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Environmental hormesis, a fundamental non-monotonic biological phenomenon with implications in ecotoxicology and environmental safety

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ABSTRACT

The biological response of individual organisms or groups of organisms to stress is crucial in several scientific disciplines, and hormesis is the most appropriate concept for studying dose-response relationships. The concept of hormesis supports that the response to low-level doses of an agent opposes the response to high-level doses and is characterized by a *J* or *U* shape outstretched in the Euclidean space. Hormesis has been widely known for chemical compounds and radiation; however, whether hormesis appears upon a variety of environmental factors remains underexplored. Here I provide evidence for the occurrence of environmental hormesis which opens Pandora's "pithos" for a wide variety of scientific disciplines. I demonstrate that plant response to environmental factors is often well described by hormetic model suggesting that dose responses should be evaluated based on a wide range of dose levels, taking into account potential effects at both low and high levels. I anticipate this study to serve as a starting point for more sophisticated experiments. The concept of environmental hormesis provides critical quantitative information for biological plasticity; is relevant to ecological and evolutionary theory; and may have long-term ecological implications within the context of global change. The concept of environmental hormesis can also be utilized for the benefit of human welfare and biosphere sustainability. However, to understand the underpinning biological or physiological mechanisms of environmental hormesis, trans-disciplinary research is needed. Environmental hormesis should be considered when developing science-based Environmental Quality Criteria (EQC).

Keywords: β -curve; biphasic; J-curve; plasticity; stimulation; U-curve

I. DOSE-RESPONSE RELATIONSHIP

33
34 The response of individual organisms or groups of organisms¹ to stress is crucial in several
35 scientific disciplines. Almost half a millennium has passed since the well-known ‘all substances
36 are poisons, there is none which is not a poison. The right dose differentiates a poison and a
37 remedy’ (Paracelsus, 1567). In order to properly answer which is the right dose, dose(or
38 exposure)-response relationships should be investigated by exposing the organisms under study
39 to different levels of exposure.

40 The threshold exposure-response model is the most commonly used model in
41 toxicology/medicine (non-carcinogenic health hazards) which assumes that exposures to a toxin
42 above a certain threshold level are dangerous, whereas exposures below the threshold level are
43 safe (Calabrese, 2011, 2014, 2015). Later, the linear no-threshold model was used in medicine
44 (carcinogens), which assumes biological injury directly proportional to the exposure. Both
45 models utilize only high exposures for hazard assessment. Such linear models have been widely
46 used in setting critical levels for protecting vegetation as well (e.g. Karlsson et al., 2004; Ferretti
47 et al, 2007; Mills et al., 2007; Watanabe et al., 2010, 2012; Sanz et al., 2016; Marzuoli et al.,
48 2017).

49 However, progress in science in the past two decades suggests that the fundamental nature of the
50 dose response is hormetic and not linear or threshold (Calabrese and Baldwin, 2001, 2003a,b;
51 Calabrese, 2003, 2004, 2009, 2013a, 2014, 2017a,b; Doss, 2013). Hormesis (ὄρμησις, from the
52 ancient Greek word ὁρμέειν, *hormáein*), termed by Southam and Ehrlich (1943), satisfies the
53 evaluation criteria and should serve as the default model in risk assessment of carcinogens and
54 noncarcinogens for the purposes of regulatory agencies (Calabrese and Baldwin, 2003a,b;
55 Calabrese, 2004, 2005, 2015; Cook and Calabrese, 2006).

56 In this article, I aim to review scientific literature so as to examine the hypothesis that plants may
57 display a hormetic response to a variety of environmental factors as a result of physiological or
58 biological stress, and provide a general overview of hormetic responses of plants to different
59 types of environmental factors.

60 II. THE CONCEPT OF HORMESIS

61 Hormesis, initially called Arndt-Schulz Law or Hueppe's Rule (Yerkes–Dodson Law in
62 experimental psychology), is an underlying concept in biology which was marginalized
63 throughout the 20th century, until recently when attracted popularity (Calabrese and Baldwin,

¹ hereafter referred as “organisms” unless specified otherwise

64 2000a; Calabrese, 2005, 2014, 2015, 2016a). A search in the Web of Science (Thomson Reuters
65 Corporation) for the years 1900-2016 revealed that 2423 articles included one or more of the
66 keywords hormesis, hormetic, hormesis, hormitic, ormetic, ormis, ormitic and ormesis (website
67 accessed on 17th September, 2016). Unsurprisingly, 2195 of the articles (91%) were published
68 from 2000 onwards, while 1044 of the articles (43%) were published within just the past five
69 years (2011-2016).

70 Hormesis is characterized by a β -shaped (Stebbing, 1982; Calabrese, 1996) or U -shaped (or J -
71 shaped) response curve with $a < 0$ or $a > 0$ (Fig. 1), depending on how it is defined and on the
72 biological endpoint measured (Calabrese and Baldwin, 2001). This concept supports that the
73 response of organisms to low-level exposures to a stressor opposes the response to high-level
74 exposures, with stimulatory effects occurring in the region of Menaechmus conic sections in the
75 Euclidean space (Fig. 1).

76 Hormesis occurs and is similar both in susceptible and resistant organisms, although some strains
77 may not generate low-level stimulatory response (Calabrese and Baldwin, 2002), and indicates
78 disruption in homeostasis (Calabrese and Baldwin, 2001; Calabrese and Mattson, 2011).
79 Whether the response of organisms in disruption in homeostasis is overcompensated remains
80 unclear (Elliott, 2011) and requires further studies examining temporal response in order to
81 understand the response over time and the long-term impacts (Poschenrieder et al., 2013;
82 Mushak, 2016). The ideal overcompensation in such a disruption is when resilience can be
83 achieved through plastic responses (Fig. 1, to the left of the toxicity threshold (NOAEL)). Hence,
84 time is an important factor in hormetic responses (Calabrese, 2001; Mushak, 2016). Hormetic
85 exposure-responses may form gamma(γ)-shaped (fish-like) curves when assessed in plant
86 physiological endpoints early and late in exposure (Fig. 1). This phenomenon of γ -shaped
87 responses indicates a modest overcompensation to disruption in homeostasis and not a direct
88 stimulatory effect. A γ -like shape of curves shows that, at low exposures, the organisms respond
89 to homeostatic disruption through overcompensation (re-allocation of resources), effectively
90 repair the temporary damage and finally re-establish homeostasis (resilience).

91 Chemical and radiation hormesis (historical foundations in Calabrese and Baldwin
92 (2000a,b,c,d,e)) commonly occurs in plants, as it has been observed more than 3100 times and in
93 more than 3000 endpoints, and has quantitative features similar to hormesis in animals, with
94 usually a maximum stimulatory response $< 200\%$ of controls and a width < 10 -fold (rarely > 100 -
95 fold) in dose range (Calabrese and Blain, 2005, 2009, 2011; Hadacek et al., 2011; Cedergreen et
96 al., 2005, 2007; Belz et al., 2008; Belz and Piepho, 2013; Calabrese, 2013b, 2015; Poschenrieder
97 et al., 2013; Abbas et al., 2017; Agathokleous, 2017). Yet, hormesis is generalized as to stressor,

98 plant species and biological endpoints (Calabrese and Baldwin, 2002, Cedergreen et al., 2007;
99 Calabrese, 2005; Calabrese and Blain, 2005, 2009, 2011).

