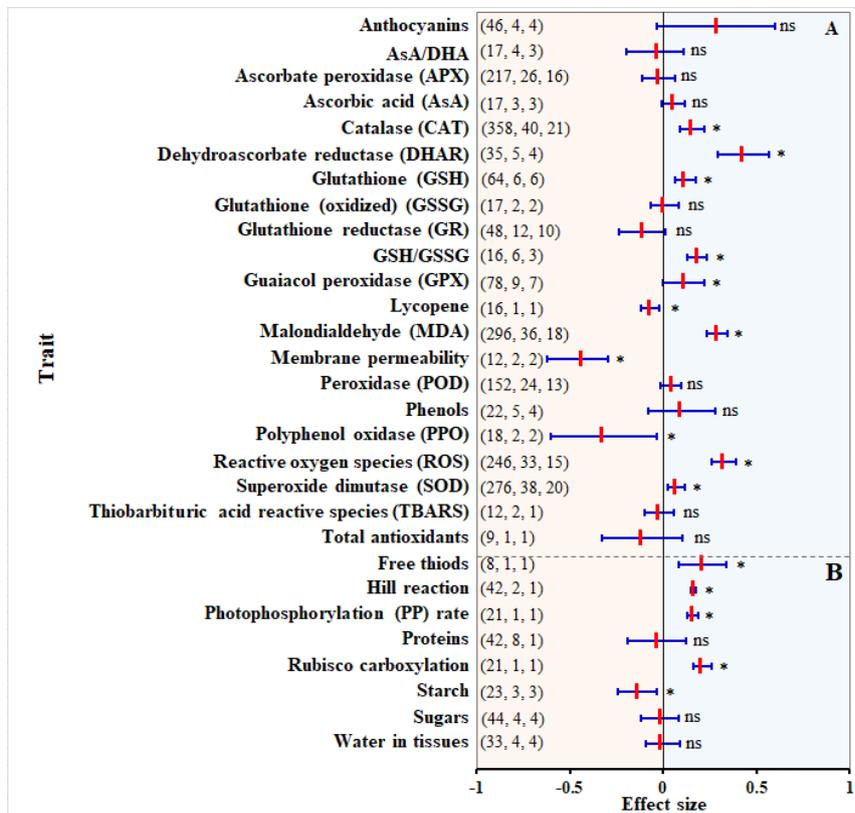
Fig. 1. Effect of cerium on different categories of plant traits. Symbols- (vertical red segments) indicate the mean natural log response ratio (rr)-of cerium application relative to control group (zero cerium dose), while the horizontal bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). Asterisk (-*) next to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect. The three -numbers in parentheses indicate the number of observations -observations number-(sample size), studies number- and species number-respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S8).

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Fig. 2. Effect of cerium on different photosynthesis-related traits. The traits represent chlorophyll fluorescence (A), gas exchange (B), and photosynthetic pigments (C). Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S9).

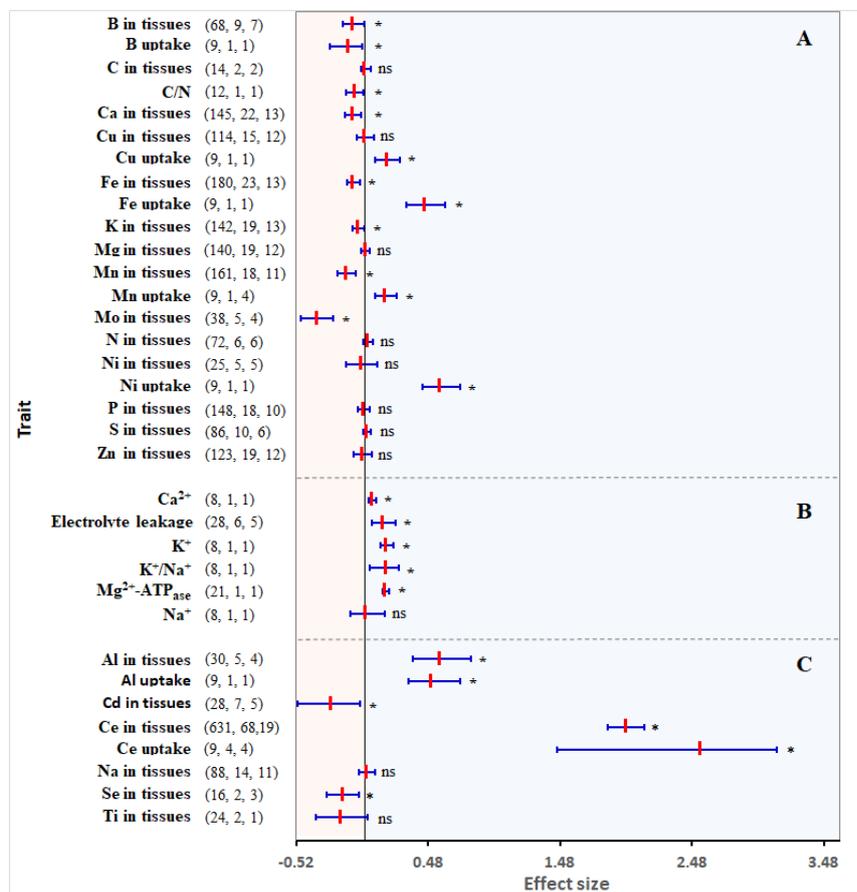


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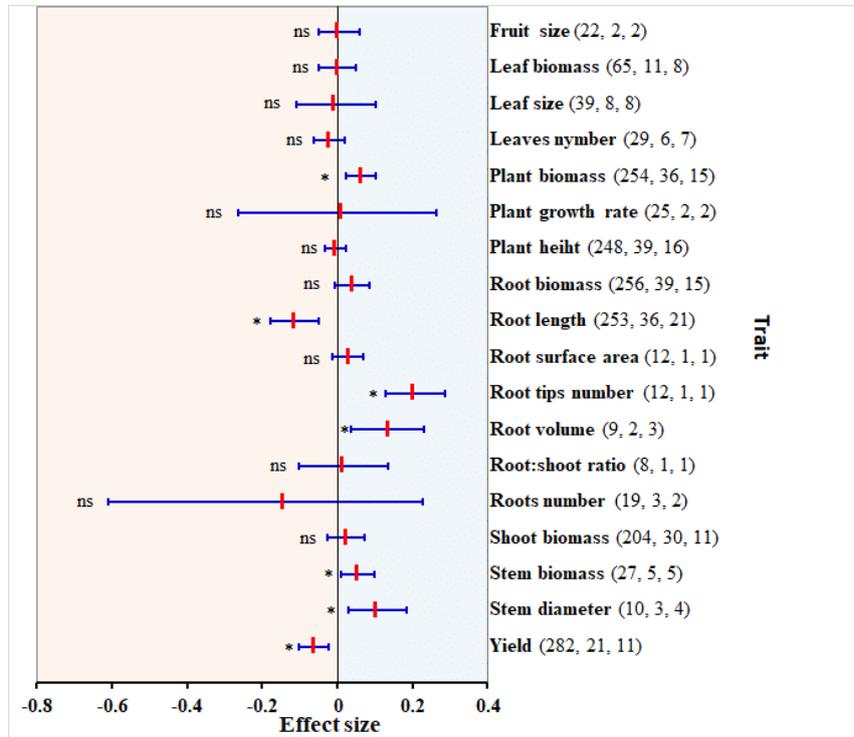
1045 **Fig. 3.** Effect of cerium on biochemical traits. The traits represent defense system (A) and other stress-
 1046 related biochemical traits (B). Symbols indicate the mean natural log response ratio of cerium
 1047 application relative to control group (zero cerium dose), while the bars around the mean value represent
 1048 the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant
 1049 cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect.

1050 The numbers in parentheses indicate the observations number (sample size), studies number, and
 1051 species number respectively (from left to right). The corresponding plot indicating percent difference
 1052 from the control is provided in Supplementary Materials 2 (Fig. S10).

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 1055 **Fig. 4.** Effect of cerium on elemental traits. The traits represent micro- and macro-nutrients essential
 1056 for plant growth (A), mineral (ion) balance (B), and non-essential elements (C). Symbols indicate the
 1057 mean natural log response ratio of cerium application relative to the control group (zero cerium dose),
 1058 while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next
 1059 to CI bars shows a statistically significant cerium effect relative to control group, whereas “ns” shows a
 1060 statistically non-significant effect. The numbers in parentheses indicate the observations number
 1061 (sample size), studies number, and species number respectively (from left to right). The corresponding
 1062 plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S11).
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1067 **Fig. 5.** Effect of cerium on different traits related to growth, productivity, and yields. Symbols indicate
 1068 the mean natural log response ratio of cerium application relative to control group (zero cerium dose),
 1069 while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next
 1070 to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns”
 1071 shows a statistically non- significant effect. The numbers in parentheses indicate the observations
 1072 number (sample size), studies number, and species number respectively (from left to right). The
 1073 corresponding plot indicating percent difference from the control is provided in Supplementary
 1074 Materials 2 (Fig. S12).

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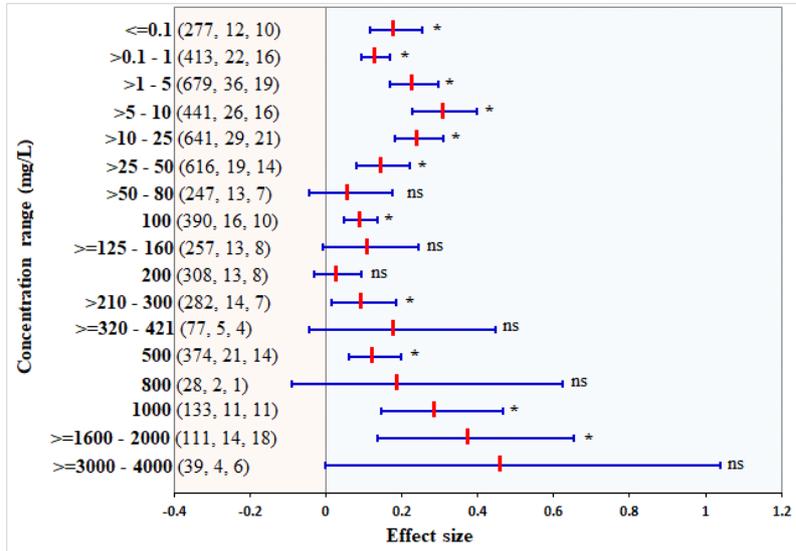
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1085 **Fig. 6.** Overall effect of cerium on plants (all traits pooled) as a function of different concentration
 1086 ranges. Symbols indicate the mean natural log response ratio of cerium application relative to the
 1087 control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95%
 1088 confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to
 1089 control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses
 1090 indicate the observations number (sample size), studies number, and species number respectively (from
 1091 left to right). The corresponding plot indicating percent difference from the control is provided in
 1092 Supplementary Materials 2 (Fig. S13). The effect of different concentrations is further partitioned to
 1093 different sources of variation (see sections 3.4.2-3.4.8).

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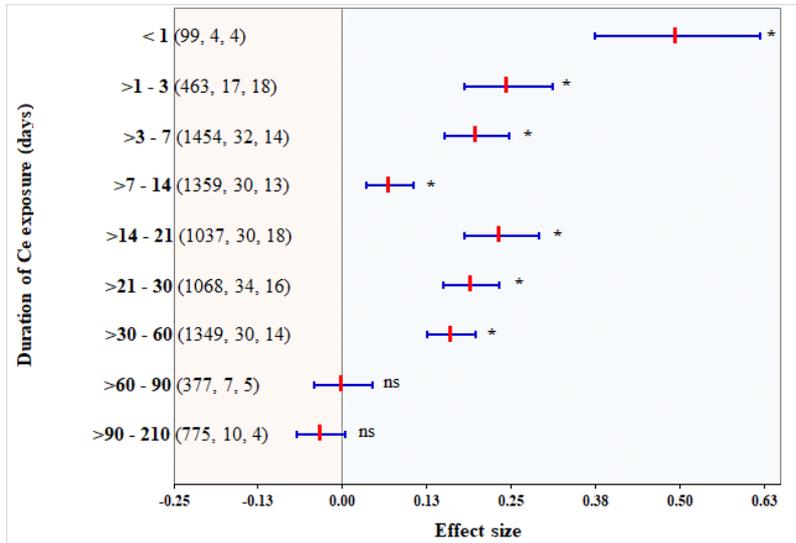
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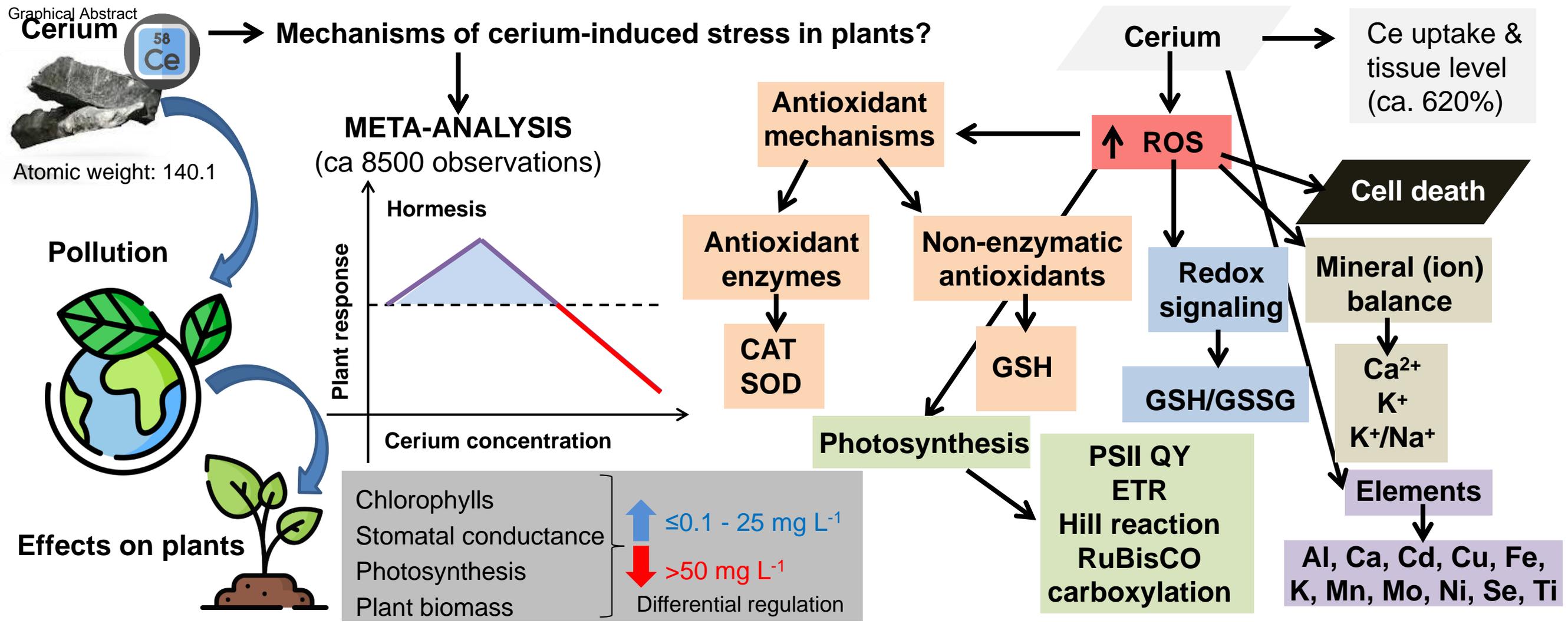
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 1102 **Fig. 7.** Overall effect of cerium on plants (all traits pooled) as a function of exposure duration. Symbols
 1103 indicate the mean natural log response ratio of cerium application relative to the control group (zero
 1104 cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence
 1105 intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group,
 1106 whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the
 1107 observations number (sample size), studies number, and species number respectively (from left to
 1108 right). The effect of different exposure durations is further partitioned to different sources of variation
 1109 (see section 3.5).



