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Predicting the effect of ozone on vegetation via linear non-threshold (LNT), threshold and hormetic dose-response models

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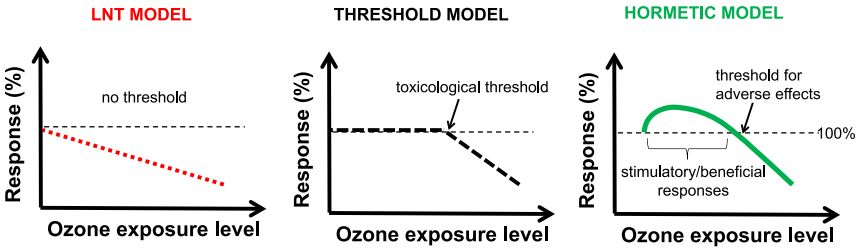
HIGHLIGHTS

- Hormesis is a biologically-based biphasic dose response phenomenon.
- Hormetic doses responses are induced by ground-level ozone (O_3) in plants.
- Hormesis represents a quantification of adaptive responses at low O_3 doses.
- Hormesis should be incorporated into the processes of O_3 hazard and risk assessment.

GRAPHICAL ABSTRACT



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ABSTRACT

The nature of the dose-response relationship in the low dose zone and how this concept may be used by regulatory agencies for science-based policy guidance and risk assessment practices are addressed here by using the effects of surface ozone (O_3) on plants as a key example for dynamic ecosystems sustainability. This paper evaluates the current use of the linear non-threshold (LNT) dose-response model for O_3. The LNT model has been typically applied in limited field studies which measured damage from high exposures, and used to estimate responses to lower concentrations. This risk assessment strategy ignores the possibility of biological acclimation to low doses of stressor agents. The upregulation of adaptive responses by low O_3 concentrations typically yields pleiotropic responses, with some induced endpoints displaying hormetic-like biphasic dose-response relationships. Such observations recognize the need for risk assessment flexibility depending upon the endpoints measured, background responses, as well as possible dose-time compensatory responses. Regulatory modeling strategies would be significantly improved by the adoption of the hormetic dose response as a formal/routine risk assessment option based on its substantial support within the literature, capacity to describe the entire dose-response continuum, documented explanatory dose-dependent mechanisms, and flexibility to default to a threshold feature when background responses preclude application of biphasic dose responses.

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Capsule: The processes of ozone hazard and risk assessment can be enhanced by incorporating hormesis into their principles and practices.

1. Introduction

The progressive elevation of background O_3 levels within the past century has drawn the attention of the research community to the effects of elevated O_3 levels on humans and vegetation (Krupa et al., 1995; Paoletti, 2006; World Health Organization (WHO), 2008; Ainsworth et al., 2012; Agathokleous et al., 2015, 2018a; Feng et al., 2015; Yuan et al., 2015; Ainsworth, 2016; Sicard et al., 2016a). The exposure index AOT40 (O_3 levels Accumulated Over the Threshold of 40 ppb) was introduced by worldwide regulatory agencies to protect vegetation (Fuhrer et al., 1997; Mills et al., 2007; Agathokleous et al., 2018a). Metrics, like AOT40, are used as predictors of plant response in dose-response relationships, instead of mean O_3 concentrations, to derive critical levels (CL). Ozone CL are dose levels above which adverse effects on vegetation can occur (Fuhrer et al., 1997). Critical levels, under the Convention on Long-Range Transboundary Air Pollution of the United Nations Economic Commission for Europe (UNECE), are defined as "concentration, cumulative exposure or cumulative stomatal flux of atmospheric pollutants above which direct adverse effects on sensitive vegetation may occur according to present knowledge" (Spranger et al., 2004), and constitute the basis of the Ambient Air Quality Directive 2008/50/EC of the European Union (E.U.).

The two models most widely applied in toxicological dose responses are the threshold and linear no threshold (LNT). The LNT model posits that the response of an organism to an agent is directly proportional to the dose (i.e. linear extrapolation down to zero dose), that is, any dose level above zero. In contrast, the threshold model assumes a dose below which there is no treatment effect. However, the use of these two models has been challenged by the hormesis model, a biphasic dose-response phenomenon in which the response at low doses is opposite that occurring at higher doses (Agathokleous et al., 2018b; Calabrese and Baldwin, 2003a; Calabrese et al., 2007; Calabrese, 2011, 2014, 2015a; Hashmi et al., 2014).

This paper: 1) reviews the literature concerning the effects of O_3 on plant biology over the entire dose (time)-response continuum for multiple key biological endpoints; 2) provides an integrated mechanistic evaluation where possible for the entire dose (time)-response continuum; and 3) evaluates the above findings within the context of the three most significant environmental assessment models, i.e., the threshold, LNT and hormetic models and the risk assessment implications.