100 III. ENVIRONMENTAL HORMESIS

101 **Plant stress induced by environmental factors**

102 Many scientific disciplines study how stress affects biological systems over a range of exposure
103 levels and a wide variety of biological endpoints. In a world with changing environment, plants
104 often undergo physiological or biological stress which can lead to negative consequences in their
105 fitness and productivity (Nali et al., 2001; Fiscus et al., 2005; Feng et al., 2008a; Saitanis, 2008;
106 Yamaguchi et al., 2011; De Marco et al., 2013; Matyssek et al., 2015; Agathokleous et al.,
107 2016a). Such stress-induced effects on plants may have further implications to biosphere and
108 human welfare by reducing the food supplies and their nutritional value (Emberson et al., 2001;
109 Feng et al., 2008a, 2015; Oksanen et al., 2013; Myers et al., 2014) and altering trophic
110 interactions, ecological processes and ecosystem dynamics (Lindroth et al., 2010; de Vries et al.,
111 2014; Karabourniotis et al., 2014; Simpson et al., 2014; Agathokleous et al., 2015, 2016a; Kitao
112 et al. 2016; Wang et al., 2016).

113 **Hormesis induced by environmental factors**

114 Although not always mentioned in the scripts, indications for overcompensation stimulation in
115 plants induced by low-level exposure to environmental factors have been previously found in the
116 scientific literature for a variety of species and endpoints (e.g. Leone and Brennan, 1975; Roberts,
117 1984; Darrall, 1989; Eamus et al., 1990; Yalpani et al., 1994; Pääkköönen et al., 1996; Ranieri et
118 al., 2000; Gray et al., 2003; Hernández et al., 2004; Luo et al., 2009; Nikolova et al., 2010;
119 Calatayud et al., 2011; Ye et al., 2011; Franzaring et al., 2013; Hoshika et al., 2013; Rozpadek et
120 al., 2013, 2015; Carriero et al., 2016). These indications were mostly based on experiments with
121 three or less exposure levels, in terms of experimental units. However, hormesis induced by
122 environmental factors has not been validated in terms of Euclidean geometry (with regards to the
123 terminological context), despite the existence of some reports on its occurrence (e.g. Vázquez-
124 Ybarra et al., 2015; Mashaeet et al., 2016; Sugai et al., 2018).

125 A review of the relevant literature revealed that hormesis occurs as a result of physiological or
126 biological stress induced by environmental factors (Fig. 2-5); however, studies with appropriate
127 experimental design and sufficient statistical power for testing hormesis are limited. The vast
128 majority of studies dealing with effects of environmental factors on plants were conducted on
129 high-level exposures (distress) and adverse effects and their background biological mechanisms

130 (see also Manning, 2005). However, the low-level effects (eustress²) and the adaptive
131 mechanisms (or resilience, Fig. 1) remain elusive, in spite of suggestions from the late 1980s that
132 stomatal responses are contrasting between low and high concentrations of air pollutants and that
133 plants may show adaptive mechanisms and recovery from damage (Darrall, 1989), which
134 altogether hint to hormesis (Calabrese, 2014).

135 I present here for the first time 52 examples of hormetic responses of plants to environmental
136 factors (Fig 2-5). These examples come from 16 taxa, of which some include more than 1
137 cultivars or genotypes, and one peatland mesocosm. Hormesis was induced by 7 environmental
138 factors in 24 unique endpoints. The maximum stimulatory response occurred within a factor of
139 <2 below the NOAEL. Forty-one out of 52 dose-response relationships displayed both LOAEL
140 and NOAEL. The average LOAEL:NOAEL ratio of these 41 relationships was <2. In 50 out of
141 52 hormetic cases, the low-level stimulatory response was up to 161% (Table 1), while in the
142 remaining 2 cases the stimulatory responses were approximately two-fold greater than the
143 control response. This is in agreement with hundreds of cases of chemical and radiation hormesis
144 explored earlier in biological organisms (Calabrese, 2013b, 2015; Calabrese and Baldwin, 2001;
145 Calabrese and Blain, 2009, 2011; Cedergreen et al., 2007). Among 52 exposure-response
146 relationships which displayed hormesis with treatments above 105% of control, 22 (42.3%) had a
147 stimulatory response of <25% of control (Table 1), which is not far from the 36% reported by
148 Calabrese and Blain (2005). However, calculations based on the modeled curves show lower
149 stimulatory responses, in agreement with earlier suggestions (Cedergreen et al., 2007). Based on
150 3166 dose responses in plants, the probability that the maximum stimulatory response being 110-
151 149% of control would be $P_{(110 \leq \text{MAX} < 150)} = 0.59$, independently from the endpoint (Calabrese and
152 Blain, 2011). The present study, based on 52 dose responses of mainly physiological, growth and
153 production endpoints to environmental factors, preliminarily suggests that this probability is
154 $P_{(110 \leq \text{MAX} < 150)} = 0.79$, whereas the probability that the maximum stimulatory response would be
155 up to 161% of control is $P_{(105 \leq \text{MAX} < 161)} = 0.96$ (Table 1). It remains to be seen whether these
156 probabilities will be re-affirmed by a larger sample size of dose response relationships, perhaps
157 from a wide variety of studies which may take place in the future, however this provides a first
158 approximation.

159 The examined studies (Figs 2-5) suggest that hormetic responses can be cultivar- or genotype-
160 specific and endpoint-specific (Kress and Skelly, 1982; Weigel et al., 1990; Yamaguchi et al.,
161 2012; Agathokleous et al., 2017a; Sugai et al., 2018). These hint to the suggestion that hormesis

² with respect to the roots of “eu” in Greek language (i.e. “εὖ”, meaning good or well), the term eustress should be used only when the stress induced by low levels of exposure is beneficial

162 is case-specific. Nevertheless, it seems to be occurring widely in a similar way both in
163 susceptible and resistant organisms, in agreement with suggestion by Calabrese and Baldwin
164 (2002). It would also be reasonable to examine exposure–response relationship separately for
165 each endpoint as hormetic response is not necessarily observed in all the endpoints (Fig. 2-5).
166 This is particularly important when assessing dry matter or biomass, which is also used in risk
167 assessment (U.S. EPA, 2014), as there are indications that hormetic responses may vary among
168 shoot, root and total plant (Fig. 5), especially for stressors which are likely to cause an imbalance
169 in root/shoot ratio (Agren and Franklin, 2003; Grantz et al., 2006; Agathokleous et al., 2016a).

170 **Environmental hormesis**

171 As explained above, it has been previously shown that hormesis can be induced by a plethora of
172 chemical compounds. This study provides evidence showing that hormesis can also be induced
173 by environmental factors, such as gaseous air pollutants. Therefore, I propose to call
174 *environmental hormesis* the phenomenon where hormesis is caused by environmental factors
175 which induce stress to biological organisms at low and high exposure levels. Therefore, with
176 respect to the suggestions by Calabrese et al. (2007) on biological stress response terminology, I
177 suggest using the phrase *environmental conditioning hormesis* to refer to the phenomenon where
178 prior stress induced by low-level exposure to environmental factors reduces the toxicity that
179 would be caused by a subsequent more massive environmental threat (Calabrese et al., 2007,
180 Calabrese, 2015, 2016b). A variety of environmental factors was found to induce *conditioning*
181 *hormesis* in plants (e.g. Yalpani et al., 1994; Ruiz-Sánchez et al., 2000; Hong and Lee, 2001;
182 Fornes et al., 2007; Navarro García et al., 2011; Rozpądek et al., 2013, 2015; Kleiber et al.,
183 2017; Li et al., 2017). The phrase *environmental postconditioning hormesis* can also be used to
184 refer to the phenomenon where a low-level exposure reduces the toxicity induced by a prior
185 high-level exposure to environmental factors (Calabrese et al., 2007; Ovize et al., 2010). The
186 environment has a central role in hormesis from a different viewpoint too. At individual level,
187 organisms may attain survival through acclimation or adjustment to harsh environment.
188 Environmental stress forces the stressed to shape acclimation, adjustment or evolution in a
189 changing environment, in such a way that the shaping depends both on the stressor and the
190 stressed (Bijlsma and Loeschke, 2005). At species or populations level, groups of individuals
191 evolve features (e.g. adaptation via natural selection) which help them survive or reproduce in
192 harsh environments. Natural selection is the cause of alterations over several generations through
193 which particular traits are developed, thereby helping in surviving at a set of environments. In
194 any case, the key point for acclimation, adjustment or evolution of features is the “environment”

195 (Bohnert et al., 1995; Bijlsma and Loeschcke, 2005; McDonnell and Hahs, 2015); therefore it
196 should be fair enough to call the phenomenon described above “environmental hormesis”.