Highlights

- Effects of cerium exposure on plants were identified through meta-analysis
- Cerium induces ROS and causes stress with benefits or toxicities depending on dose
- Both antioxidant enzymes and non-enzymatic antioxidants are induced by cerium
- Cerium alters redox signaling, ion homeostasis, and plant nutrient dynamics
- Chlorophylls, photosynthesis, and biomass decrease or increase depending on dose

1 **1. Introduction**

2 Rare earth elements (REEs) have been extensively introduced into the environment in the
3 last decades, due to their wide use in agriculture, technology (e.g., electronics), and
4 medicine (Li et al., 2016; Migaszewski and Galuszka, 2015; Srikant et al., 2021). China,
5 the major producer of REEs worldwide, mined 140,000 tons in 2020. Another 24,700 tons
6 were produced by Australia (17,000), India (3000), Russia (2700), Brazil (1000), and
7 Vietnam (1000) (Tao et al., 2022). REE contents in the soils of mining and non-mining
8 areas in different countries were reported to range from 18 to 27,550 mg kg⁻¹ (Mihajlovic et
9 al., 2019; Tao et al., 2022). In sediment samples from different countries, values of relative
10 REE abundance were also reported to range from 11 to 3,041 mg kg⁻¹ (Tao et al., 2022).
11 Hence, the levels of REEs in soils and sediments display a high spatial variability and reach
12 relatively high values. This raises ecotoxicological concerns in recognition of documented
13 effects of REEs on animals and other organisms as well as potential links to human
14 disorders and diseases, especially in areas with elevated REE pollution (González et al.,
15 2015; Pagano et al., 2015; Tao et al., 2022).

16 Cerium is the 25th most abundant element in the Earth's crust (62 mg kg⁻¹), surpassing
17 elements like Cu (60 mg kg⁻¹) and Pb (13 mg kg⁻¹) (Migaszewski and Galuszka, 2015; Tao et
18 al., 2022). It belongs to the most extensively applied REEs, leading to its widespread
19 accumulation in the environment (Liang et al., 2005). The long and extensive application of
20 REE microfertilizers in the agricultural practice, in China, considerably enhanced the yields
21 and qualitative value of many crops (Migaszewski and Galuszka, 2015). However, cerium
22 also has a distinct property, that is, its Ce³⁺ form is separated from other trivalent REEs due to

23 its oxidation to Ce^{4+} in aqueous environments with somewhat increased pH or redox potential
24 (Eh) (Migaszewski and Galuszka, 2015). The reverse conversion from Ce^{4+} to Ce^{3+} , due to
25 valence change and electron addition, also occurs in organisms (Farias, 2018). Such chemical
26 transformations suggest the possibility for unpredicted effects of cerium on non-target plants
27 and other organisms. In recent years, nano-forms of cerium have also received increased
28 interest, not only for improving plant health (Hu et al., 2020; Rodrigues et al., 2021; Sharifan
29 et al., 2020) but also for medical purposes (e.g., cerium oxide nanoparticles) because of their
30 antimicrobial activity, high oxygen buffering and free radical-scavenging potential, among
31 other properties (Farias, 2018; Jakupec et al., 2005; Li et al., 2016). In many cases the activity
32 of nano-forms of cerium is similar to that of two key antioxidant enzymes, namely, catalase
33 (CAT) and superoxide dismutase (SOD), thus enhancing pro-oxidant activity, although
34 adverse effects, such as on respiratory tract, have also been reported (Li et al., 2016). Because
35 of the relatively high natural abundance of cerium and its increased anthropogenic emissions
36 into the environment, there is a need to better comprehend its effects on plants and other
37 organisms.

38 A literature survey with keywords ‘cerium’, ‘plant’, and ‘review’ (PubMed; 9 July, 2022)
39 revealed that no comprehensive review focusing on the overall mechanisms underlying
40 cerium effects on plants has been published. Nevertheless, the increasing interest in nano-
41 cerium led to some reviews on the effects of cerium oxide (CeO_2) nanoparticles on plants.
42 These suggested suppression of root biomass but enhancement of shoot biomass in many
43 plants (Lizzi et al., 2017). These reviews also suggest decreased photosynthetic pigments and
44 enhanced gas exchange related to photosynthesis, as well as modified yields and nutritional

45 quality of edible plant products (Lizzi et al., 2017; Prakash et al., 2021). However, the effects
46 varied among studies and plant growth conditions, indicating the degree to which the
47 mechanistic understanding remains incomplete (Lizzi et al., 2017; Prakash et al., 2021).

48 Some plant species can (hyper)accumulate REEs (Tao et al., 2022). However,
49 hyperaccumulators represent a tiny fraction of ‘elite’ species, e.g., only approximately 0.2%
50 of the currently known vascular plant species have been identified as hyperaccumulators of
51 metals (Calabrese and Agathokleous, 2021). For ‘normal’, non-(hyper)accumulator plant
52 species, the REE contents are, generally, considerably low; however, with considerable
53 variation amongst spermatophytes (Tao et al., 2022). For example, REE contents in
54 spermatophytes can range from 0.028 to 386 mg kg⁻¹ depending on plant species and tissues
55 (Tao et al., 2022). Nevertheless, such REEs still enter the food chain, undergo
56 bioaccumulation/biomagnification, and potentially affect ingesting organisms (Adeel et al.,
57 2019). Importantly, REEs, including lanthanum (La) and cerium (Ce), have also been
58 measured in considerable levels in human blood, hair, and sperm (Li et al., 2013; Marzec-
59 Wróblewska et al., 2015; McDonald et al., 2017). These observations further indicate the
60 widespread presence of REEs, facilitated by trophic transfer, where plants act as a major
61 primary entrance to the trophic chain. Therefore, it is profoundly important to understand
62 cerium effects on plants, not only for revealing the underlying plant mechanisms but also for
63 understanding how plants may drive risks to the health of herbivores.

64 Despite the widespread application of REEs in agriculture to increase crop productivity,
65 there is lack of systematic assessments on positive versus negative effects of REEs on living
66 organisms, even though some literature reviews highlight the occurrence of hormesis

67 (Agathokleous et al., 2019c; Pagano, 2016; Tommasi et al., 2021, 2022). Such an evaluation
68 can be facilitated by the use of meta-analytic tools that permit summarizing large amounts of
69 data. Meta-analysis is an important statistical tool that can give answers to questions that
70 cannot be answered by traditional narrative literature reviews. It increases the number of
71 observations, while accounting for study-specific variance, and enhances the statistical power.
72 Meta-analysis also improves the estimated effect size of experimental treatments, and can be
73 utilized to extract quantitative conclusions from an abundant scientific literature. It removes
74 reviewer bias due to subjective –at least to some degree– review, identifies general trends and
75 patterns, and reduces data processing errors, thus advancing theories and scientific
76 understanding. To date, there has been no meta-analysis on the effect of cerium or other REEs
77 on any organisms (Web of Science; keywords: “cerium” or “rare earth” and meta-analysis (all
78 fields); last update on 28 April 2022), although some regular reviews have examined the
79 effects of REEs on plants and other organisms (Agathokleous et al., 2019c; Cassee et al.,
80 2011; Tao et al., 2022; Tommasi et al., 2021, 2022).

81 This study aimed at identifying general impacts of cerium on plants (regardless species)
82 after collating a meta-database including approximately 8,500 entries (control-treatment
83 observations). To further partition sources of variance, the effect of cerium was examined for
84 different functional groups, crop types, orders, families, genera, and species of plants, plant
85 ontogenic stages subjected to cerium (seed, vegetative stages, or both), application route
86 (seed, foliage, root, or combinations of them), and growing media (soil or solution). This
87 study also aimed at identifying concentrations that generally produce significant positive
88 effects or toxicities across a spectrum of concentration-response ranges and exposure duration

89 intervals within the context of hormesis. This can provide a cost-benefit information platform
90 to reduce the inputs of cerium into the environment and optimize the benefits from cerium
91 application. It was of further interest to examine whether the effect of different concentration
92 ranges varies with key plant traits, plant ontogenic stage treated, cerium particle size (nano or
93 bulk), cerium molecular formula, exposure duration, growing medium, and application route.
94 Finally, it was of similar interest to evaluate whether application route, growing medium,
95 cerium form, and treated plant ontogenic stage modify the effect of cerium at different
96 exposure duration intervals. This meta-analysis reveals the integrated mechanisms by which
97 cerium affects plants, advancing the scientific understanding. It also provides a pathway to
98 address the issue of cerium toxicities and risks in the environment, and offers a novel
99 perspective to tackle this issue at a global scale.

100 **2. Materials and methods**

101 **2.1 Literature screening**

102 Literature screening was conducted in the Web of Science
103 (<http://apps.webofknowledge.com>), and covered the entire period with available publications;
104 the last update was conducted on 23 December, 2020. The combination of keywords (method:
105 Topic) included (cerium) AND (angiosperm OR bryophyte OR cutting OR grass OR
106 gymnosperm OR forest OR hedge OR herb OR herbaceous OR plant OR sapling OR seed OR
107 shrub OR tree OR vegetation OR woody) (Supplementary Materials 1, Fig S1). The search
108 revealed 2,275 publications in English language, and inclusion-exclusion criteria were then
109 applied (Supplementary Materials 1, Fig S2). First, publications were filtered to exclude non-

110 original research (e.g., books, editorials, reviews, and news) based on the type, title, and
111 abstract of publication. Second, articles reporting no application of cerium on plants were
112 excluded based on title and abstract, resulting in 446 publications proceeding to the next stage
113 which was duplicates checking. After excluding duplicates, 233 articles were examined in
114 detail for inclusion eligibility. At this stage, articles and observations were excluded if one or
115 more of the following conditions held true: (1) the experimental organisms were not higher
116 plants; (2) measures of dispersion of data around the mean (standard error (SE) or standard
117 deviation (SD)) were not reported, and their estimation was not permitted by the existing
118 information; and (3) the experimental treatments were not replicated. This screening resulted
119 in 146 articles that were finally selected for inclusion in the created database (Supporting
120 Information 1, Table S2). The screening of literature, selection of articles, extraction of data,
121 and database preparation were performed in parallel by three independent reviewers under the
122 lead author's supervision, without using workflow-management software.

123 **2.2 Data preparation**

124 The values of means of experimental conditions/groups, the values of given measure of
125 dispersion around the mean (SE or SD), sample size (N), and number of replicates for both
126 the control group (typically zero cerium added) and cerium treatments were gathered in a
127 database. Qualitative information was also collected and recorded in the database in order to
128 study sources of variation (see next section). Data presented in the text or in tables of the
129 reviewed articles were extracted directly. Data that were presented only in graphs were mined
130 with GetData Graph Digitizer v. 2.26 (<http://getdata-graph-digitizer.com>), with an accuracy of
131 $\pm 1\%$ compared to the actual values (Xie et al., 2014). Multiple observations reported in a

132 single article/study were considered to come from independent studies if concerning different
133 genotypes, cultivars, species, cerium concentrations, application techniques, or measurement
134 periods (Feng et al., 2010; Wittig et al., 2009). Therefore, all relevant data from studies
135 reporting both stimulatory and inhibitory effects were included in the database and meta-
136 analysis, regardless of the direction of the effect. Regarding dependent observations in studies
137 reporting traits with multiple treatment data and a common control, the mean values of
138 treatment or control groups were used, according to Lajeunesse (2016). Moreover, if different
139 levels of a stressor were applied to plants in a study, the average value was calculated. The
140 information of plants considered in the meta-analysis is provided in Supplementary Materials
141 1 (Table S1).

142 **2.3 Sources of variation**

143 To clarify variation in cerium effects and reduce potential confounding of factors other
144 than cerium treatment with uneven distribution across datasets, a plethora of sources of
145 variation were considered. These included functional groups (eudicots or monocots and crops,
146 shrubs, or trees), crop types (cereals, fruit trees, legumes, medicinal, oilseed crops, pasture,
147 vegetable, and wild herbs), orders, families, genera, and species of plants with eligible (see
148 previous section) and sufficient number (see next section) of entries. Furthermore, variation
149 was partitioned into plant traits, plant ontogenic stages subjected to cerium (seed, vegetative
150 stages, or both), cerium concentration ranges and treatment duration, cerium particle size
151 (nano or bulk), cerium molecular form, application route (seed, foliage, root, or combinations
152 of them), and growing medium (soil or solution). In plant ontogenic stages, seed represents
153 cerium application to germinating or non-germinated seeds whereas vegetative stage

154 represents cerium application to plants at any stage after completion of germination.
155 Regarding the effect of cerium concentration, the majority of studies reported concentrations
156 in mg L⁻¹. Therefore, wherever they could be converted accurately with the reported
157 information, the units were changed into mg L⁻¹ for harmonization. For a considerable
158 number of entries (about 2700), the concentration unit was mg kg⁻¹. Hence, entries of the two
159 units were analyzed separately. To cover the entire continuum of dose-response relationship
160 in order not to preclude the identification of both subtoxic and toxic effects widely occurring
161 in biphasic dose responses, arbitrary concentration ranges were created based on the
162 abundance of entries to provide ranges with logical arrangement of spacing. Given the
163 abundant literature with considerably high number of entries, 17 and 15 segments were
164 created ranging from ≤0.1 mg L⁻¹ to 4,000 mg L⁻¹ and from >1 mg kg⁻¹ to 2,000 mg kg⁻¹, thus
165 permitting the evaluation of potentially antithetic effects between low and high
166 concentrations. Exogenously applied chemicals exhibit important variation in their effects
167 depending on the treatment period (Agathokleous et al., 2021). Hence, various arbitrary
168 segments of treatment duration were created. Specifically, 11 segments were created, ranging
169 from few hours (<1 day) to 210 days, in order to account for homeostatic controls as well as
170 long-term effects.

171 **2.4 Meta-analysis**

172 Natural log response ratio (rrX) was used to estimate the effect size of cerium as

173
$$rr = \ln\left(\frac{X_t}{X_c}\right)$$

174 where rr is the natural logarithm (\ln) of the average of cerium-treated group (X_t) divided by
175 the average of the control group (X_c) (Feng et al., 2010; Hedges et al., 1999; Wittig et al.,
176 2009). The control group is theoretically cerium-free, e.g., a water-based solution with no
177 added cerium. An $rr=0$ suggests that the cerium-treated group does not differ from the control
178 group. An $rr>0$ suggests a positive effect, whereas an $rr<0$ suggests a negative effect of
179 cerium treatment compared to control condition. The positive or negative rr values are
180 interpreted as biologically positive or negative effects, depending on plant trait under
181 consideration (see results and discussion). Whether an effect is statistically significant or not
182 depends on the variance around the mean, and is determined by the statistical model of meta-
183 analysis.