2. Linearity & vegetation: basis for LNT, AOT40 & perspectives

2.1. Basis for LNT - the AOTX metric for O_3 (an LNT/threshold combination)

The Accumulated O_3 levels Over a Threshold *X* (AOT*X*) is an O_3 metric utilized as predictor of plant response in dose-response relationships to derive CL (Supplementary materials 1, Fig. 1S). A linear dose-response model has been typically applied for AOT*X*-derived CL, whereas worldwide regulatory agencies have adopted 40 ppb for *X* threshold (see Kärenlampi and Skärby, 1996; Fuhrer et al., 1997; Grünhage et al., 1999; Agathokleous et al., 2018a, for historical foundations of the AOT metric).

2.2. AOT40 as a predictor of biological response

2.2.1. History

In the early 1990s, the AOT*X* metric concept was proposed at a workshop of UNECE in the U.K. (Ashmore and Wilson, 1992), which was later adopted and set at a threshold of 40 ppb (current AOT40) at a workshop in Switzerland based on a modification of Haber's rule (exposure concentration rate × duration = constant) that would permit a threshold at lower doses and a more dose-dependent response at progressively higher concentrations (Fuhrer and Achermann, 1994). A value of 40 ppb O_3 was selected as threshold, since it provided "good" fit to linear relationships for a number of species, while the O_3 concentrations found in many areas were in the range 10–40 ppb (WHO, 2000). AOT40-based CL values were proposed for different kinds of vegetation at a workshop in Finland (Kärenlampi and Skärby, 1996). A CL of 3000 ppb h (i.e., growing season's cumulative hourly ozone exposure) was derived from an LNT model using data from 10 wheat cultivars from different experiments conducted in 6 countries over a decade (Fuhrer et al., 1997). This value was accepted in the UNECE Workshop "Critical Levels for Ozone – Level II" in 1999 (Fuhrer and Achermann, 1999) and proposed to the Working Group on Strategies and Review for assessing O_3 risk to crop plants (Karlsson et al., 2003). The UNECE International Cooperative Programme on Effects of Air Pollution on Natural Vegetation and Crops (ICP-Vegetation) subsequently initiated projects to investigate the risk of vegetation from O_3 pollution (Karlsson et al., 2003). This was the initial process by which O_3 risk assessment was established as a type of a linear dose-response process. Several CLs were thereafter derived from LNT dose-response models (Karlsson et al., 2003, 2004; Mills et al., 2007; Sicard et al., 2016a; Agathokleous et al., 2018a).

2.2.2. Why not the threshold model?

There is no published research why a threshold model was not considered/used for the dose-response relationships for the AOT*X*(40), even though a threshold perspective was supported based on evidence for threshold or non-linear threshold-like responses of visible foliar injury, biomass, growth and yield endpoints of several species to increasing AOT*X* or mean O_3 levels[1] (Supplementary materials 1).

2.2.3. The limitations of AOT40

The AOT40 metric has four limitations:

(1) *Lower threshold may be better*

First, AOT40 was challenged in 1995, by showing that lower thresholds (e.g. AOT0, AOT30) can be equally or more effective than AOT40 (Pleijel et al., 1995; Skärby and Pleijel, 1996). Change to lower thresholds remained an open discussion in later UNECE workshops (Karlsson et al., 2003), which has never been addressed (Agathokleous et al., 2018a).

(2) O_3 *damage can be repaired*

Second, AOT40 was based on the belief that O_3 injury is irreparable. However it was mentioned from the early stages of its adoption that this is not supported by a mechanistic basis (Fuhrer et al., 1997). For instance, perennial plants can display acclimation to harsh environments over prolonged periods (Tissue and Lewis, 2012; see also Section 3.5).

[1] Heck et al., 1966; Ting and Dugger, 1968; Heagle et al., 1972; Harward and Treshow, 1975; Oshima et al., 1975; Heck and Dunning, 1976; Carnahan et al., 1978; Heck et al., 1982; Kress and Skelly, 1982; Roberts, 1984; Endress and Grunwald, 1985; Reich and Lassoie, 1985; Kress et al., 1985; Shafer et al., 1987; McLeod et al., 1988; Darrall, 1989; Tenga et al., 1990; Sanders et al., 1992; Matyssek et al., 1993; Pleijel et al., 1995.

(3) *Lack of chamber* versus *field study agreement*

Third, in the report of the Gothenburg workshop, it was also suggested that dose responses based on chamber experiments appear linear or non-linear and that this phenomenon is not in line with observations from the ambient environments where biological responses do not always increase with increasing O_3 exposure (Karlsson et al., 2003; see Section 3). Furthermore, the yield responses to AOT40 can significantly differ between chamber and chamberless environments (Feng et al., 2018a).