197 **Suggestions**

198 It is now realized that environmental hormesis widely occurs in insects, nematodes and other
199 animals (Cypser and Johnson, 2002; Luckey and Lawrence, 2006; Rattan, 2008; Bocci et al.,
200 2009; López-Martínez and Hahn 2012, 2014; López-Martínez et al., 2014, 2016a,b; Kishimoto et
201 al., 2017; Kumsta and Hansen, 2017; Kumsta et al., 2017) as well as in plants.

202 Environmental hormesis is not upon a direct effect of the abiotic stressor, but upon an indirect
203 effect through stress-induced changes in plant endogenous agonists. Oxidation–reduction
204 reaction chemistry may play a central role in hormesis (Hadacek et al., 2011). Air pollutants,
205 such as O₃, and other environmental factors such as drought, are known to induce changes in
206 reactive oxygen species. Hormesis may become more pronounced by time or may be a transient
207 event (Calabrese et al., 1999; Mushak, 2016) as in Fig. 1, and thus adequate selection of time
208 points would be needed. There is, however, a long way to go to conclude whether the stimulatory
209 effects of environmental hormesis are beneficial in the longer term. Plant dry matter production
210 may be a more appropriate endpoint for deciding whether hormesis is beneficial in the long run
211 and for risk assessment as it reflects the accumulated plant stress (Larcher, 2003) and is already
212 used in the ecological risk assessment (U.S. EPA, 2014).

213 Further research is needed on low-exposure response to test the effects on plants of poor
214 robustness and in adult and mature trees with closed canopy (hormesis age-dependency).
215 Environmental hormesis (Fig. 2-5) has been mainly found in semi-open or closed experimental
216 facilities with controlled environment. A big challenge for the next decades would be to assess
217 hormesis in pristine or to use open experimental facilities, where plants grow in a natural
218 environment with interacting biotic and abiotic factors. For example, plants of the same species
219 showed hormetic response to H₂S in diffusive conductance to CO₂ when O₃ was theoretically
220 zero but no hormetic response when O₃ was elevated (Fig. 2d). This can be explained by the
221 decreased conductance which often occurs under elevated O₃ (Felzer et al., 2007; Feng et al.,
222 2008a; Ainsworth et al., 2012).

223 By testing the concept of hormesis, currently-unknown physiological and biological knowledge
224 can be obtained. However, hormetic response duration (progression of stress) should be further
225 investigated along with investigations of molecular mechanisms in order to enlighten
226 environmental hormesis. Trans-disciplinary research is needed to understand the underpinning
227 biological or physiological mechanisms of hormesis and develop hormesis as a biological

228 principle. Multi-omics approaches may play a key role in elucidating the biological mechanisms
229 of hormesis (Horgan and Kenny, 2011; Aliferis and Jabaji, 2011; Watanabe et al., 2015).

230 IV. RELEVANCE TO HUMAN WELFARE & BIOSPHERE SUSTAINABILITY

231 **Hormesis in human nutrition and medicine**

232 Plant stress induced by low-level exposures to environmental factors requires urgent studies
233 because it may be occurring nowadays and may lead to changes in qualitative and quantitative
234 properties of such important compounds.

235 Studies on accumulation of antioxidants, secondary metabolites and other stress-induced
236 compounds within the context of environmental hormesis would be valuable since they are major
237 players in plant stress and important for human nutrition and medicine (Piironen et al., 2000;
238 Kintzios, 2006; Hadacek et al., 2011; Döring et al., 2013; Karabourniotis et al., 2014;
239 D'Angiolillo et al., 2015). In this framework, low-level exposures of plants to environmental
240 factors can be utilized in an efficient way to accelerate the achievement of marketable quality in
241 cultivated crops and enhance the production of antioxidant compounds or other important to
242 human nutrition compounds (e.g. Yalpani et al., 1994; Ranieri et al., 2000; Munné-Bosch, 2005;
243 Wang et al., 2008; Rozpądek et al., 2013, 2015). Experimental results relevant to this concept
244 suggest that environmental hormesis can provide critical information which can also be used for
245 enhancing plant defense to a subsequent threat (Yalpani et al., 1994; Rozpądek et al., 2013,
246 2015; Li et al., 2017), and thus sustain higher yields.

247 **Conditioning hormesis in post-harvest engineering**

248 Environmental hormesis can be utilized not only to accelerate the achieving of marketable
249 quality in cultivated crops and enhance the production of important to humans compounds by
250 plants, but also for post-harvest purposes. One use would be to increase the post-harvest fruit
251 adaptation to environmental stresses along with fruit quality in terms of human nutrition. For
252 example, it has been suggested that preheating of grape berries (*Vitis vinifera* L. cv. Cabernet
253 Sauvignon) induced accumulation of stilbene synthase (EC 2.3.1.95) mRNA and synthesis of a
254 new protein of stilbene synthase (Wang et al., 2008). Stilbene synthase may enhance the
255 phytoalexin defense mechanism against fungal pathogens of plants, and is of importance to
256 human nutrition and medicine (Darvill and Albersheim, 1984; Kuć, 1995; Hammerschmidt,
257 1999; Piironen et al., 2000; Grayer and Kokubun, 2001). Furthermore, exposure of chilled-stored
258 'Thompson' seedless grapes, 'Black Amber' plums, 'Mareta' tomatoes and 'Nules' clementines
259 to O₃ protected them against grey mould (*Botrytis cinerea* Pers.: Fr (teleomorph: *Botryotinia*

260 *fuckeliana*) (Tzortzakis et al., 2007), a worldwide important fruit disease (Jacometti et al., 2009;
261 Li et al., 2012). The authors suggested that “ozone may constitute a desirable and effective
262 residue-free alternative to traditional postharvest fungicide practices” (Tzortzakis et al., 2007). In
263 a further experiment, tomato fruits (*Lycopersicon esculentum* Mill. cv. Mareta) were exposed to
264 0.05 $\mu\text{mol O}_3 \text{ mol}^{-1}$ for up to six days and then wounded and/or inoculated with grey mould and
265 transferred to clean air in chilled storage for one or two weeks post-fumigation exposure: It was
266 found that O_3 protected against grey mould with down-regulation of ethylene (C_2H_4)-, jasmonate
267 ($\text{C}_{13}\text{H}_{20}\text{O}_3$)- and pathogenesis-related genes (Tzortzakis et al., 2011). Other studies suggest that
268 an optimum O_3 exposure can be used to delay ripening of fruits by mediating ethylene
269 biosynthesis inhibition and cell wall dismantling regulation and to enhance the physicochemical
270 characteristics, antioxidative capacity, and quality of fruits after harvest (e.g. Ali et al., 2014;
271 Minas et al., 2014; Segade et al., 2017; explanations also in Rice, 2002 and Martínez -Romero et
272 al., 2007).

273 **Suggestions**

274 The concept of environmental hormesis can be utilized for the benefit of human nutrition and
275 health by preserving food supplies and controlling chemical compounds produced by plants,
276 thereby ensuring human welfare and biosphere sustainability. However, attention should be paid
277 to diseases, pests and pathogens that may become more injurious to plants (Braun and Flückiger,
278 1989; Paoletti et al., 2007; Mashaeet et al., 2015; Agathokleous et al., 2017c; Abu ElEla et al.,
279 2018).