184 To pool effect sizes and conduct analyses, a random-effects model was applied, based on
185 the hypothesis that inter-group differences (among studies and groups of comparisons) come
186 from sampling errors as well as from true random variation (Xie et al., 2014). To reduce the
187 uncertainty underlying the estimation, 64,999 bootstrap iterations (maximum number of
188 iterations permitted by the software) were applied to re-sample data and construct confidence
189 limits around the size of effect and effect size variance (Rosenberg et al., 2000). The
190 estimates of effect size were classified significant when zero (0) was outside the confidence
191 interval (CI) of 95% (Wittig et al., 2009). The total heterogeneity (Q_T) was partitioned to
192 within-group heterogeneity (Q_W) and between-group heterogeneity (Q_B) in order to compare
193 differences between and within categories. A randomized p value <0.05 derived from the
194 resampling technique indicates that ≥ 2 levels significantly differed between them. In order a
195 categorical level (group) to be included in the meta-analysis, it should be composed of ≥ 10

196 observations regardless the number of independent studies or of >5 observations obtained
197 from ≥ 3 independent studies (Feng et al., 2010; Wittig et al., 2009). The mean effect size and
198 the bootstrapped 95% CIs of each categorical level were calculated for each variable. The
199 meta-analysis was performed with MetaWin v. 2.1.3.4 (Sinauer Associates, inc., Sunderland,
200 MA, USA).

201 **3. Results**

202 **3.1 Plant taxonomic groups (order, family, genus, species)**

203 The pooled effect of cerium on different plant taxonomic groups was examined across all
204 studies with random-effects model, independently of other conditions; sources of variance are
205 analyzed in succeeding sections.

206 Cerium application had a significant positive effect on 17 orders of plants, representing many
207 thousands of species and covering a vast array of food crops as well as plants used for
208 domestic animal feed (Supplementary Materials 2, Fig. S1). The average effect was
209 commonly up to approximately 50% of the control, except for two orders, Apiales (81%) and
210 Dioscoreales (214%), which also had a greater variance and were composed of a relatively
211 small sample size (Supplementary Materials 2, Fig. S1). This increased effect of cerium on
212 Apiales and Dioscoreales (applied at 63-500 and 100-1000 mg kg⁻¹, respectively) was also
213 contributed by the high number of entries regarding Ce in plant tissues (22.2 and 54.5 % of all
214 entries, respectively), of which response is multi-fold greater (see also section 3.3).

215 Cerium also had a significant positive effect on 17 families and a negative effect on 1 family
216 (Supplementary Materials 2, Fig. S2). The negatively affected Liliaceae was comprised of

217 only 13 observations, 2 studies, and 1 species, and the effects included statistically significant
218 inhibitions of individual-level endpoints based on the original studies too. In these studies
219 either Ce^{3+} (2-50 mg L⁻¹) (Kotelnikova et al., 2019) or nano-cerium oxide (CeO_2 ; 250-1000
220 mg L⁻¹) (Andersen et al., 2016) was applied, but with more super-NOAEL (no-observed-
221 adverse-effect-level) concentrations, thus leading to an overall negative pooled effect.
222 Similarly to the effect on orders, the average effect on families was commonly up to
223 approximately 54% of the control, except for two families, Apiaceae (81%) and
224 Dioscoreaceae (214%), with enlarged effect and variance (Supplementary Materials 2, Fig.
225 S2).

226 Overall, 27 genera were positively affected, 3 genera were negatively affected, and 8 genera
227 were non-significantly affected by cerium application (Supplementary Materials 2, Fig. S3).
228 The average positive effect was commonly up to approximately 75% relative to control,
229 except for *Dioscorea* that exceeded 200% as aforementioned for its family and order
230 (Supplementary Materials 2, Fig. S3). The negative effect was below 20% (Supplementary
231 Materials 2, Fig. S3). Similarly to the aforementioned studies with negative effects on
232 Liliaceae family (Andersen et al., 2016; Kotelnikova et al., 2019), the negative effect on
233 *Nicotiana*, *Pisum*, and *Spirodela* genera stems from more decreases in elements and/or more
234 doses above NOAEL, with even biphasic dose responses observed, and includes significant
235 inhibition of growth too (Skiba et al., 2020; Skiba and Wolf, 2019; Song et al., 2018; Xu et
236 al., 2017). The overall numerically positive effect can also be regarded biologically positive
237 effect for the plants because the vast majority of plant traits covered represent traits of which
238 increase reflects a biologically positive outcome of the plants, such as increased pigments and

239 yields (see section 3.3). That is, the number of observations of traits of which increase can
240 lead to biologically negative effects (e.g., reactive chemical species) is considerably limited in
241 the overall analyses (see section 3.3).

242 Across all studies, cerium treatment positively affected 30 species, negatively affected 4
243 species, and had no significant effect on 11 species (Supplementary Materials 2, Fig. S4; see
244 Fig. S5 for an analysis per plant common name). It should also be noted that this represents an
245 overall effect, and the non-significant effect on 11 species does not imply absence of effect on
246 each one of these species. This is because the effect depends upon the traits studied (including
247 also the number of negatively affected versus the number of positively affected) and treatment
248 concentrations as shown in other meta-analyses too (Agathokleous et al., 2021). The negative
249 effect on the 4 species (*Allium cepa*, *Nicotiana tabacum*, *Pisum sativum*, *Spirodela*
250 *polyrrhiza*) is attributed to the reasons explained previously for families and genera, and was
251 below 20% relative to control except for *Allium cepa* that reached 45% (Supplementary
252 Materials 2, Fig. S4). The degree of average positive effect varied widely with species, but
253 was commonly up to $\approx 50\%$ except for *Capsicum annuum* (68%), *Coriandrum sativum* (55%),
254 *Cucumis sativus* (78%), *Dioscorea esculenta* (207%), *Lycopersicon esculentum* (184%), and
255 *Medicago sativa* (61%).

256 **3.2 Plant type groups**

257 Across studies, cerium had a significant positive effect on cereals (18%), fruit trees
258 (18%), legumes (22%), medicinal plants (23%), oilseed crops (10%), pastures (17%),
259 vegetables (10%), and wild herds (7%) (Supplementary Materials 2, Fig. S6). The effect of
260 cerium was smaller on vegetables and wild herbs than on cereals, legumes, medicinal plants,

261 and pasture.

262 A further grouping of plant functional types across studies revealed that cerium
263 positively affected plants regardless the functional group (Supplementary Materials 2, Fig.
264 S7). Specifically, a similar average effect was observed among crops (16%), shrubs (14%),
265 and trees (16%), as well as between eudicots (14%) and monocots (17%) (Supplementary
266 Materials 2, Fig. S7).

267 **3.3 Plant traits (mechanisms)**

268 **3.3.1. Trait groups**

269 Cerium significantly enhanced chlorophyll fluorescence (6%), defense system (15%),
270 development (11%), and gas exchange (17%) (Fig. 1; Supplementary Materials 2, Fig. S8). It
271 also positively affected mineral (ion) balance (10%) and increased non-essential elements
272 (305%), which were mainly comprised of cerium and heavy metals (Fig. 1). Conversely,
273 cerium application decreased essential micro- (7%) and macronutrients (4%) as well as
274 photosynthetic pigments (8%), whereas the overall effect on growth, productivity and yields
275 was insignificant (Fig. 1). Hereafter, the results are analyzed for different traits per trait
276 category.

277 **3.3.2. Photosynthesis-related traits**

278 Regarding chlorophyll fluorescence-related traits, cerium increased the actual
279 photosynthetic efficiency of PSII (14%), the coefficient of photochemical quantum yield in
280 dark (2%), the PSII effective quantum yield (4%), the electron transport rate (11%), and the
281 maximal quantum yield (1%) (Fig. 2A; Supplementary Materials 2, Fig. S9).

282 Gas exchange analysis revealed that photosynthetic rate (22%) and stomatal conductance

283 (13%) were also significantly increased by cerium (Fig. 2B).

284 Chlorophyll *a* (12%), chlorophyll *b* (13%), and carotenoids (12%) were significantly
285 decreased; however, total chlorophylls (*a+b*) and chlorophyll *a* to chlorophyll *b* ratio were not
286 significantly affected (Fig. 2C). It should be clarified that the total chlorophylls (above zero
287 but CI overlapping zero) consisted of nearly twice the number of observations, and this trait
288 represented a more robust group compared to the individual chlorophyll pigments.

289 3.3.3. Biochemical (stress-related) traits

290 Cerium affected the plant defense system in diverse ways (Fig. 3A). It increased CAT
291 (17%), dehydroascorbate reductase (DHAR; 54%), glutathione (GSH; 12%), reduced GSH to
292 oxidized glutathione ratio (GSH/GSSG; 20%), malondialdehyde (MDA; 33%), reactive
293 oxygen species (ROS; 38%), and SOD (7%) (Fig. 3A; Supplementary Materials 2, Fig. S10).
294 Conversely, it decreased lycopene (7%), membrane permeability (35%), and polyphenol
295 oxidase (28%) (Fig. 3A; Supplementary Materials 2, Fig. S10). Similarly, cerium decreased
296 starch (13%) but increased free thiols (24%), Hill reaction (18%), photophosphorylation rate
297 (17%), and RuBisCO carboxylation (23%) (Fig. 3B; Supplementary Materials 2, Fig. S10).

298 3.3.4. Elemental/mineral traits

299 Regarding essential elements, cerium decreased B uptake (13%) and its levels in tissues
300 (10%) and the ratio of carbon to nitrogen (C/N; 8%) (Fig. 4A; Supplementary Materials 2,
301 Fig. S11). It also decreased the levels of Ca (12%), Fe (11%), K (5%), and Mo (31%) in
302 tissues, but increased the uptake of Cu (19%), Fe (58%), Mn (20%), and Ni (76%), although
303 the latter increases are based on a considerably small number of observations (Fig. 4A).

304 As to non-essential elements, cerium application led to significantly decreased Cd (23%)

305 and Se (13%) levels in tissues and increased Ce (624% and 623%) and Al (67% and 77%)
306 uptake and their levels in tissues (Fig. 4C; Supplementary Materials 2, Fig. S11).

307 Cerium also altered mineral (ion) balance, with significant increases in Ca^{2+} (9%),
308 electrolyte leakage (15%), K^+ (20%), K^+/Na^+ (19%), and Mg^{2+} -ATP_{ase} (20%) (Fig. 4B;
309 Supplementary Materials 2, Fig. S11).

310 **3.3.5. Growth, productivity, and yields**

311 Cerium significantly increased the total plant biomass (7%), number of root tips (23%),
312 root volume (15%), stem biomass (6%), and stem diameter (11%), and decreased root length
313 (11%) and yields (6%) (Fig. 5; Supplementary Materials 2, Fig. S12). Traits that were overall
314 negatively affected by cerium are further analyzed by concentration ranges (see section 3.4.6).

315 **3.4. Applied cerium concentration**

316 **3.4.1. Overall concentration ranges**

317 As explained before, the majority of observations, specifically 5,313 observations,
318 concerned the concentration unit of mg L^{-1} , representing approximately 62% of the total
319 number of observations in the entire database. An additional 2,648 observations concerned the
320 concentration unit of mg kg^{-1} , that is approximately 31% of the total number of observations
321 in the entire database. Therefore, emphasis was placed on the analysis of data given in
322 concentration units of mg L^{-1} .

323 Across studies, cerium had either a positive or a non-significant effect on plants (Fig. 6).
324 Importantly, the significant positive effect occurred from concentrations as low as $\leq 0.1 \text{ mg L}^{-1}$
325 $^{-1}$, which was kept at similar levels up to 50 mg L^{-1} (%). The concentration of 100 mg L^{-1} also
326 had a positive effect similar to that of concentrations $\leq 0.1 \text{ mg L}^{-1}$ (Fig. 6). For concentrations

327 $\geq 125-800 \text{ mg L}^{-1}$, only concentrations $> 210-300 \text{ mg L}^{-1}$ and 500 mg L^{-1} had a positive effect.
328 Cerium concentrations of 1000 and $\geq 1600-2000 \text{ mg L}^{-1}$ also led to a positive effect. All these
329 effects were similar to that of concentrations $\leq 0.1 \text{ mg L}^{-1}$ (Fig. 6). Similar results were
330 revealed for the observations with cerium concentrations in mg kg^{-1} , with significant positive
331 effects of different ranges from as low as $> 1-5 \text{ mg kg}^{-1}$ to 1000 mg kg^{-1} and negative effect at
332 600 mg kg^{-1} (Supplementary Materials 2, Fig. S13).

333 **3.4.2. Concentration ranges as a function of application route**

334 The overall effect of cerium, regardless of other factors, showed no clear pattern of
335 variation due to the application route, with only few differences (Supplementary Materials 2,
336 Fig. S14-S15). For instance, root and foliage+root applications had a significant positive
337 effect at concentrations $> 0.1-1 \text{ mg L}^{-1}$, but foliage and seed applications had not. This
338 distinction was no longer present at concentrations $> 1-5 \text{ mg L}^{-1}$, where all application routes
339 led to a significant positive effect on plants. At concentrations $> 5-10 \text{ mg L}^{-1}$, foliage
340 application did not significantly affect, root and foliage+seed application positively affected,
341 and seed application negatively affected plants. At $> 10-25 \text{ mg L}^{-1}$, foliage and root application
342 positively affected and seed application negatively affected. The only significant effect
343 at $> 50-80 \text{ mg L}^{-1}$ was a positive influence of seed application. However, at 100 mg L^{-1} the
344 only significant effect was a positive influence of root application (Supplementary Materials
345 2, Fig. S14-S15). For concentrations $\geq 125-160 \text{ mg L}^{-1}$, foliage and seed applications but not
346 root application positively affected plants. Regarding concentrations from 200 to 421 mg L^{-1} ,
347 no specific application route had positive effects. Then, 1000, $\geq 1600-2000$, and $\geq 3000-4000$
348 mg L^{-1} significantly positively affected plants when applied to root (Supplementary Materials

349 2, Fig. S14-S15). For all the significant positive effects, the effects were similar among the
350 different concentration ranges. Since, the unit of mg kg^{-1} does not include foliage application,
351 data given in mg kg^{-1} were not considered worth of more detailed analysis.

352 **3.4.3. Concentration ranges as a function of cerium particle size**

353 The effect of cerium (mg L^{-1}) on plants differed between the nano-form and bulk cerium,
354 with half of the concentration ranges showing superiority of nano-cerium (Supplementary
355 Materials 2, Fig. S16). Specifically, nano-cerium had an increased effect at concentrations
356 $\leq 0.1, >1-5, >10-25, >25-50, 100,$ and $>210-300 \text{ mg L}^{-1}$ relative to bulk cerium
357 (Supplementary Materials 2, Fig. S16). Less clear was the difference for the analysis of the
358 effect of cerium concentrations in mg kg^{-1} (Supplementary Materials 2, Fig. S17). Specifically,
359 nano-cerium had a better effect at $>25-50 \text{ mg kg}^{-1}$ but bulk cerium had a significant positive
360 effect at $\geq 125-500 \text{ mg L}^{-1}$ when nano-cerium had either negative or non-significant effect
361 (Supplementary Materials 2, Fig. S17).

362 **3.4.4. Concentration ranges as a function of cerium molecular formula**

363 Approximately 10 molecular formulas of cerium were analyzed across different
364 concentrations ranges, depending on the availability of observations and sample size
365 (Supplementary Materials 2, Figs. S18-S19). However, the most extensively applied form is
366 cerium dioxide (CeO_2), which widely produced positive effects at various concentrations, e.g.,
367 at $\leq 0.1, >0.1-1, >5-10, >10-25, >25-50,$ and $>210-300 \text{ mg L}^{-1}$ and at $>25-50, >210-300,$ and
368 500 mg kg^{-1} . The lowest concentrations ($\leq 0.1 \text{ mg L}^{-1}$) produced equal or greater effects than
369 higher concentrations.

