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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

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

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

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

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

II. THE CONCEPT OF HORMESIS

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

¹ hereafter referred as “organisms” unless specified otherwise

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

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

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

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

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

III. ENVIRONMENTAL HORMESIS

Plant stress induced by environmental factors

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

Hormesis induced by environmental factors

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

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

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

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

The examined studies (Figs 2-5) suggest that hormetic responses can be cultivar- or genotype-specific and endpoint-specific (Kress and Skelly, 1982; Weigel et al., 1990; Yamaguchi et al., 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

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

Environmental hormesis

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

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

Suggestions

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

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

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

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

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

IV. RELEVANCE TO HUMAN WELFARE & BIOSPHERE SUSTAINABILITY

Hormesis in human nutrition and medicine

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

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

Conditioning hormesis in post-harvest engineering

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

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

Suggestions

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

V. RELEVANCE TO ECOLOGICAL AND EVOLUTIONARY THEORY

Hormesis beyond individual level

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

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

Hormesis and competition

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

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

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

Hormesis and plasticity

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

Hormesis and interactions between plants and other organisms

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

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

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

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

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

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

Suggestions

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

VI. CONCLUSIONS: THE PATH FORWARD

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

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

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

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

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

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

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Table 1

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

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

Figure Legends

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

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

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

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

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

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

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

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

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

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

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

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

Fig 1

Fig 2

Fig 3

Fig 4

Fig 5