280 V. RELEVANCE TO ECOLOGICAL AND EVOLUTIONARY THEORY

281 **Hormesis beyond individual level**

282 A big effort has been put by the air pollution research community and plant scientists to
283 understand the effects of future environmental change scenaria; however, do hormetic effects
284 (Fig. 3-5) indicate that plants are already facing environmental stress? Although knowledge
285 remains inadequate, evidence indicates that there are taxa showing hormetic response to
286 pollutant levels that are common nowadays in Northern Hemisphere (Fig. 3-5). Taking into
287 account species-specific responses at low-level exposures (Fig. 3-5), it can be postulated that
288 changes in composition of communities may already be in process and this may act as a driving
289 force in ecological succession. This postulation is supported by recent findings where N
290 deposition ($1\text{-}19 \text{ kg ha}^{-1} \text{ yr}^{-1}$) effect on herbaceous richness of more than 15000 forest, grassland,
291 shrubland and woodland sites across the continental United States was assessed to test the

292 vulnerability to N deposition (Simkin et al., 2016). The authors revealed a unimodal relationship
293 where richness increased at lower levels of exposure and decreased at higher level of exposure
294 (8.7 and 13.4 kg N ha⁻¹ yr⁻¹ for open- and closed-canopy vegetation) and exceedance of N
295 deposition critical loads for loss of plant species richness in 24% of the sites. One model/theory
296 that predicts the shape of relationship between productivity and richness is the Grime humped-
297 back model (HBM; Grime, 1973, 1979, 2001). This is a classical example of hormesis where few
298 plant species can tolerate at low levels of productivity, many species thrive at intermediate levels
299 of productivity, and thus species richness peaks, and few species with high competitive capacity
300 can dominate at high levels of productivity. A recent study was conducted using data from
301 coordinated surveys conducted throughout grasslands of various site productivities worldwide
302 (Fraser et al., 2015). The findings of this study supported the pattern of the HBM at regional and
303 global extents. A review study of global scale based on long-term field studies estimated a
304 maximum stimulation of carbon sequestration by forest ecosystem at N deposition levels
305 between 15 and 35 Kg N ha⁻¹ yr⁻¹ (De Vries et al., 2014). This is in line with further European
306 studies which report hormetic responses of tree growth to N deposition (De Vries and Posch,
307 2011; Braun et al., 2017). There is also evidence for modeled hormetic responses of trees to N
308 deposition plus N fixation (De Vries et al., 2017). All these high resolution studies validate the
309 hypothesis that hormesis is not only a phenomenon of individual response to stress but also a
310 phenomenon occurring at different organizational levels like communities or populations
311 (Constantini et al., 2010), thus re-affirming the significance of the phenomenon of hormesis in
312 ecological theory.

313 **Hormesis and competition**

314 Overcompensation stimulatory effects can be a critical driving force in competition when plants
315 compete for light, mineral nutrients, water or space, and may lead to negative effects through
316 trade-offs between survival and reproduction (Calabrese, 1996). In the examples examined here,
317 the metabolic costs for allocating resources to survival (Fig. 4a-e) affected negatively the
318 reproduction (Fig. 4f) of the hybrid larch; however, this was not the case for the co-growing
319 Japanese larch. It should be noted that hybrid larch displays heterosis (Agathokleous et al.,
320 2017b; Wang et al., 2018), which was observed in the experiment of Fig. 4 (Sugai et al., 2018).
321 Therefore, hybrid larch followed a competitive strategy in relatively productive and undisturbed
322 vegetation, whereas Japanese larch followed a stress-tolerant strategy (Grime, 1977). It seems
323 hybrid larch, with low capacity for defense against stress, experienced adverse effects in

324 productive capacity, whereas Japanese larch, with high defense capacity, experienced beneficial
325 effects in productive capacity.

326 Four decades have passed since Grime (1977) suggested the existence of three primary strategies
327 in vascular plants, according to which low stress with low disturbance generates competitive
328 plants; high stress with low disturbance generates stress-tolerant plants; and low stress with high
329 disturbance generates ruderal plants. However, the present review suggests that the CSR Triangle
330 and R* theories need further examination in relation to the progress of hormesis over time as a
331 potential modifier of competition. Furthermore, does a revisit to the Intermediate Disturbance
332 Hypothesis indicate that it is nothing more, nothing less than hormesis? Nonetheless, the theory
333 of facilitation, which influences community organization (Bruno et al., 2003), may also have
334 implications to hormesis (or hormesis to facilitation) as, for example, in ectomycorrhizal tree
335 species. In turn, hormesis should be implemented within the Menge–Sutherland model.

336 **Hormesis and plasticity**

337 As shown above, hormesis is inseparable from the evolutionary principles of homeostasis and
338 optimization (Rozman and Doull, 2003). Plasticity is ‘a basic and primitive biologically selected
339 characteristic’ (Calabrese and Mattson, 2011) which links to evolution. Hormesis can provide
340 generalized estimates of biological plasticity (Calabrese and Mattson, 2011). In particular, it can
341 provide quantitative information both for the range of exposure levels at which plants show
342 plastic responses and the lower and upper boundaries for the plastic responses without
343 reproductive costs to the plants (Table 1, Fig. 1). This plasticity underpinning hormesis is
344 evolutionarily critical as it provides evidence for homeostasis and optimization and promotes
345 resilience through adaptation (Fig. 1). Therefore, the hormesis concept should be implemented to
346 truly learn more about ‘metabolism, its flexibility, its limits, and its diversity’ (Bohnert et al.,
347 1995). Ecotypes could be used for assessment of physiology and fitness traits so as to evaluate
348 the physiological findings of hormesis from ecological viewpoint.

349 **Hormesis and interactions between plants and other organisms**

350 High-level abiotic stress can disrupt the McNew’s conceptual model of *disease triangle*
351 (Chappelka and Grulke, 2016), which shows interactions between the environment, a host and a
352 stressor, and has further relevance to public health (Scholthof, 2007). The evidence provided
353 here indicates that low level stress may also affect the disease triangle. For instance, stimulation
354 of photosynthesis (Figs 2,4) may lead to reduced plant defense against biotic stress as the leaf
355 photosynthetic capacity is negatively correlated with the phenolic pool (Karabourniotis et al.,
356 2014), which is important for plant defense against biotic stress. Therefore, the carbon-nutrient

357 balance hypothesis along with plant homeostatic features (Hamilton et al., 2001) requires further
358 validation in relation to progressive hormesis.

359 Defensive chemicals produced by plants may induce hormesis in sequestering specialist insects
360 (Ali and Agrawal, 2012). Hormetic-like effects were also recently found in fruit flies (*Ceratitis*
361 *capitata* Wiedemann) as a result of exposure to essential oils (limonene) produced by citrus
362 plants (Papanastasiou et al., 2017) and in maize weevil (*Sitophilus zeamais* Motschulsky) as a
363 result of treatment with essential oils produced by cinnamon (*Cinnamomum zeylanicum* L), clove
364 (*Syzygium aromaticum* L.) and tea oil (*Melaleuca alternifolia* (Maiden & Betche) Cheel) plants
365 (Haddi et al., 2015; Liao et al., 2016). Hence, changes in chemical constituents of plants as a
366 result of exposure to low level environmental stress may affect plant-insect interactions in a
367 hormetic framework. An example of stimulation by environmental stress is the stimulation of
368 insect nutritional performance which was found when insects were fed with O₃-treated leaves
369 (Agathokleous et al., 2017c; Abu ElEla et al., 2018).

370 Furthermore, stress induced by environmental factors may generate biphasic emissions of
371 biogenic volatile organic compounds (VOCs), such as isoprene, suggesting the occurrence of
372 hormesis (Calfapietra et al., 2009; Yuan et al., 2016; Jiang et al., 2017; Tani et al., 2017). VOCs
373 enable a plant-to-plant communication and act as a signal for insect herbivores (Blande et al.,
374 2014). Thus, alteration of VOC emission at low-level exposures of plants to abiotic stressors may
375 alter plant-insect interactions too (Cui et al., 2014, 2016).