370 Diammonium cerium (IV) nitrate ($\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$) had smaller effects at $\leq 0.1 \text{ mg L}^{-1}$

371 and similar effects at higher concentrations compared to CeO₂. Cerium (III) nitrate
372 hexahydrate (Ce(NO₃)₃×₆H₂O) led to similar or higher effects at low doses (≤0.1-1 mg L⁻¹),
373 but there were indications toward negative effects at concentrations >5-10 mg L⁻¹. This was
374 also the case for cerium (III) chloride (CeCl₃) for similar significant positive effects up to 25
375 mg L⁻¹, followed by a trend toward negative effects at >25-50 and ≥125-160 mg L⁻¹.
376 Compared to CeO₂, Ce(NO₃)₃ had smaller positive effects at concentrations ≤0.1 mg L⁻¹,
377 similar effects at concentrations >0.1-10 mg L⁻¹, and greater positive effects at
378 concentrations >10 mg L⁻¹ (Figs. S18-S19). Then, the effect of Ce(NO₃)₃ became non-
379 significant or negative at higher concentrations. The observations were insufficient for other
380 molecular formulas for an insightful assessment of the concentration-response spectrum.
381 Furthermore, the number of studies for molecular formulas other than CeO₂ was extremely
382 small for concentrations in mg kg⁻¹, and thus such formulas were not analyzed further.

383 **3.4.5. Concentration ranges as a function of growing medium**

384 The effect of cerium (mg L⁻¹) had little differences between soil and solution growing
385 media (Supplementary Materials 2, Fig. S20). Soil application had no significant effect
386 at >10-25, >25-50, ≥1600-2000, and ≥3000-4000 mg L⁻¹, concentrations at which application
387 to solution positively affected plants. Conversely, application of cerium to solution did not
388 significantly affect plants at 100, ≥125-160, 200, >210-300 mg L⁻¹, while these concentrations
389 had a positive effect in soil medium (Supplementary Materials 2, Fig. S20).

390 **3.4.6. Concentration ranges as a function of ontogenic stage treated**

391 This analysis revealed that at several concentration ranges within which seed treatment
392 had no significant effect (>5-10, >10-25, >210-300, 1000, and ≥1600-2000 mg L⁻¹), treatment

393 at vegetative stages or at both seed and vegetative stages produced significant positive effects
394 (Supplementary Materials 2, Fig. S21). Conversely, at $>50-80$ and $\geq 125-160$ mg L⁻¹ seed
395 treatment, but not treatment at vegetative stages, significantly positively affected plants
396 (Supplementary Materials 2, Fig. S21). For the observations in mg kg⁻¹, the effects were more
397 variable and included both negative and positive effects for seed treatment (Supplementary
398 Materials 2, Fig. S22). Overall, seed treatment showed less significant effects; however, the
399 number of observations and studies for seed treatment are limited and such results should be
400 interpreted with caution.

401 **3.4.7. Concentration ranges as a function of plant trait**

402 The effect of different cerium concentration ranges was analyzed also as a function of
403 selected traits that are key to individual level fitness, namely photosynthetic pigments,
404 photosynthetic rate and stomatal conductance, plant biomass, and yields, some of which were
405 negatively affected in the overall analyses per plant trait (see section 3.3).

406 Chlorophyll *a* and chlorophyll *b* were significantly increased by concentrations $>1-5$ mg
407 L⁻¹ and decreased by $>50-80$ and $\geq 125-160$ mg L⁻¹ and $\geq 320-421$ mg kg⁻¹; chlorophyll *b* was
408 also decreased by 100 mg kg⁻¹ (Supplementary Materials 2, Fig. S23). Total chlorophylls (*a+b*)
409 were significantly increased by concentrations $>0.1-1$, $>10-25$, and 100 mg L⁻¹ and $>25-50$
410 and $>210-300$ mg kg⁻¹, with no negative effects occurring at any concentration range. No
411 significant effect was observed for carotenoids at the analyzed concentration ranges
412 (Supplementary Materials 2, Fig. S23).

413 Photosynthetic rate was enhanced by concentrations $>10-25$ mg L⁻¹ and $>5-10$, 100, and
414 1000 mg kg⁻¹, with no negative effects occurring at the partitioned concentration ranges

415 (Supplementary Materials 2, Fig. S23). Stomatal conductance was significantly affected
416 by >5-10 and 100 mg kg⁻¹ only, effects that were positive (Supplementary Materials 2, Fig.
417 S23).

418 Plant biomass was increased by concentrations ≤0.1, >0.1-1, >1-5, and 100 mg L⁻¹ and
419 100 mg kg⁻¹, whereas it was decreased by ≥125-160 and 500 mg L⁻¹ (Supplementary
420 Materials 2, Fig. S23). However, the only significant effect on yields was suppression by >50-
421 80 and ≥320-421 mg kg⁻¹ (Supplementary Materials 2, Fig. S23).

422 **3.4.8. Concentration ranges as a function of exposure duration**

423 A common pattern observed in all the five intervals of low concentrations from ≤0.1 to
424 10 mg L⁻¹ (a 100-fold concentration range) is the common maximization of the positive effect
425 within three days of exposure (Supplementary Materials 2, Figs. S24-S25). This outcome was
426 followed by a decline in response over the course of exposure, but often maintained at
427 significantly positive levels for up to approximately 13 weeks, depending on the
428 concentrations (Supplementary Materials 2, Figs. S24-S25). No clear time-dependent pattern
429 was observed for concentrations >10-100 mg L⁻¹, where significant positive effects were
430 observed at different times depending on the concentration (Supplementary Materials 2, Figs.
431 S24-S25). Lack of a specific time-dependent pattern was also observed for concentrations
432 ≥125 mg L⁻¹, where positive effects occurred early and/or late during the exposure, depending
433 on the cerium concentration (Supplementary Materials 2, Figs. S26-S27). Regarding analysis
434 of meta-data in mg kg⁻¹ (>5-1000 mg kg⁻¹), observations were considerably less abundant and
435 available only for >7-210 days. No specific time-dependent trend was revealed; however,
436 both low and high concentrations induced significant effects early and/or late in the exposure,

437 depending on the concentration range (Supplementary Materials 2, Figs. S28-S29).

438 **3.5. Exposure duration**

439 In accordance with the common time-dependent pattern of low concentrations of cerium
440 (see preceding section), cerium overall effect (regardless other factors) maximized within the
441 first 24 h of exposure, and then declined but remained at significant positive levels up to 60
442 days, and neutralized >60-210 days after exposure (Fig. 7).

443 No clear time-dependent pattern among cerium application routes was observed,
444 although treatment of seed had significant overall negative effects at >1-3 and >60 days of
445 exposure (Supplementary Materials 2, Fig. S30).

446 No clear time-dependent pattern was observed between soil and solution treatment either.
447 (Supplementary Materials 2, Fig. S31). However, treatment of plants grown in solution led to
448 more significant positive effects than treatment of soil-grown plants. Specifically, cerium
449 application to soil-grown plants had no significant overall effect at >1-3 and >60-90 days.

450 Regarding the influence of ontogenic stage treated, when analyzed per the different
451 exposure duration intervals, cerium had fewer significant positive effects or more significant
452 negative effects when applied to seed only than when applied to vegetative growth stages
453 (Supplementary Materials 2, Fig. S32). The number of observations for application at both
454 seed and vegetative stages was limited in this analysis.

455 The time-dependent pattern was generally similar between nano-cerium and bulk cerium
456 (Supplementary Materials 2, Fig. S33).

457 **3.6. Other effects (sources of variation)**

458 Regarding cerium application routes, the overall effect of seed treatment was non-
459 significant, with the majority of values negative (Supplementary Materials 2, Fig. S34).
460 Foliage, root, and seed+foliage application produced a similar positive effect. Moreover, there
461 was no evidence that combined root and foliage application offers an improved effect
462 compared to foliage or root application individually (Supplementary Materials 2, Fig. S34).

463 As to the plant growing medium, application of cerium into soil substrate produced
464 a significant overall average effect of +12% (Supplementary Materials 2, Fig. S35). However,
465 the effect was significantly higher (19%) when cerium was applied into solution
466 (Supplementary Materials 2, Fig. S35).

467 Regarding the ontogenic stage treated, the average overall effect of seed treatment
468 was non-significant (Supplementary Materials 2, Fig. S36). There was also no significant
469 difference between the significant positive effects of cerium application at vegetative growth
470 stages or at both seed and vegetative growth stages; however, the number of observations for
471 the latter category was considerably small (Supplementary Materials 2, Fig. S36).

472 **4. Discussion**

473 Across all studies, cerium application had an overall positive effect on a plethora of plant
474 orders, representative of over 161,000 species (based on data from www.britannica.com;
475 accessed 11 May 2022), regardless traits and other factors. This is further substantiated by the
476 many families, genera, and species significantly affected by cerium application. The finding
477 that cerium application had an overall positive effect on cereals, fruit trees, legumes,

478 medicinal plants, oilseed crops, pastures, vegetables, and wild herbs shows the potential of
479 cerium to widely affect numerous plants used as main food and dietary supplements of
480 humans and other animals as well as for the production of herbal extracts and
481 pharmaceuticals. Nevertheless, the effect of cerium depends on the type of plants, with a
482 smaller effect on vegetables and wild herbs. These suggest that vegetables and wild herbs
483 may be less responsive to cerium than cereals, fruit trees, and pastures; however, these results
484 should be interpreted with caution due to the considerably small number of studies for cereals,
485 fruit trees, and pastures. The effect of cerium did not differ among crops, shrubs, and trees or
486 between eudicots and monocots, indicating a more homogenous effect of cerium at higher
487 levels of plant functional groups.

488 Cerium overall enhanced chlorophyll fluorescence and gas exchange. Specifically, the
489 actual photosynthetic efficiency of PSII, the coefficient of photochemical quantum yield in
490 dark, the electron transport rate, the PSII effective quantum yield, and the maximal quantum
491 yield were overall increased, mechanisms that are tightly linked to diverse reaction processes
492 in photosynthesis (Moustakas et al., 2022; Peng et al., 2021). The enhancement of these traits
493 indicates increased efficiency of the PSII electron transfer chain, higher internal efficiency in
494 converting light energy, improved efficiency in capturing primary light energy when PSII is
495 partially closed, and, thus, higher photosynthesis potential of plants under stress (Moustakas
496 et al., 2022; Peng et al., 2021). This is further supported by the overall increased
497 photosynthetic rate and its linked stomatal conductance that this meta-analysis revealed,
498 indicating higher CO₂ uptake by plants and increased photosynthetic rate. Hill reaction
499 reflects the O₂ evolution during the illumination-dependent steps in the process of

500 photosynthesis, which along with the ‘Mehler reaction’ can contribute to photoprotection in
501 photosynthesizing organisms (Shevela et al., 2012). The effect on Hill reaction activity may
502 also imply analogous effects on CO₂ assimilation, NADP reduction, and phosphorylation
503 inactivation during stress conditions. Cerium also increased the photophosphorylation rate, a
504 stress-indicating status, suggesting the possibility of enhanced needs of ion uptake and
505 management of ion export in stressed cells (Fork and Herbert, 1993). RuBisCO carboxylation
506 capacity is fundamental for improving photosynthesis and yield (Iñiguez et al., 2021). The
507 overall increased RuBisCO carboxylation by cerium indicates that the enhancement of
508 photosynthesis by cerium is not only due to physiological driving mechanisms (e.g., stomatal
509 conductance) but also due to a biochemical mode of action of cerium. However, this meta-
510 analysis revealed no evidence that the overall enhanced photosynthetic rate is due to increased
511 chlorophylls. Conversely, chlorophyll *a*, chlorophyll *b*, and carotenoids were overall
512 decreased by cerium application, suggesting that cerium causes oxidative stress in plants. As
513 to carotenoids, lycopene in fruit was also decreased by cerium, which further suggests that
514 cerium can affect the nutraceutical value of plant products routinely used for enhancing
515 human health (Imran et al., 2020). Further partitioning the variance into different cerium
516 concentration ranges revealed that total chlorophylls were increased by various concentration
517 ranges from as small as >0.1-1 mg L⁻¹. Moreover, chlorophyll *a* and chlorophyll *b* were
518 increased by low concentrations (>1-5 mg L⁻¹) but decreased by higher concentrations (>50
519 mg L⁻¹). These findings suggest that cerium causes a biphasic-hormetic dose response, with
520 low concentrations increasing and higher concentrations decreasing chlorophylls. This
521 hormetic pattern of photosynthetic pigments (and photosynthetic rate) was found in numerous

522 photosynthesizing organisms exposed to a wide array of pollutants and other xenobiotics,
523 reflecting an improved defense capacity against environmental challenges (Agathokleous,
524 2021). Apart from the leaf level, this biphasic-hormetic pattern was also revealed for total
525 plant biomass, which was increased by concentrations $\leq 0.1-5$ and 100 mg L^{-1} (and 100 mg kg^{-1})
526 and decreased by concentrations $\geq 125 \text{ mg L}^{-1}$. These findings demonstrate the hormetic
527 function of cerium as a xenobiotic inducing oxidative stress, a hypothesis that is further
528 supported by a different perspective. Specifically, the cerium effect was commonly up to 50%
529 relative to control, across all analyses, indicating that it is commonly rather modest. These
530 findings further demonstrate that the positive effect of cerium on plants is not due to a
531 ‘fertilizer effect’. Instead, this effect is similar with that induced by xenobiotics within the
532 framework of hormesis, with a maximum low-dose positive effect of typically 30-60%, which
533 is constrained by the biological plasticity bounds (Calabrese et al., 2019; Calabrese and Blain,
534 2009), even if Ce uptake and its levels in tissues increase by approximately 620% as this
535 meta-analysis revealed.

536 The mechanisms underlying the observed effects caused by cerium are similar to those
537 induced by various biotic and abiotic stressors, from viruses to pollutants (Awasthi, 2020;
538 Carvalho et al., 2020; Moustakas et al., 2022; Poschenrieder et al., 2013). Cerium also had
539 further multiple overall effects on different traits related to the defense system and redox
540 homeostasis. It increased CAT, DHAR, GSH, GSH/GSSG, ROS, and SOD. These effects
541 further support the conclusion that cerium acts as a xenobiotic, with its positive effects
542 attributed to stimulation via adaptive responses activated by low doses of oxidative stress.
543 CAT is an antioxidant enzyme of profound importance in the mitigation of oxidative stress,

544 and its increase indicates an enhanced capacity to eliminate cellular H_2O_2 , a ROS, to produce
545 O_2 and H_2O (Nandi et al., 2019). Therefore, an increase in CAT indicates the existence of
546 oxidative stress. This is also the case of SOD, an enzyme catalyzing the $\text{O}_2^{\cdot-}$ into H_2O_2 , and
547 providing a first-line defense against ROS-induced damage (Poschenrieder et al., 2013; Zhao
548 et al., 2021). In addition to these enhanced antioxidant enzymes (SOD and CAT), cerium
549 increased also non-enzymatic antioxidants. Specifically, it increased GSH, a thiol molecule
550 playing a central role in stress signaling and antioxidant defense system, which also alters the
551 GSH/GSSG redox state (Hasanuzzaman et al., 2017; Poschenrieder et al., 2013). Free thiols
552 were also enriched, indicating the overall involvement of thiols in enhancing stress tolerance
553 (Tausz et al., 2003; Zagorchev et al., 2013). Thiol-based redox regulation is important for a
554 swift response of chloroplast metabolism to light intensity (Cejudo et al., 2019). Similarly,
555 DHAR is important to couple the GSH and ascorbate pools with the metabolism of H_2O_2 , and
556 is involved in plant defense, development, and growth (Ding et al., 2020; Hasanuzzaman et
557 al., 2017). GSH/GSSG ratio reflects homeostasis (redox state) and can serve as an indicator of
558 oxidative stress, which is often increased together with increased CAT, SOD, and GSH
559 (Hasanuzzaman et al., 2017). The GSH/GSSG redox pair plays a major role in controlling
560 redox signaling (Hasanuzzaman et al., 2017; Szalai et al., 2009). As such, increased cellular
561 GSH level and GSH/GSSG ratio are essential for maintaining plant health under oxidative
562 stress (Hasanuzzaman et al., 2017; Szalai et al., 2009). These increases in CAT, DHAR, GSH,
563 GSH/GSSG, ROS, and SOD suggest that the overall increase of ROS by cerium application
564 did not exceed the threshold level for adverse effects. ROS and associated antioxidant
565 molecules act as signaling agents modulating cellular metabolism, in accordance to

566 endogenous and exogenous stimuli, and affect cellular redox homeostasis (De Gara et al.,
567 2010). Polyphenol oxidase is also an antioxidant enzyme driving the conversion of phenols
568 into quinones, and is linked to detoxification and elimination of ROS (Taranto et al., 2017).
569 Their overall significant response to cerium revealed by the meta-analysis (including leaves
570 and roots) indicates their involvement in plant response to cerium-induced stress. A basal
571 level of ROS is beneficial for health and optimal growth, and a mild increase in ROS triggers
572 a hormetic defense response, followed by inhibitory effects at levels above specific thresholds
573 (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). Because excessive ROS
574 inhibit chlorophyll synthesis and accumulation (Moustakas et al., 2022; Ruban, 2015), it can
575 be postulated that decreased chlorophylls by higher doses of cerium stems, at least partly,
576 from excessive ROS. Since ETR should also be restricted below some levels to avoid ROS
577 accumulation (Moustakas et al., 2022), it can also be argued that ETR and ROS are involved
578 in the high-dose inhibition of chlorophylls, although the overall effect on non-photochemical
579 quenching was non-significant in the two studies that included it. The stressor mode of action
580 of cerium is further illustrated by the significant alteration of membrane permeability and
581 starch (in leaf and fruit) revealed by the meta-analysis. Starch metabolism plays a key role in
582 the plant response to stress, and its decrease has been shown in numerous plants under various
583 abiotic stresses (Thalmann and Santelia, 2017). Starch reserve remobilization is important to
584 make energy, sugars, and metabolites available to facilitate stress mitigation (Thalmann and
585 Santelia, 2017). Also, decreased membrane permeability, expected at low cerium doses, may
586 protect against increased ion leakage as the stress progresses, whereas high cerium doses
587 would increase it, thus changing the ion balance and promoting ion leakage in damaged

588 tissues (Filek et al., 2012; Mansour, 2013; Niu and Xiang, 2018). The significant stress-
589 related role of cerium is also extended to increased electrolyte leakage, Ca^{2+} , K^+ , K^+/Na^+ ,
590 which indicates that K^+ and Na^+ homeostasis plays a significant role in the response of plants
591 to cerium and that cerium further alters mineral (ion) balance. Increased electrolyte leakage is
592 usually linked to increased ROS, with potentially activated K^+ efflux, and can promote
593 programmed cell death under severe stress (Demidchik et al., 2014). However, under lower
594 doses of stress, K^+ efflux can stimulate catabolic processes and save metabolic energy that is
595 needed for the processes of damage repair and adaptation (Demidchik et al., 2014).
596 Furthermore, higher cytosolic K^+/Na^+ ratio is regarded an important mechanism for higher
597 tolerance to stress (Almeida et al., 2017). Overall, these mechanisms underlying the effects of
598 cerium on plants indicate the presence of oxidative stress and the existence of dual biological
599 responses with positive biological effects up to some stress level followed by adverse effects
600 (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). These mechanisms are
601 similar to those found for various air and soil contaminants, such as heavy metals and toxic
602 anions, ground-level ozone, pesticides, nanomaterials, and pharmaceuticals (Agathokleous et
603 al., 2019a, 2019b, 2018; Carvalho et al., 2020; Jalal et al., 2021; Moustakas et al., 2022;
604 Poschenrieder et al., 2013; Shahid et al., 2020).

605 This meta-analysis also revealed various alterations in essential and non-essential
606 elements as well as in the mineral (ion) balance in plants. The decreased C/N ratio may be
607 partly attributed to the increased allocation of C to C-based metabolites that increase under
608 cerium-induced stress. Coordination of the metabolism of C and N is essential for optimal
609 development and growth, and disrupted signaling driven by C/N balance may have further

610 implications within ecosystems, such as changing the interaction of plants with pests, the
611 quality of plant litter and its decomposition, and altering the ecosystem response to other
612 environmental conditions such as atmospheric CO₂ (Chen et al., 2015; Zheng, 2009). As to
613 essential elements, cerium treatment decreased the uptake of B and increased the uptake of Cu,
614 Fe, Mn, and Ni. It also decreased B, Ca, Fe, K, and Mo levels in tissues. The observation that
615 cerium overall increased the uptake of Fe while decreasing its levels in tissues may suggest its
616 key role in cerium stress as Fe homeostasis must remain under control in stressed plants.
617 Accumulation of Fe within cells can lead to toxicities, and its decreased levels due to cerium
618 treatment may indicate a mechanism to reduce potential Fe-induced toxicity and/or that more
619 Fe is used for photosynthesis and respiration electron-transport chains, to produce electron
620 transport chain components and/or enzyme cofactors (Connolly and Guerinot, 2002;
621 Connorton et al., 2017). The decrease of several essential elements (B, Ca, Fe, K, and Mo) in
622 tissues due to cerium indicates altered elemental homeostasis with unknown implications to
623 plant health in the long term. These alterations extend to non-essential elements too, as
624 cerium treatment decreased Cd and Se in tissues and increased Al uptake and its levels in
625 tissues, although for Al uptake this is weakly supported because it is based on only one study
626 (Trujillo-Reyes et al., 2013). Some of these elements typically do not have beneficial effects
627 on plants but widely induce phytotoxicities at high concentrations (Schmitt et al., 2016;
628 Watanabe, 2022). The mechanisms of the increased uptake by plants and their levels in
629 tissues are not understood; however, the possibility of their binding with cerium (e.g.,
630 attached on cerium particles) and subsequent release into plant tissues cannot be excluded.
631 The mechanisms of decreasing other non-essential elements in tissues are unknown,

632 warranting further studies.

633 While Ce uptake and plant tissue levels were increased by approximately 620% due to
634 cerium treatment, the average effect of cerium on other chemical elements ranged from 10%
635 to 77%. However, these effects are significant and raise ecological and human health
636 concerns rising from the arbitrary application of cerium within the agricultural practice. This
637 is because it is now shown that cerium extensively alters the chemical composition of plant
638 tissues decreasing several micronutrients that are important for human health while increasing
639 some heavy metals and decreasing others. Similar to the hormetic effects of cerium on plants
640 at individual level, cerium changes mineral nutrient concentrations in a dose-dependent
641 fashion too (Ramírez-Olvera et al., 2018). Therefore, the applied concentration of cerium is a
642 key for minimizing ecological and human health risks.

643 Besides the physiological and biochemical responses, this meta-analysis revealed an
644 overall negative effect of cerium on root length and yields, which demonstrates that cerium-
645 induced oxidative stress suppressed growth and reproduction traits that are critical to plant
646 fitness. The yield suppression occurred at concentrations $>50 \text{ mg kg}^{-1}$, in line with the
647 inhibition of chlorophylls *a* and *b* by concentrations $>50 \text{ mg kg}^{-1}$, as shown by the meta-
648 analysis results. However, total plant biomass was decreased by concentrations $>125 \text{ mg L}^{-1}$.
649 Hence, there was no evidence that cerium enhances yields (often decreases them), and yields
650 appear to be more sensitive than plant biomass. These findings indicate that cerium pollution
651 can cause adverse effects to vegetation. Importantly, concentrations that were revealed here to
652 cause various adverse effects on plants widely occur in the environment and specifically in
653 agroecosystems, indicating the potentially hazardous nature of cerium (Moreira et al., 2019;

654 Wiseman et al., 2016). However, numerous factors affect the REE bioavailability to plants
655 including soil physicochemical traits (cation exchange capacity, humic acid, metal oxides,
656 organic and inorganic ligands, pH, redox potential), REE valence, REEs interacting with
657 compounds, Casparian strip in plant root exudates (organic acids), and rhizospheric microbes
658 (Liang et al., 2005; Tao et al., 2022). Thus, the real outcomes can be hardly predicted based
659 on the ‘dose’ only, and new studies that incorporate such factors in addition to the ‘dose’
660 component are needed.

661 Given that fitness critical traits (photosynthesis rate, photosynthetic pigments, and plant
662 biomass) were enhanced by cerium concentrations as small as $\leq 0.1\text{-}25\text{ mg L}^{-1}$ (or $>5\text{-}100\text{ mg}$
663 kg^{-1}), depending on the trait, new studies should focus the shift to lower concentrations in the
664 range of $\leq 0.1\text{-}25\text{ mg L}^{-1}$ (or $>5\text{-}100\text{ mg kg}^{-1}$). This is especially important since the number of
665 observations of yield response was extremely limited at concentrations $\leq 25\text{ mg L}^{-1}$ (and
666 studies typically lacking a proper ‘dose-response’ component), which underlines that the
667 notion that the higher dose is always the best for enhancing yields is invalid. These results can
668 provide the basis to highly reduce the load of cerium into the environment, which can be
669 further promoted by turning into nano-cerium as this meta-analysis showed it is equally or
670 even more effective than its bulk counterpart. Cerium-carrying nanoparticles can have
671 positive effects on humans too (Li et al., 2016), and thus nano-cerium effects deserve more
672 attention.

673 Making a further step, this meta-analysis provides insightful information regarding the
674 role of cerium molecular formula within a concentration-response spectrum. Based on this
675 information, molecular formulas with lower potency for toxic effects on organisms but with

676 adequate positive effects (e.g., CeO₂) can be selected over more potentially toxic formulas
677 (e.g., CeCl₃, Ce(NO₃)₃·6H₂O, Ce(NO₃)₃). However, there is a gap of knowledge about the
678 effect of several molecular formulas of cerium within the full concentration-response
679 continuum.

680 More research is also needed into combinations of seed treatment and application of
681 cerium at vegetative stages to potentially maximize the positive effect of cerium by
682 appropriately treating seeds under controlled conditions and reducing the load on the field.
683 Besides, the results of meta-analysis call for cost-benefit evaluations to conclude whether
684 cerium should be actively applied in agriculture, considering the potentially limited positive
685 effects and the large uncertainties about long-term environmental implications of this
686 agricultural practice.

687 **5. Conclusion**

688 This meta-analysis revealed major physiological mechanisms underlying the response of
689 plants to exogenous application of cerium. It is demonstrated that cerium application leads to
690 up to ≈620% increase in Ce uptake and its levels in tissues, on average, offering various
691 positive effects of commonly up to ≈60% relative to control. At concentrations as low as
692 ≤0.1 to 25 mg L⁻¹ cerium commonly enhances chlorophylls, *g_s*, *A*, and plant biomass;
693 however, at concentrations >50 mg L⁻¹ cerium causes various negative effects on plants at
694 trait-specific concentrations. This hormetic pattern is driven by the oxidative stress mode of
695 action of cerium, increasing ROS and their tightly linked antioxidant enzymes and non-
696 enzymatic antioxidants.

697 Cerium further alters the redox signaling and mineral (ion) balance, including changes in
698 K^+ and Na^+ homeostasis. Various chlorophyll fluorescence traits can be improved by cerium,
699 enhancing photosynthetic efficiency and quantum yield of PSII, while the increase in A is also
700 linked to biochemical drivers, namely Hill reaction and RuBisCO carboxylation. However,
701 the potential of cerium application to benefit plant yields remains blurred due to lack of data
702 for low concentrations of cerium and negative effects at concentrations $>50 \text{ mg kg}^{-1}$.

703 Cerium changes the uptake and level in tissues of several micro- and macro-nutrients,
704 including heavy metals that can pose risks to ingesting organisms. As cerium can decrease the
705 levels of several micronutrients, its arbitrary application in agriculture further suggests that
706 cerium pollution may have further implications for disease risk.

707 To reduce ecological and human health risks associated to cerium pollution, a shift is
708 needed from very high concentrations of cerium to considerably small concentrations (≤ 0.1 to
709 25 mg L^{-1}), often a 1000-fold or higher decrease. This study also offers further technical
710 information about the application of cerium that can help to maximize cerium positive effects
711 while minimizing its load in the environment and its associated risks.

712

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716

717 **Conflict of Interest** E.A. is the Managing Editor of the Virtual Special Issue in which this

718 article is published; however, he was not involved in the peer-review process of this article.

719 The authors declare that they have no conflict of interest.

720

721 **Author contributions** E.A. conceived the idea, and all authors participated in the study

722 design. E.A. had a leading role and supervised the production of the manuscript. B.Z., C.G.,

723 and J.X. surveyed literature, extracted data, and created the data bases with inputs from E.A.,

724 C.J.S., and Z.F. B.Z. analyzed data and created display elements with inputs from G.C., J.X.,

725 E.A., and Z.F. E.A. drafted the paper, and all coauthors reviewed the draft and contributed

726 intellectual input. All authors approved the final version of manuscript for publication.

727

728 **Supplementary Materials (for online publication only)**

Filename	Description
Supplementary Materials 1	Display elements illustrating the keyword combination (Fig. S1), the procedure of literature survey and selection (Fig. S2), description of plants considered in the meta-analysis (Table S1), as well as the complete list of references finally included in the meta-analysis database (Table S2).
Supplementary Materials 2	Figures reporting effect sizes of additional results of further meta-analyses as well as supplementary figures with calculated arithmetic per cent for aiding interpretation by readers (Figs. S1-S36).

729

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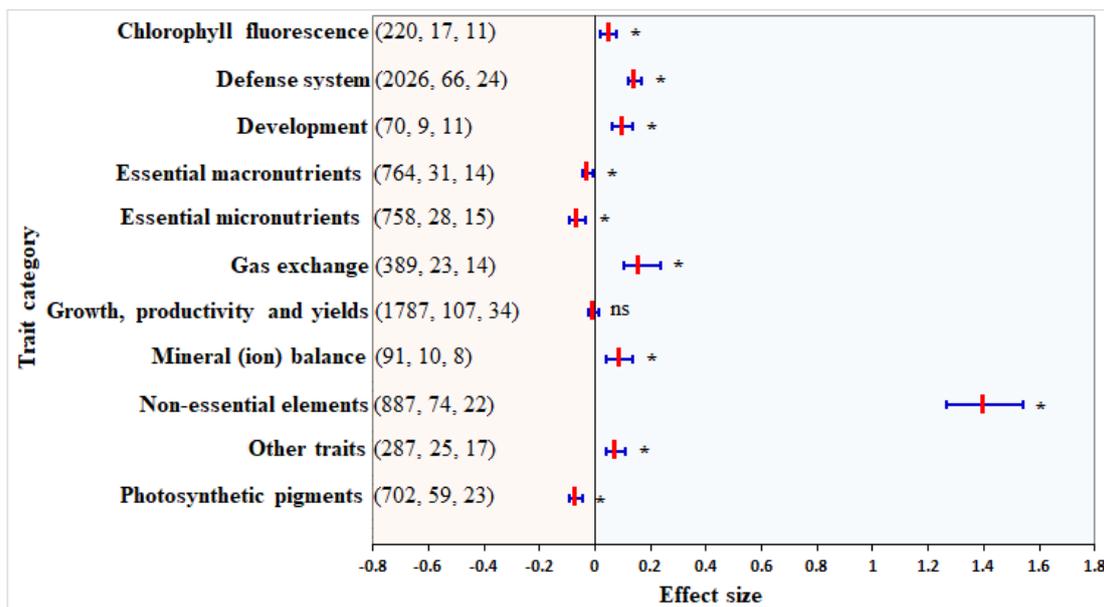
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986

987 **Figures**



988

989 **Fig. 1.** Effect of cerium on different categories of plant traits. Symbols (vertical red segments) indicate
 990 the mean natural log response ratio (tr) of cerium application relative to control group (zero cerium
 991 dose), while the horizontal bars around the mean value represent the bootstrapped 95% confidence
 992 intervals (CIs). Asterisk (*) next to CI bars shows a statistically significant cerium effect relative to the
 993 control group, whereas “ns” shows a statistically non-significant effect. The three numbers in
 994 parentheses indicate the number of observations (sample size), studies and species respectively (from
 995 left to right). The corresponding plot indicating percent difference from the control is provided in
 996 Supplementary Materials 2 (Fig. S8).