376 Similarly to plants, tolerance of insects and nematodes to environmental stress can be achieved
377 by regulating proteins (Cypser and Johnson, 2002; Hayward et al., 2004; Rinehart et al., 2006,
378 2007; Benoit et al., 2010; Kishimoto et al., 2017; Kumsta and Hansen, 2017; Kumsta et al.,
379 2017). For example, it has been revealed that heat shock proteins, Hsp70 and Hsp90, contributed
380 to the dehydration tolerance of three mosquito species, *Aedes aegypti*, *Anopheles gambiae* and
381 *Culex pipiens* (Benoit et al., 2010). This suggests that the tolerance can be inherited, and thus it
382 would be of utmost importance to study the consequences of hormesis over generations. Support
383 to this assumption is provided by an experiment where the heat-shock factor HSF-1 and the
384 insulin/insulin-like growth factor (IGF) signalling effector DAF-16/FOXO in the parental
385 somatic cells mediated the generation of epigenetic memory in animal biological models which
386 exhibited environmental stress (Kishimoto et al., 2017). It was suggested that the epigenetic
387 memory was "maintained through the histone H3 lysine 4 trimethylase complex in the germline
388 across generations" grown under unstressed conditions (Kishimoto et al., 2017). By using
389 *Caenorhabditis elegans* as a biological model, it was shown that heat stress in a hormetic
390 framework or HSF-1 overexpression may induce autophagy and reduce accumulation of

391 polyglutamine (PolyQ) aggregates, and thus contribute to stress tolerance (Kumsta and Hansen,
392 2017; Kumsta et al., 2017). All these lines of evidence suggest that stimulation in the framework
393 of hormesis may lead to enhanced health and tolerance to stress in insects and nematodes.
394 Apart from environmental hormesis in plants, indications for environmental hormesis have been
395 revealed in fungi (mostly upon indirect effects via changes in plants; Manning et al., 1969;
396 Manning and Tiedemann, 1995; McLeod et al., 1988; Paoletti et al., 2007; Mashaheet, 2016),
397 insects (López-Martínez and Hahn, 2012, 2014; López-Martínez et al., 2016a,b), and nematodes
398 (Cypser and Johnson, 2002; Kishimoto et al., 2017; Kumsta and Hansen, 2017; Kumsta et al.,
399 2017). For instance, it has been recently found that the free-living nematode *C. elegans* showed
400 transgenerationally inheritable survival advantages via germline-to-soma communication and
401 autophagy as a result of environmental stress (Kishimoto et al., 2017; Kumsta and Hansen, 2017;
402 Kumsta et al., 2017). Potential biological stimulation of insects, e.g. increased longevity and
403 enhanced sexual performance, by low-level exposures to abiotic factors (López-Martínez and
404 Hahn 2012, 2014; López-Martínez et al., 2014, 2016b) may have implications to biosphere
405 sustainability. Insects may become more tolerant to subsequent exposures to stressors (López-
406 Martínez and Hahn 2012, 2014; López-Martínez et al., 2014, 2016a,b), i.e. *environmental*
407 *conditioning hormesis*, and finally more injurious to plants and their productivity.

408 **Suggestions**

409 Environmental hormesis is a biological phenomenon with relevance not only to toxicology but
410 also to ecology and evolution. Insect-insect, insect-plant and generally trophic interactions may
411 be altered as a result of environmental hormesis.

412 VI. CONCLUSIONS: THE PATH FORWARD

413 Plants may display hormetic responses to a variety of environmental factors as a result of
414 physiological or biological stress, and this may affect trophic interactions in highly complex
415 ecosystems.

416 The evidence provided here indicates that response of plants to environmental stimuli should be
417 tested by incorporating the entire exposure–response continuum. In novel experimental setups, it
418 should be tested whether low-level exposure of plants to environmental factors reduces the
419 damage caused by a prior high-level exposure, i.e. *environmental postconditioning hormesis*.

420 The target of ecotoxicology is communities/populations and not individual organisms, and here it
421 is shown that hormesis can occur at organizational levels beyond the individual level. Therefore,

422 one challenging task will be to set critical exposure levels for protecting communities and
423 populations when stimulatory responses are taken into account.

424 The present findings support that environmental hormesis is a fundamental biological
425 phenomenon which can occur in nature. Graduate schools at universities should consider
426 implementing environmental hormesis in relevant courses so as to increase the awareness of
427 students regarding the existence of low exposure effects and to contribute in advancing science
428 by new generations of scientists.

429 One of the difficulties will be the required higher number of exposure levels with narrower
430 spacing (Calabrese and Baldwin, 2003c), to effectively identify hormesis and have at least two
431 exposure levels below NOAEL, with consequent large sample size (Calabrese, 1996). Sample
432 size would be further increased if temporal investigations with destructive sampling are taken
433 into account. Importantly, depending on the stressor, investigations of environmental hormesis
434 will require large number of well-replicated experimental units and can be prohibitive in terms of
435 financial costs. Funding agencies and policy makers should consider the importance of such
436 researches in investigating the adaptive mechanisms of vegetation to stress for resilience,
437 ecosystem health and finally biosphere sustainability. Human welfare would also be benefited
438 directly by sustaining natural pharmacological compounds used in medicine and vegetable
439 products of nutritional value and indirectly by sustaining biosphere.

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973 Table 1

974 **Table 1** Quantitative properties of exposure-response relationships which displayed hormesis.
975 Hormesis was observed in 52 relationships of which 38 displayed both LOAEL and NOAEL.
976 Max indicates maximum stimulatory response and NOAEL:max the factor at which the
977 maximum stimulatory response occurred below the NOAEL. With regards to magnitude range,
978 the number of curves falling within the corresponding magnitude range is given along with the
979 percentage of 52 hormetic curves in parenthesis.

980 Note: In one dose-response relationship, the maximum stimulation was lower than 105% (102%)
981 however statistically significant and thus was considered as 105% in the calculations of the
982 magnitude range.

Maximum stimulation (52 relationships)	
Arithmetic mean max	130.6%
Geometric mean max	129.1%
Minimum max	102.0%
Maximum max	212.0%
Magnitude range (52 relationships)	
105% < max ≤ 125%	25 (48.1%)
126% ≤ max ≤ 150%	23 (44.2%)
151% ≤ max ≤ 200%	4 (7.7%)
105% < max ≤ 124%	22 (42.3%)
110% < max < 150%	41 (78.8%)
125% ≤ max ≤ 161%	28 (53.8%)
NOAEL:max (52 relationships)	
Arithmetic mean NOAEL:max	1.56
Geometric mean NOAEL:max	1.44
Minimum NOAEL:max	1.00
Maximum NOAEL:max	4.00
LOAEL:NOAEL (41 relationships)	
Arithmetic mean LOAEL:NOAEL	1.86
Geometric mean LOAEL:NOAEL	1.77
Minimum LOAEL:NOAEL	1.08
Maximum LOAEL:NOAEL	4.39

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996 Figure Legends

997 **Fig 1.** The concept of hormesis. The figure is created based on data reported by Agathokleous et
998 al. (2016b), where the rate of non-photochemical quenching of chlorophyll *a* fluorescence (*NPQ*)
999 was measured in *Lemna minor* L. (duckweed) at 24 (early response), 72 (intermediate response)
1000 and 120 (late response) h from the initiation of exposure to 0, 148, 593, 1185 or 2370 mg l⁻¹
1001 ethylenediurea in the growing solution media. *NPQ* indicates the heat dissipation of excitation
1002 Energy (Moustakas et al., 2017).

1003 Note: The change in biological endpoints in response to treatment (exposure level) relative to the
1004 control group (% control) was calculated as $Response = \mu_c / \mu_T \times 100$, where μ_c is the mean
1005 value of μ of the control group and μ_T is the mean value of μ of each exposure level, such that
1006 reference point is 100 %. The curves are modeled based on the calculated response data and log-
1007 transformed EDU concentrations on abscissa.