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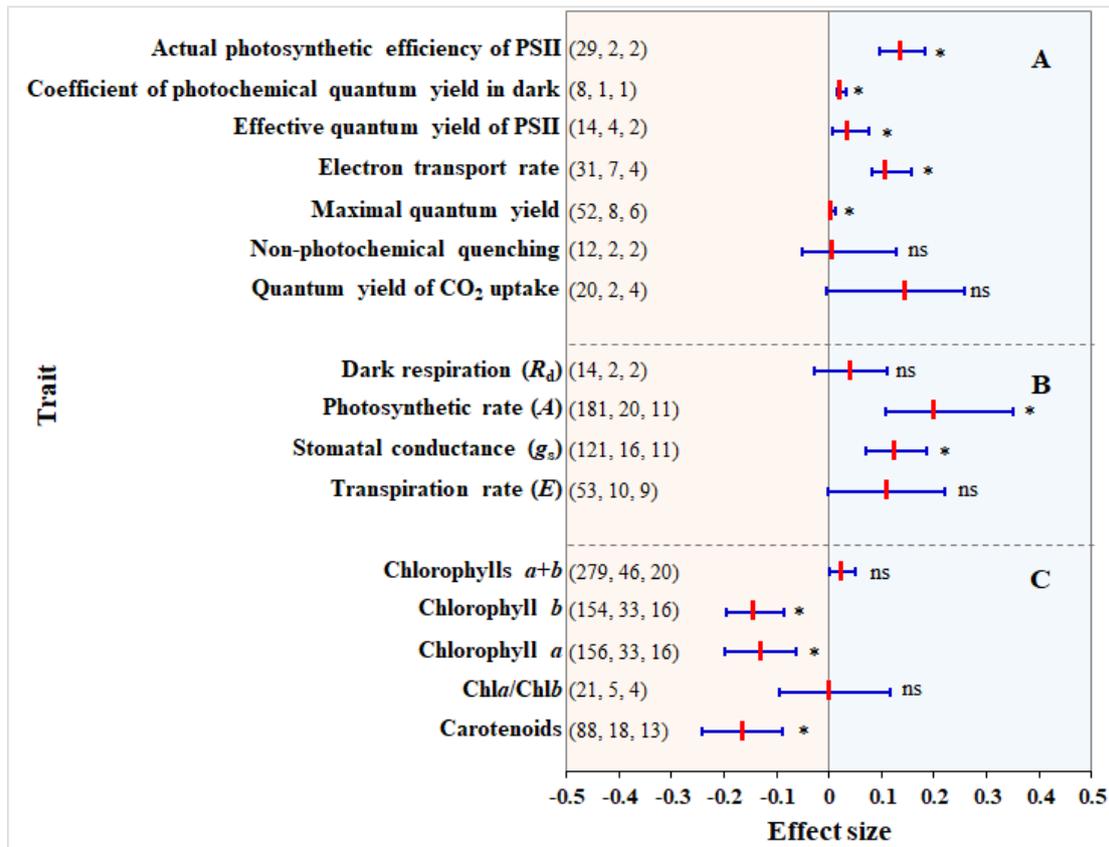
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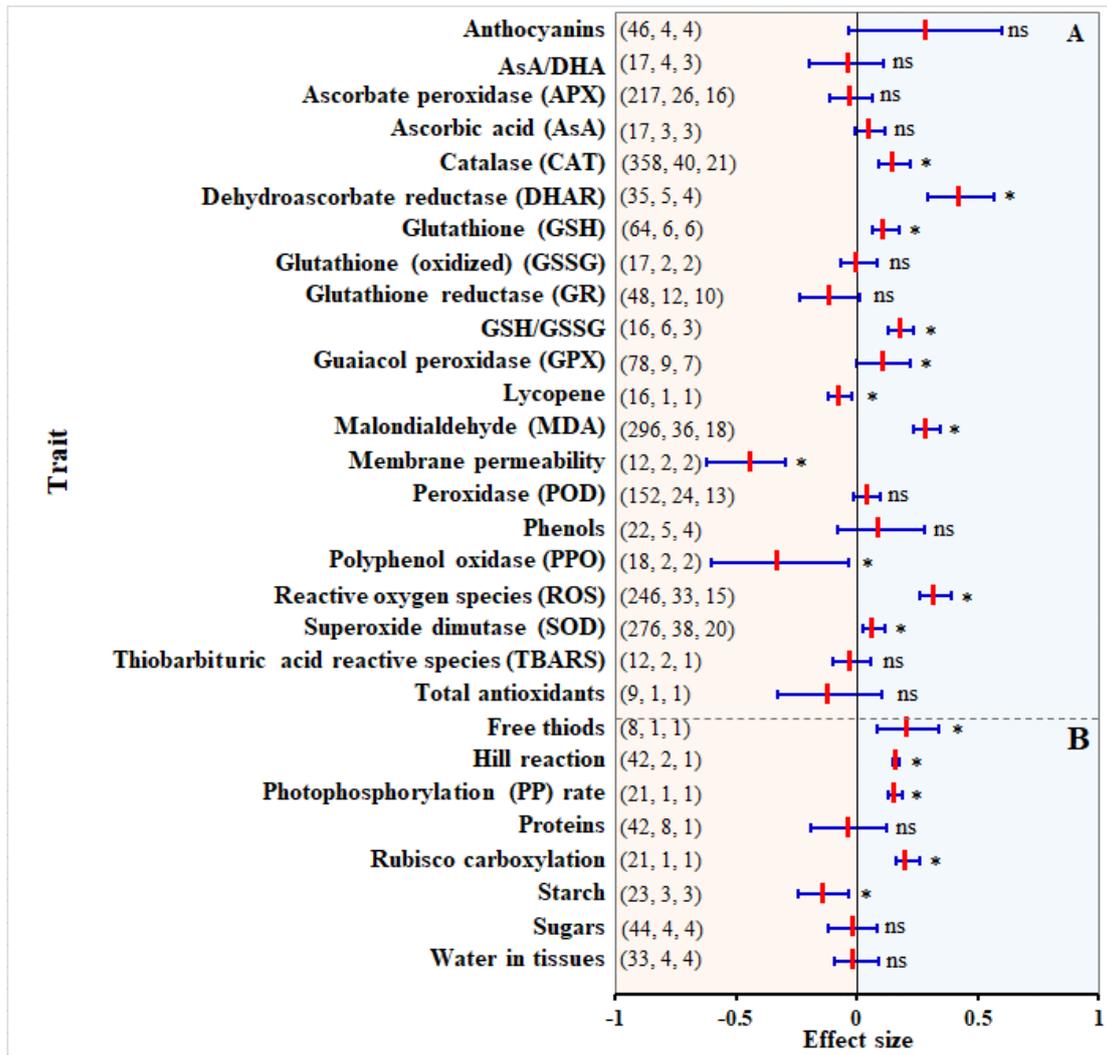
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Fig. 2. Effect of cerium on different photosynthesis-related traits. The traits represent chlorophyll fluorescence (A), gas exchange (B), and photosynthetic pigments (C). Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S9).

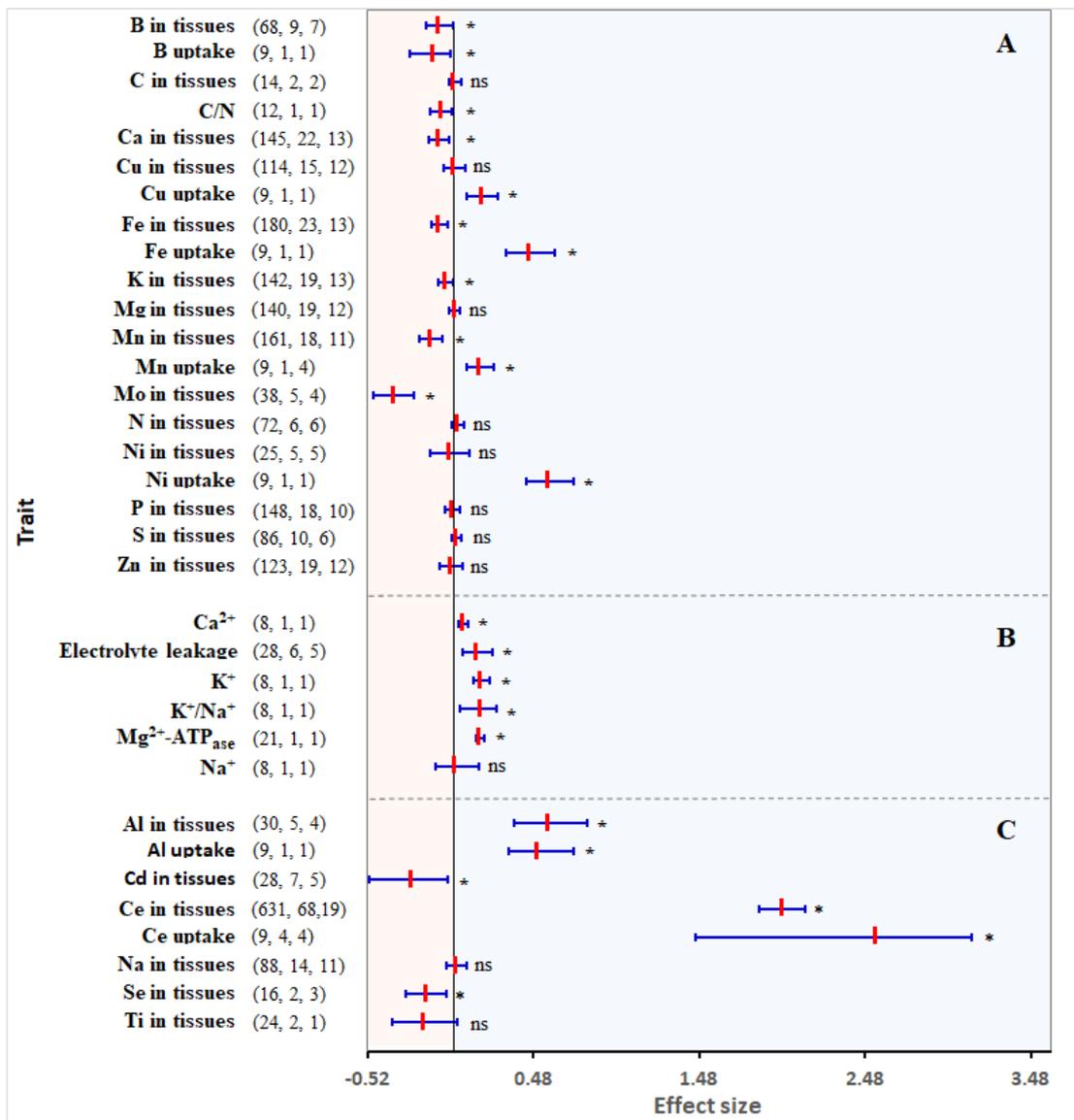


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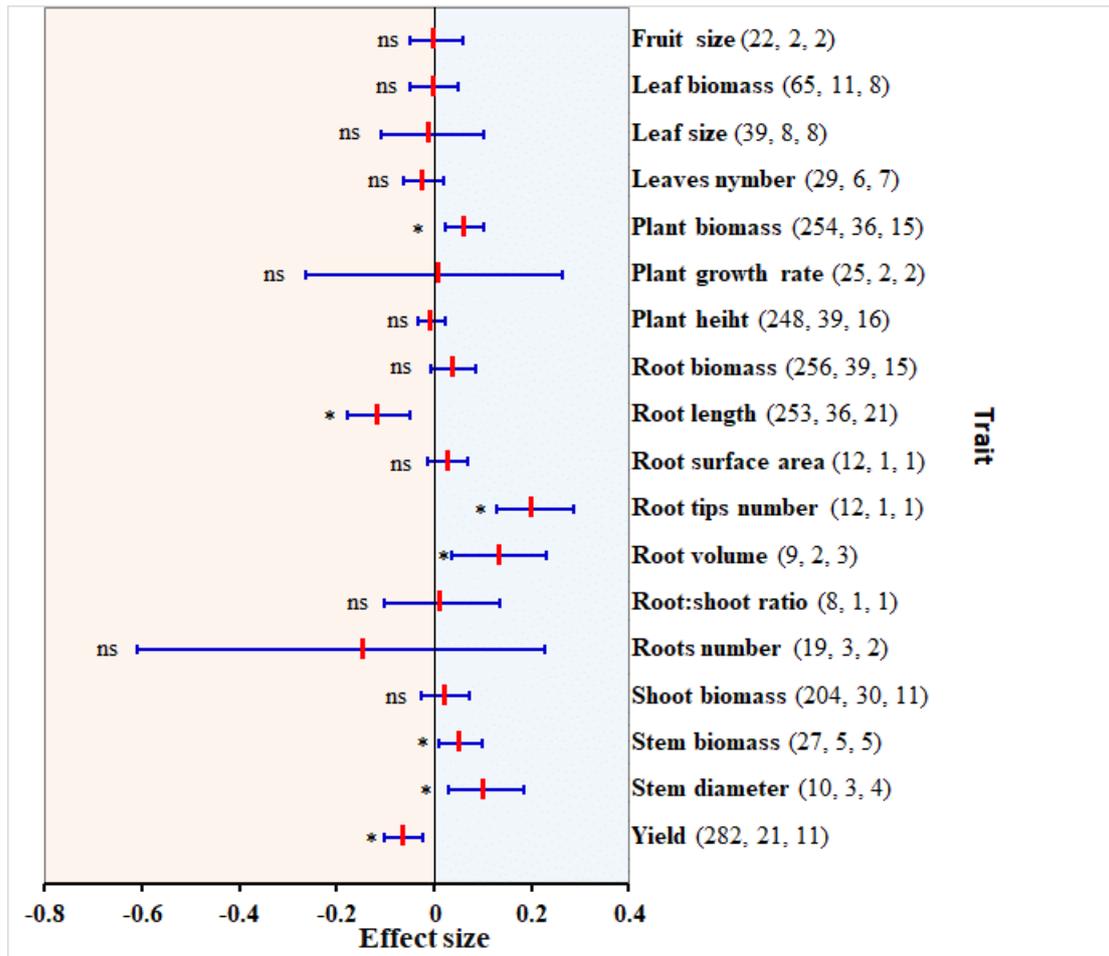
1025 **Fig. 3.** Effect of cerium on biochemical traits. The traits represent defense system (A) and stress-
 1026 related biochemical traits (B). Symbols indicate the mean natural log response ratio of cerium
 1027 application relative to control group (zero cerium dose), while the bars around the mean value represent
 1028 the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant
 1029 cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect.

1030 The numbers in parentheses indicate the observations number (sample size), studies number, and
 1031 species number respectively (from left to right). The corresponding plot indicating percent difference
 1032 from the control is provided in Supplementary Materials 2 (Fig. S10).

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 1035 **Fig. 4.** Effect of cerium on elemental traits. The traits represent micro- and macro-nutrients essential
 1036 for plant growth (A), mineral (ion) balance (B), and non-essential elements (C). Symbols indicate the
 1037 mean natural log response ratio of cerium application relative to the control group (zero cerium dose),
 1038 while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next
 1039 to CI bars shows a statistically significant cerium effect relative to control group, whereas “ns” shows a
 1040 statistically non-significant effect. The numbers in parentheses indicate the observations number
 1041 (sample size), studies number, and species number respectively (from left to right). The corresponding
 1042 plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S11).
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1047 **Fig. 5.** Effect of cerium on different traits related to growth, productivity, and yields. Symbols indicate
 1048 the mean natural log response ratio of cerium application relative to control group (zero cerium dose),
 1049 while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next
 1050 to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns”
 1051 shows a statistically non- significant effect. The numbers in parentheses indicate the observations
 1052 number (sample size), studies number, and species number respectively (from left to right). The
 1053 corresponding plot indicating percent difference from the control is provided in Supplementary
 1054 Materials 2 (Fig. S12).

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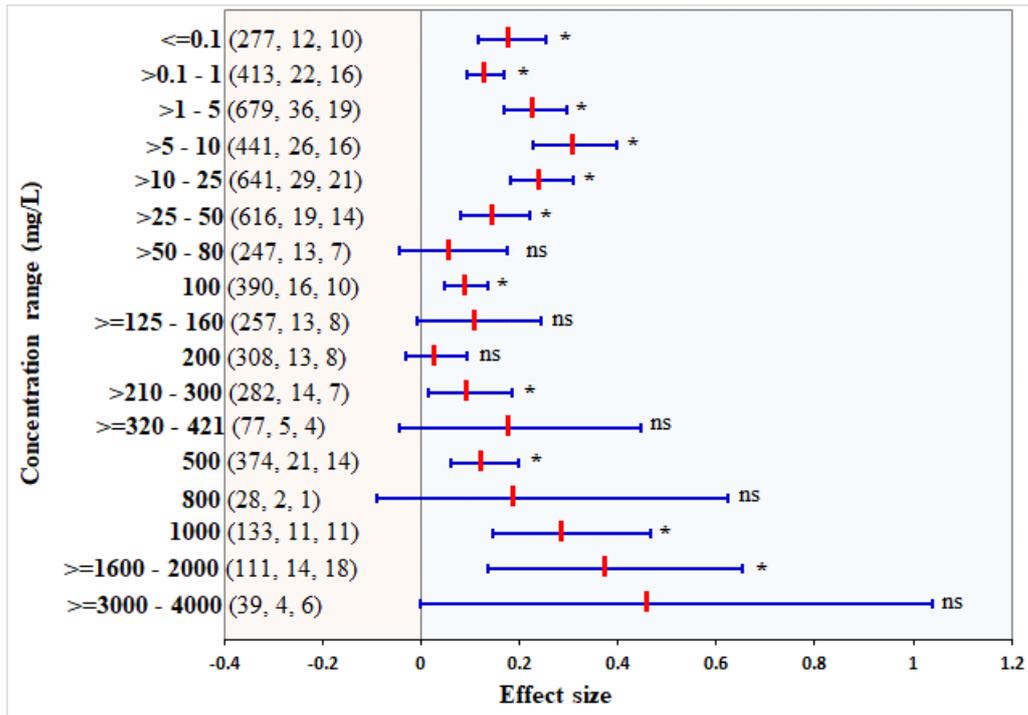
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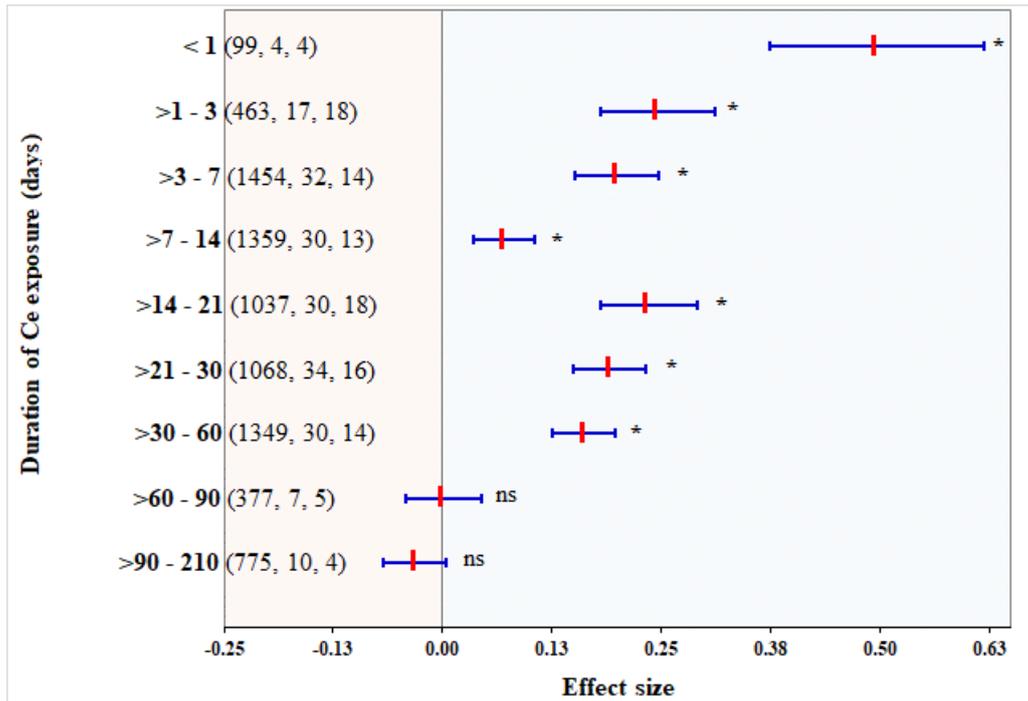
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Fig. 6. Overall effect of cerium on plants (all traits pooled) as a function of different concentration ranges. Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S13). The effect of different concentrations is further partitioned to different sources of variation (see sections 3.4.2-3.4.8).



1081

1082 **Fig. 7.** Overall effect of cerium on plants (all traits pooled) as a function of exposure duration. Symbols

1083 indicate the mean natural log response ratio of cerium application relative to the control group (zero

1084 cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence

1085 intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group,

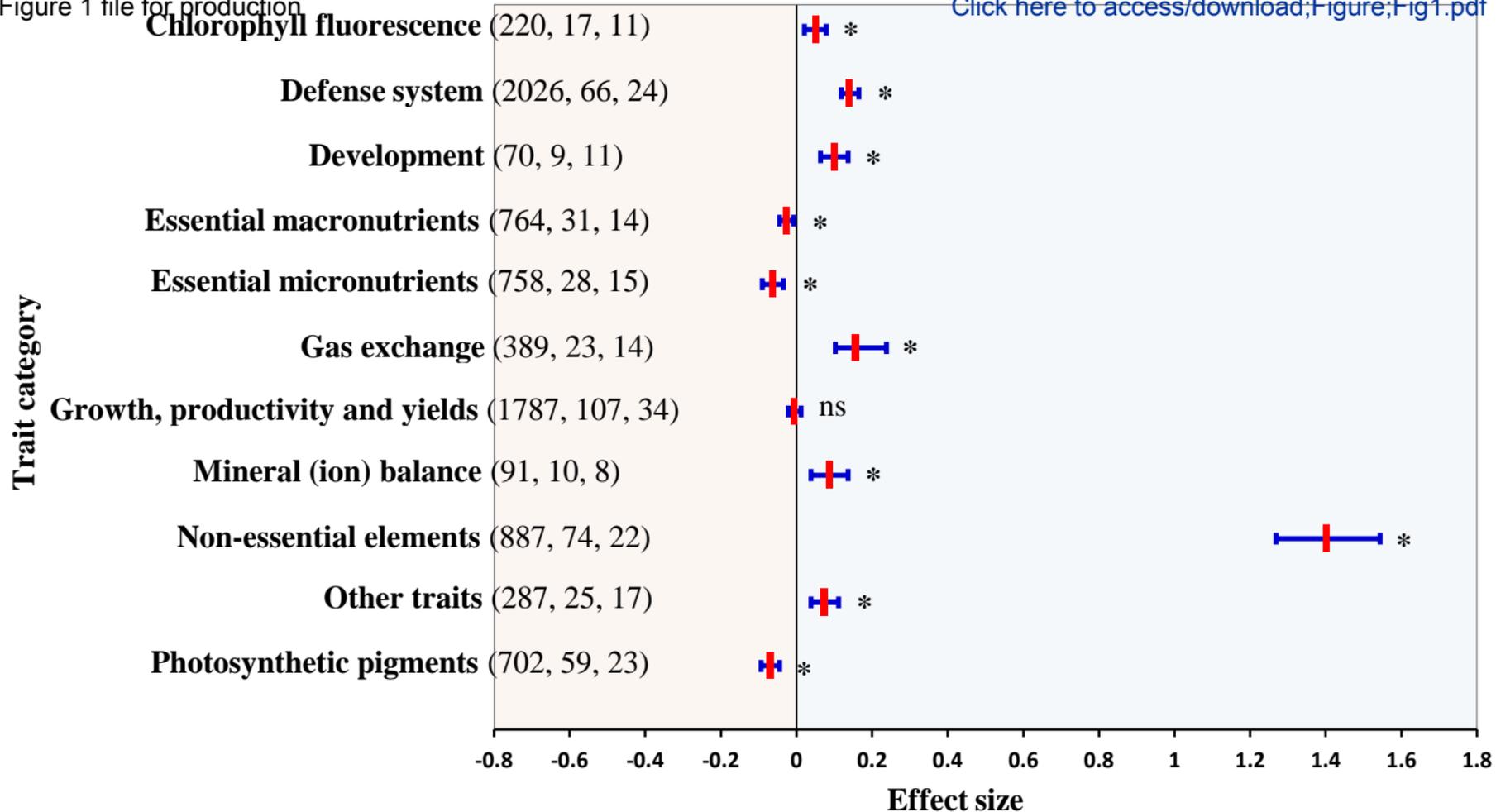
1086 whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the

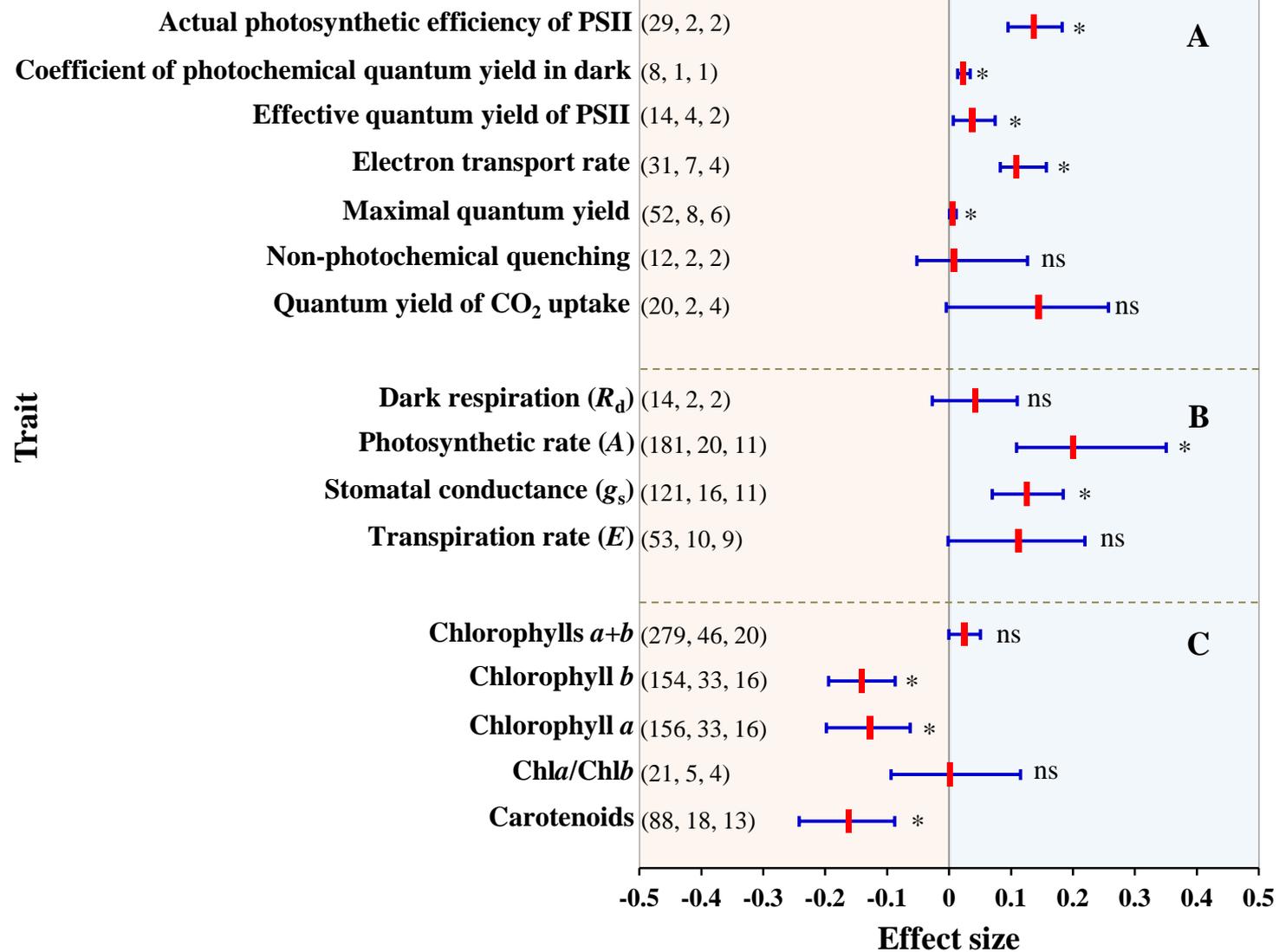
1087 observations number (sample size), studies number, and species number respectively (from left to

1088 right). The effect of different exposure durations is further partitioned to different sources of variation

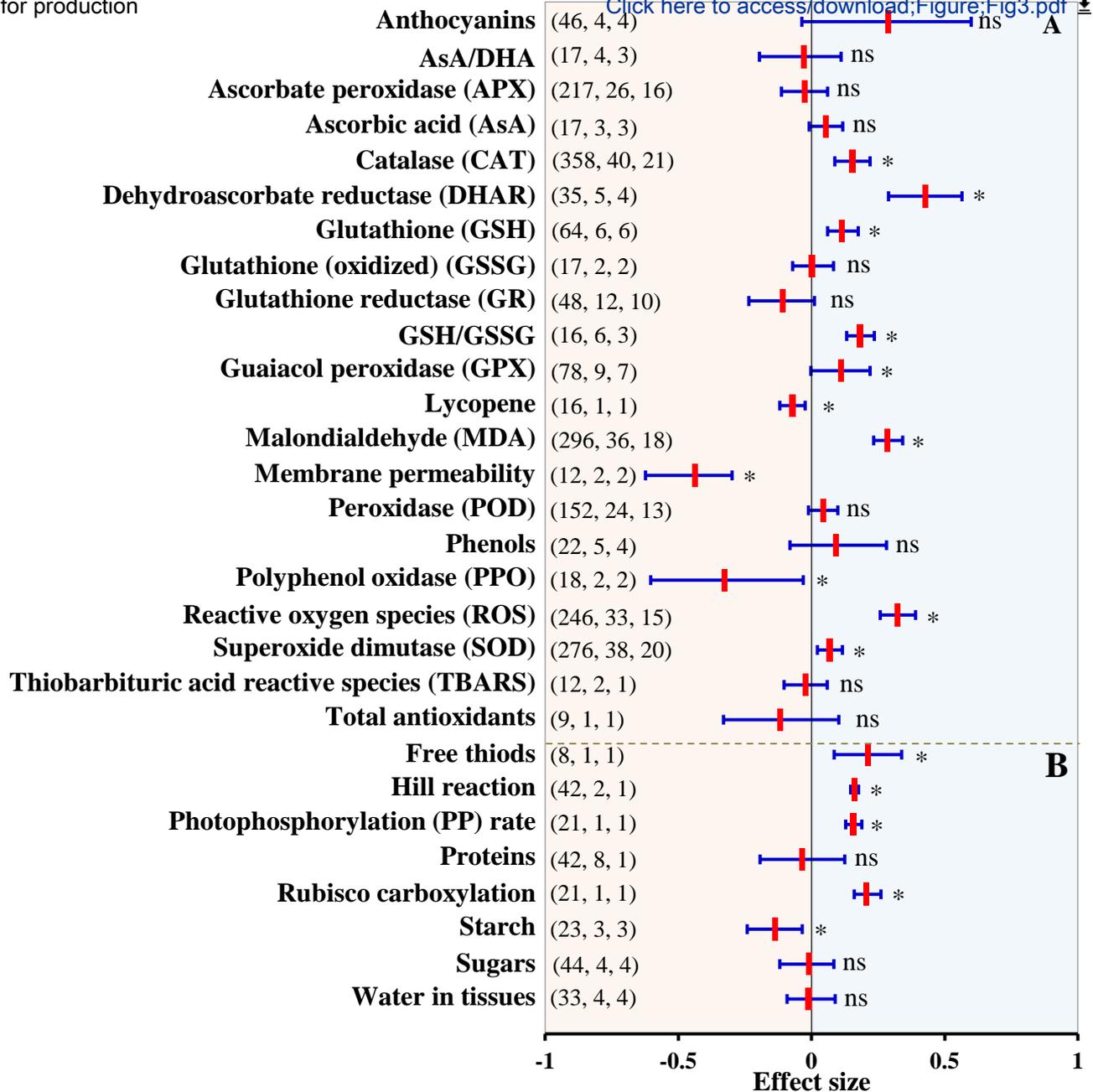
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(see section 3.5).