1008 **Fig 2.** Representative examples of *U*-shaped dose–response curves induced by different types of
1009 environmental factors. Curves are plotted across observed data (solid curves) and modeled ones
1010 (dashed curves), using several endpoints: a) number of pods; b) total plant leaf area; c) net
1011 photosynthetic rate at 1700 $\mu\text{mol CO}_2 \text{ mol}^{-1}$ (A_{max}); d) diffusive conductance; e) shoot dry matter
1012 and malondialdehyde (MDA) content; f) relative growth rate (RGR) and net assimilation rate
1013 (A_{net}); g) yield and shoot dry matter; h) total plant leaf area, number of pods per plant, seed
1014 weight and yield; i) straw and ears dry weight; and j) grain yield and total dry weight. The
1015 endpoints were measured in different biological models: (a) Pot-grown seedlings of an O₃-
1016 sensitive (S156) and an O₃-tolerant (R123) genotype of snap bean (*Phaseolus vulgaris* L.)
1017 chronically exposed to increasing levels of ambient air temperature in outdoor plant environment
1018 chambers (OPECs) (Agathokleous et al., 2017a); (b) Pot-grown seedlings of *Quercus serrata*
1019 Murray 1784 (deciduous), *Fagus crenata* Blume (deciduous) and *Castanopsis sieboldii* (Makino)
1020 Hatus (evergreen) chronically (two growing seasons) exposed to increasing levels of SO₂ gas in
1021 open top chambers (OTCs) and theoretically 0 kg ha⁻¹ year⁻¹ soil nitrogen deposition (Yamaguchi
1022 et al., 2012); (c) Pot-grown seedlings of *F. crenata* chronically (two growing seasons) exposed to
1023 increasing levels of simulated nitrogen deposition with soil HNO₃ (Izuta et al., 2004); (d) Pot-
1024 free-grown snap beans seedlings (*P. vulgaris* L. cv 'GV50') exposed to increasing levels of H₂S
1025 gas for 18 ±2 d (66 hours in total) in rectangular minimum interference chambers when O₃ in
1026 atmosphere was either 0 (theoretically) or 72 nmol mol⁻¹ (Coyne and Bingham, 1978); (e) Pot-
1027 grown seedlings of spring barley (*Hordeum vulgare* L.) exposed to increasing levels of UV-B
1028 rays in phytotron chambers for one week (Kacienė et al., 2015); (f) Pot-grown seedlings of

1029 sunflower (*Helianthus annuus* L. cv Russian Mammoth) exposed to increasing levels of NO₂ in
1030 artificially lit growth cabinets for two weeks (Okano et al., 1985); (g) Pot-grown seedlings of
1031 barley (*H. vulgare* cv Hockey) and rape (*Brassica napus* L. cv Callypso) exposed to increasing
1032 levels of SO₂ gas in OTCs for about three months (Weigel et al., 1990); (h) Pot-free-grown
1033 seedlings of bean (*P. vulgaris* L. cv Nerina) exposed to increasing levels of O₃ in OTCs for about
1034 three months (Sanders et al., 1992); and (i-j) Pot-free-grown plants of winter barley (*H. vulgare*
1035 L. cv. Sonja) exposed to increasing levels of SO₂ in an open-air exposure system from November
1036 to July (McLeod et al., 1988).

1037 Note 1: The control UV-B exposure level in Kacienė et al. (2015) is not given, and, thus, it is
1038 considered 0.25 kJ m⁻² d⁻¹ because the exposure levels in the experiment were increasing on a
1039 two-fold power. The response of each treatment in McLeod et al. (1988) is based its own
1040 corresponding control plots, thus the lowest exposure level is around 105%.

1041 Note 2: When possible, data of each group (exposure level) were averaged per experimental unit
1042 and the averages were further averaged to give one estimate for each exposure level. The change
1043 in biological endpoints in response to treatment (exposure level) relative to the control group (%
1044 control) was calculated as $Response = \mu_c / \mu_T \times 100$, where μ_c is the mean value of μ of the
1045 control group and μ_T is the mean value of μ of each exposure level, such that reference point is
1046 100 %. Extraction of data from reviewed articles, when it was needed, was done using image
1047 analysis software (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA,
1048 USA).

1049 **Fig 3.** Representative examples of U-shaped exposure–response curves induced by O₃ stress.
1050 Curves are plotted across observed data (solid curves) and modeled ones (dashed curves), using
1051 different endpoints: a) stem height and water use efficiency (WUE); b) mesophyll conductance
1052 (g_m); c) methane fluxes; d) carotenoids content; e) height growth; and f) leaf area per pod and
1053 kernel yield. The endpoints were measured in different biological models: (a) Pot-grown
1054 seedlings of *Metasequoia glyptostroboides* exposed to 7.5, 50, 100 and 200 nmol O₃ mol⁻¹ in
1055 open top chambers (OTCs) for 25 days and 8 hours per day (09:00-17:00) (Feng et al., 2008b);
1056 (b) Pot-grown seedlings of an O₃-sensitive (S156) and two O₃-tolerant (R123, R331) genotypes
1057 of snap bean (*Phaseolus vulgaris* L.) exposed to 0.93, 14.79, 30.05 and 59.33 nmol O₃ mol⁻¹ (12-
1058 h average, 08:00-20:00) in outdoor plant environment chambers (OPECs); the experiment was
1059 conducted from 21 November 2003 to 12 February 2004 and from 20 February 2004 to 13 May
1060 2004 (Flowers et al., 2007); (c) Peatland mesocosms from an upland peat bog in UK were
1061 exposed to eight O₃ levels in solardomes from May to August (24 h AOT0) (Williamson et al.,

1062 2016); d) Pot-grown seedlings of spring barley (*Hordeum vulgare* L.) exposed to 11.25, 22.5, 45,
1063 90 and 180 nmol O₃ mol⁻¹ in phytotron chambers for one week and 12 hours per day (Kacienė et
1064 al., 2015); e) Pot-grown seedlings of sugar maple (*Acer saccharum* Marsh.) and yellow poplar
1065 (*Liriodendron tulipifera* L.) exposed to 0, 50, 100 and 150 nmol O₃ mol⁻¹ in indoor exposure
1066 chambers for 28 days and six hours per day (Kress and Skelly 1982); and f) Pot-grown plants of
1067 winter wheat (*Triticum aestivum* L., genotype MD01W-28-08-11) exposed to 10, 50, 75 and 100
1068 nmol O₃ mol⁻¹ in OTCs from heading to harvest (Mashaheet, 2016), and pot-free-grown
1069 seedlings of bean (*P. vulgaris* L. cv Nerina) exposed to 10, 20, 26, 32, 38, 45 and 50 nmol O₃
1070 mol⁻¹ in OTCs for about three months (Sanders et al., 1992). More information regarding
1071 calculations can be found in Note 1 of Fig 2.

1072 Notes: The lowest exposure level in Feng et al. (2007) was reported as <15 nmol mol⁻¹ and thus
1073 it was considered 7.5 nmol mol⁻¹ as the average between 0 and 15 nmol mol⁻¹. The control O₃
1074 exposure level in Kacienė et al. (2015) is not given, and, thus, it is considered 11.25 nmol mol⁻¹
1075 because a) the maximum O₃ mixing ratio in charcoal-filtered chambers is around this level and
1076 b) the other O₃ exposure levels in the experiment were increasing on a two-fold power. The
1077 control O₃ exposure level in Mashaheet (2016) is not clearly given, and, thus, it is considered 10
1078 nmol mol⁻¹ because the maximum O₃ mixing ratio in charcoal-filtered chambers is commonly
1079 around this level. The leaf area per pod in Sanders et al. (1992) was calculated as the average
1080 dose responses of two harvests conducted at different time points.