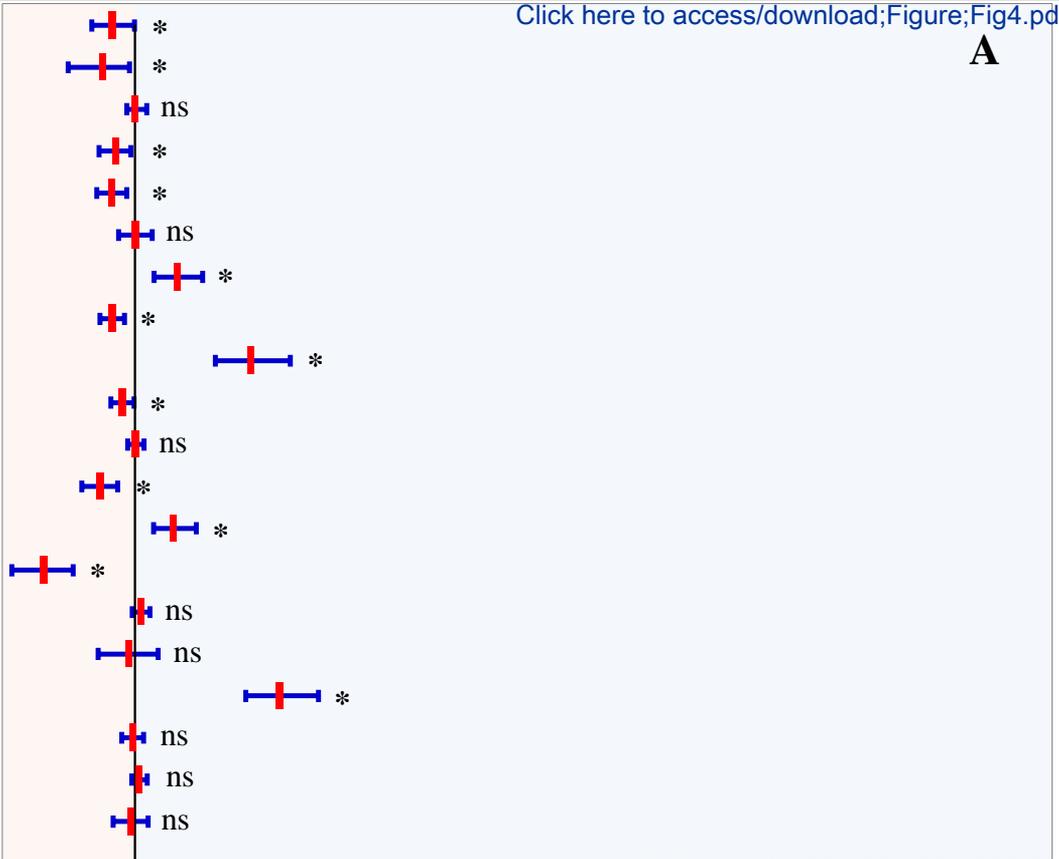
Trait



A

Trait

- B in tissues** (68, 9, 7)
- B uptake** (9, 1, 1)
- C in tissues** (14, 2, 2)
- C/N** (12, 1, 1)
- Ca in tissues** (145, 22, 13)
- Cu in tissues** (114, 15, 12)
- Cu uptake** (9, 1, 1)
- Fe in tissues** (180, 23, 13)
- Fe uptake** (9, 1, 1)
- K in tissues** (142, 19, 13)
- Mg in tissues** (140, 19, 12)
- Mn in tissues** (161, 18, 11)
- Mn uptake** (9, 1, 4)
- Mo in tissues** (38, 5, 4)
- N in tissues** (72, 6, 6)
- Ni in tissues** (25, 5, 5)
- Ni uptake** (9, 1, 1)
- P in tissues** (148, 18, 10)
- S in tissues** (86, 10, 6)
- Zn in tissues** (123, 19, 12)



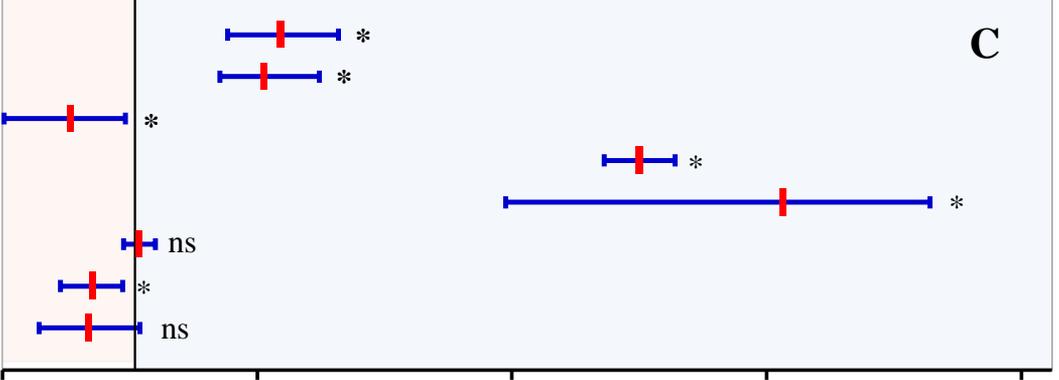
B

- Ca²⁺** (8, 1, 1)
- Electrolyte leakage** (28, 6, 5)
- K⁺** (8, 1, 1)
- K⁺/Na⁺** (8, 1, 1)
- Mg²⁺-ATP_{ase}** (21, 1, 1)
- Na⁺** (8, 1, 1)



C

- Al in tissues** (30, 5, 4)
- Al uptake** (9, 1, 1)
- Cd in tissues** (28, 7, 5)
- Ce in tissues** (631, 68, 19)
- Ce uptake** (9, 4, 4)
- Na in tissues** (88, 14, 11)
- Se in tissues** (16, 2, 3)
- Ti in tissues** (24, 2, 1)



Effect size

-0.52 0.48 1.48 2.48 3.48

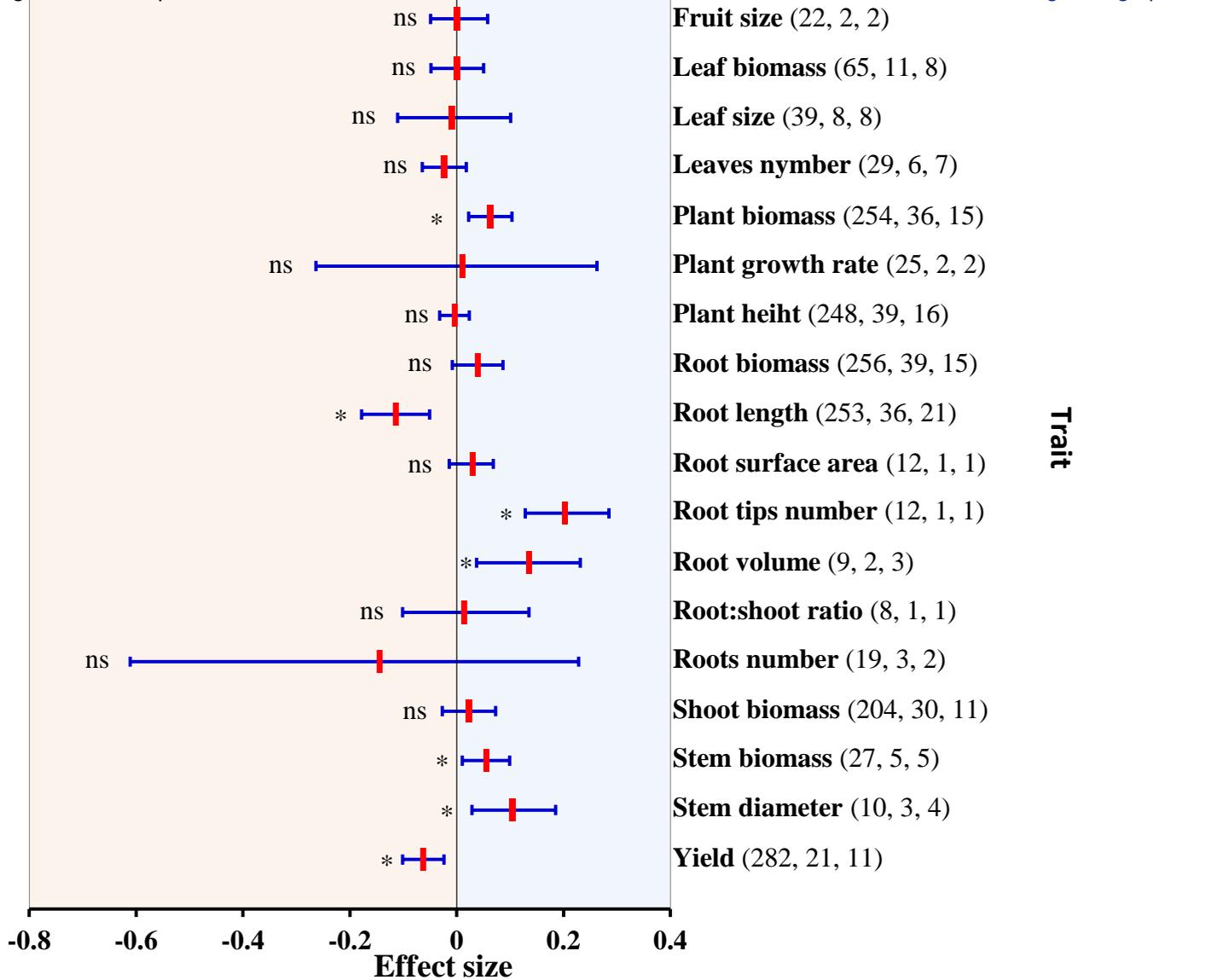


Figure 6 file for production

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Concentration range (mg/L)

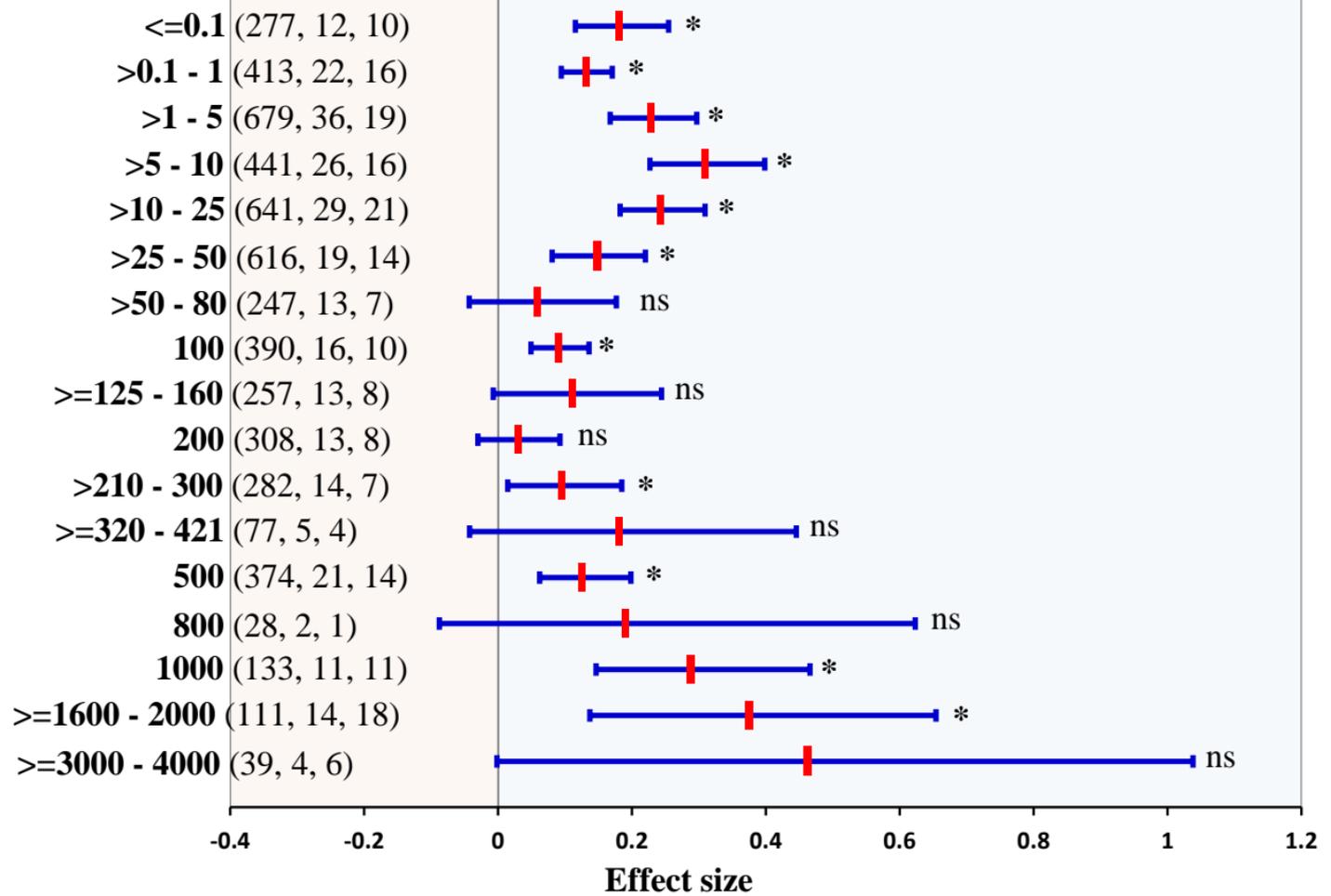


Figure 7 file for production

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Duration of Ce exposure (days)