1081 **Fig 4.** Ozone-induced hormesis in two competitive larches. Observations come from pot-free-
1082 grown seedlings of the decidua conifers Japanese larch (*Larix kaempferi* (Lamb.) Carr.) and its
1083 hybrid larch F₁ (*Larix gmelinii* var. *japonica* (Maxim. ex Regel) Pilg. × *L. kaempferi*) exposed to
1084 increasing levels of O₃ in open top chambers (OTCs) for two growing seasons, during day-light
1085 hours (Sugai et al. 2018). The lowest O₃ level is comparable to pre-industrial O₃ levels. Net
1086 photosynthetic rate at saturated CO₂ (A_{max}), transpiration rate at ambient CO₂ (E_{380}), maximum
1087 rate of Ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO) carboxylation (V_{Cmax}),
1088 maximum rate of photosynthetic electron transport (J_{max}), total chlorophyll content per needle
1089 area and total plant dry matter (above and below ground) are shown. More information regarding
1090 calculations can be found in Note 1 of Fig 2.

1091 **Fig 5.** Species-specific hormesis in three evergreen and seven deciduous species depicted by root,
1092 shoot and total plant dry matter as biological endpoints. The exposure–response curves are
1093 plotted across observed data (solid curves) and modeled ones (dashed curves) of pot-grown
1094 seedlings of ten tree species exposed to 0, 50, 100 and 150 nmol O₃ mol⁻¹ in indoor exposure
1095 chambers for 28 consecutive days and six hours per day (Kress and Skelly, 1982). The evergreen

1096 species were: a) loblolly pine full-sib collection (*Pinus taeda* L.); b) pitch pine (*P. rigida* Mill.);
1097 c) Virginia pine (*P. virginiana* Mill.). The deciduous species were: d) sweetgum (*Liquidambar*
1098 *styraciflua* L.); e) American sycamore (*Platanus occidentalis* L.); f) sugar maple (*Acer*
1099 *saccharum* Marsh.); g) yellow poplar (*Liriodendron tulipifera* L.); h) white ash (*Fraxinus*
1100 *americana* L.); i) green ash (*F. pennsylvanica* Marsh); and j) willow oak (*Quercus phellos* L.).
1101 More information regarding calculations can be found in Note 1 of Fig 2.

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Fig 1

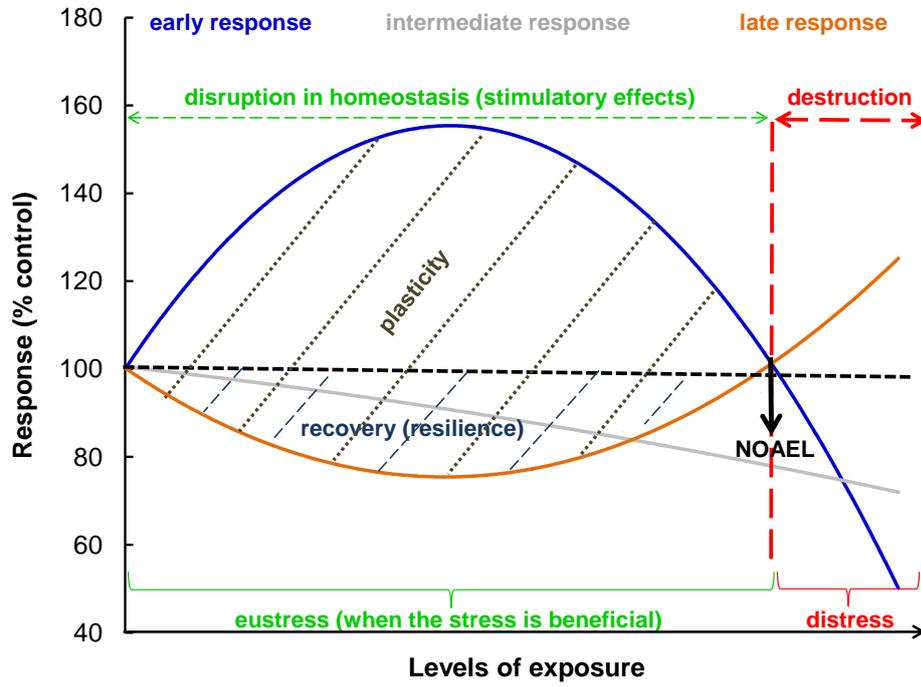


Fig 2

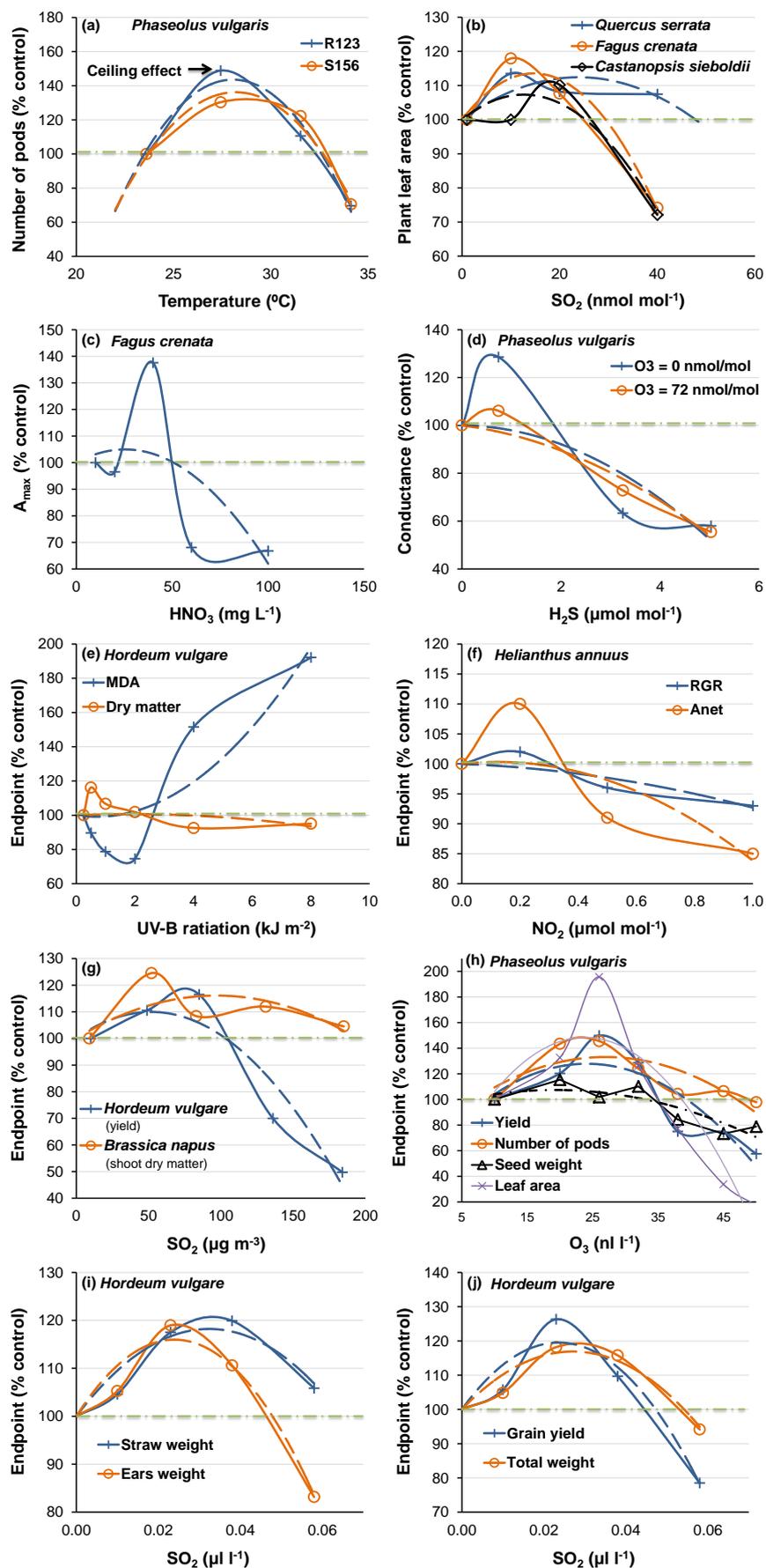


Fig 3

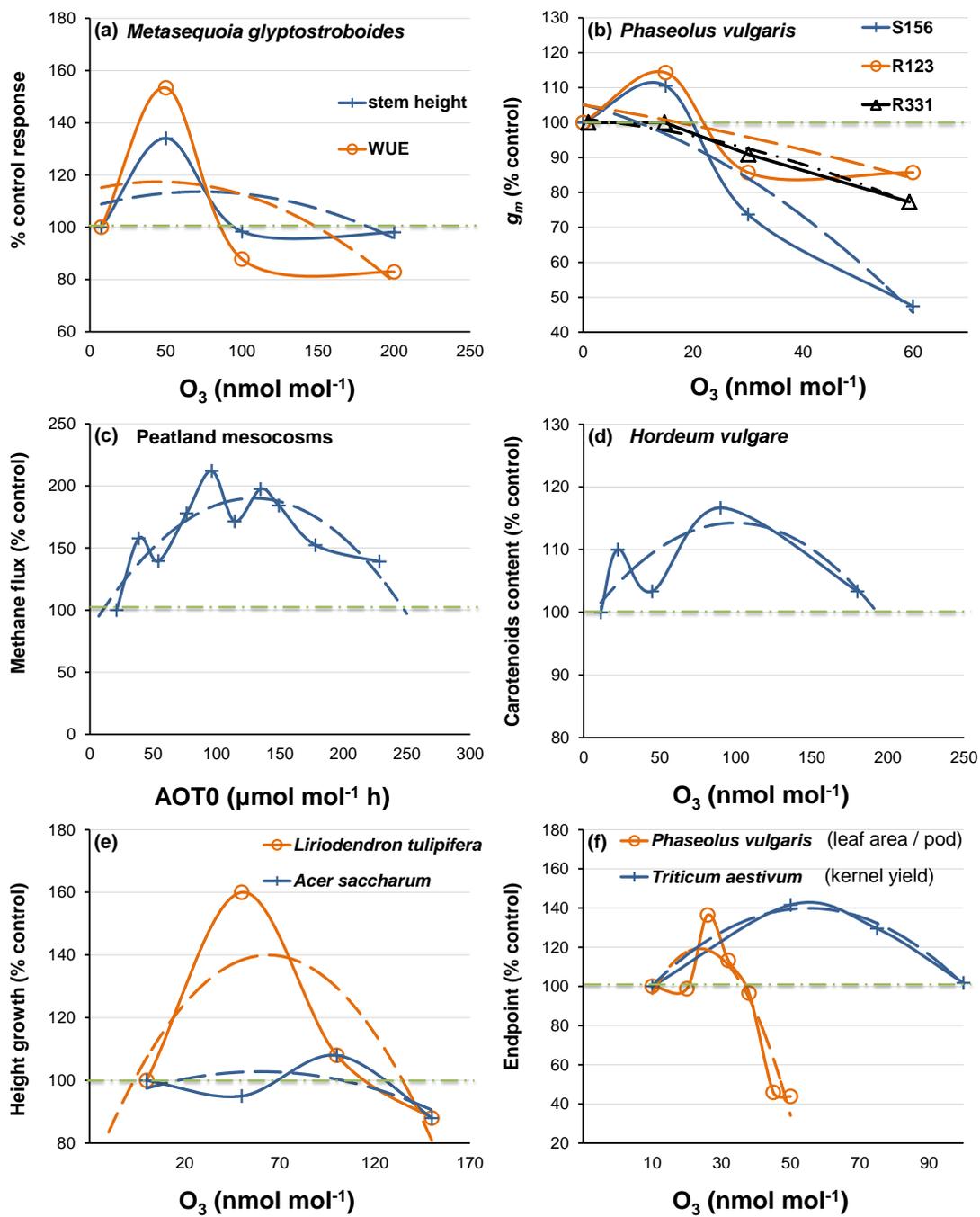


Fig 4

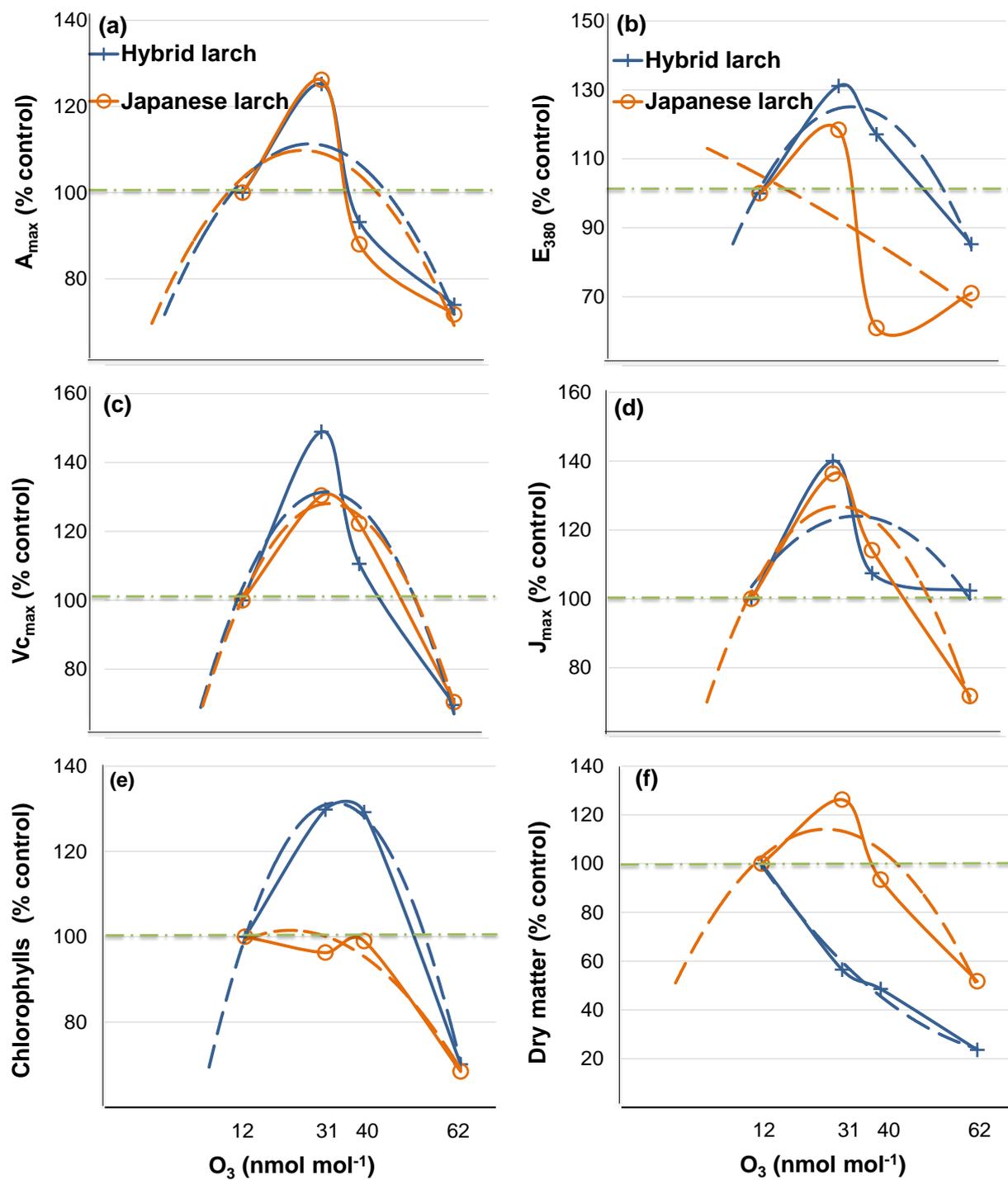


Fig 5