(4) *Fails to adequately address plant stress response*

Fourth, in the same report, several limitations are described which show that the current O_3 CL were derived in an era (1990s) where the scientific understanding about dose responses and plant stress were limited. The biphasic dose responses and dynamic stress biological mechanisms with dual action of reactive oxygen species (ROS) and reactive nitrogen species in plant stress, with stimulatory response at low exposure levels, were recognized mainly in the last two decades (Cedergreen et al., 2007; Valko et al., 2007; Pham-Huy et al., 2008; Hadacek et al., 2010; Shapiguzov et al., 2012; Lushchak, 2014; Schieber and Chandel, 2014; Ye et al., 2015; Abbas et al., 2017; Agathokleous, 2018; Agathokleous et al., 2018c). Despite these limitations, AOT40-based CL, derived from LNT model, have been adopted by worldwide regulatory authorities such as U.S. EPA, and UNECE (Agathokleous et al., 2018a). AOT40-based standards were also introduced by the Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe.

2.3. Visible foliar injury for O_3 critical levels & risk assessment

Visible foliar injury (necrosis or discoloration other than chlorosis) is a more effective biomarker of phytotoxic levels of O_3 than any other endpoint, and occurs across different environments (Grulke, 2003; Agathokleous et al., 2017). Ozone-induced foliar injury is also more realistic than crown discoloration and defoliation because the latter endpoints can be affected by biotic factors (Sicard et al., 2016b; Agathokleous et al., 2017). However, hormesis cannot appear when visible foliar injury is the endpoint because visible injury can only increase relative to control asymptomatic leaves. This is because visible injury is arbitrarily estimated as a percentage of the leaf area that displays typical O_3 symptoms rather than a subjective measure of leaf greenness; i.e. there is no beneficial visible injury (there is either no visible injury or there is visible injury in a range of values such as 1–100%). On the other hand, LNT ignores: i) detoxification processes that are dynamic and cannot be represented by a constant threshold value (Musselman et al., 2006); ii) evidence that O_3 induces visible foliar injury only above species-specific dose thresholds (Ting and Dugger, 1968; Bergmann et al., 1999; Grulke, 2003; Schaub et al., 2010); and iii) the values at which the visible injury is estimated are percentages in the range 0–100 or even in a very narrow range on the basis of a Likert-type scale.

While the threshold model could be used for visible foliar injury (VanderHeyden et al., 2001; Graham et al., 2009), a sigmoid model or extensions of it, such as generalized logistic model (Richards' curve) or Gompertz model, with finite limits could be more effective when the exposure levels spacing is narrow (Heck et al., 1966; Carnahan et al., 1978). Sigmoidal dose-response relationships were also found in an ecological risk assessment on Species Sensitivity Distribution where fractions with values in the range 0 to 1 were used as endpoints against the AOT40 index (van Goethem et al., 2013). The Standard Hill model could be utilized to generate sigmoidal dose-response curves (Veroli et al., 2015).

2.4. Limitations of visible injury as marker for O_3 damage

Even though visible injury is the most representative biomarker of O_3–induced damage, its use as endpoint for deriving CLs has three major limitations:

(1) *Failure to Identify Subclinical Damage*

First, O_3-induced visible injury may be generated at later stages of chronic exposure to high O_3 levels, which gradually exhausts antioxidant defenses and depletes other plant resources, or after an acute exposure to O_3 levels much higher than the threshold for visible injury (Mashaheet, 2016). However, invisible injury can induce clinical damage without the presence of immediate visible foliar injury (Kress and Skelly, 1982; Agathokleous et al., 2015).

(2) *Incorrect Causal Inference*

Second, symptoms may be an epiphenomenon of ecosystem processes caused by numerous other biotic factors (e.g. diseases, viruses, pathogens, insects), and, yet, they do not necessarily linearly correlate with measurable biomass losses (Kress and Skelly, 1982; Chappelka and Samuelson, 1998; Bussotti and Pollastrini, 2015) (see also Supplementary materials 1).

(3) *Measurement Lacks Sufficient Objectivity*

Third, in contrast to other endpoints (e.g., photosynthesis, growth, biomass), which are "measured" with standardized methods, visible injury is subjective.

These limitations suggest that whatever model is used, O_3 risk may be under- or overestimated when visible foliar injury is the endpoint. Visible foliar O_3 injury and biomass losses should be integrated as real-world plant parameters for field surveys (Sicard et al., 2016a).

2.5. Ozone dose response metrics

Ozone concentration thresholds were adopted for the O_3 exposure metrics, such that concentrations below the defined threshold (e.g. 40 ppb for AOT40 metric) are excluded during the calculation of the metric which is eventually utilized as response predictor in the dose-response relationship (Supplementary materials 1, Fig. 1S). Implementing thresholds in the O_3 exposure metric (response predictor) rather than in the dose-response relationship is biologically and toxicologically inappropriate because rather low O_3 concentrations can induce biological responses (Figs. 1–3). Even if O_3 injury was cumulative, what is toxicologically appropriate is to use the average O_3 concentrations or the total exposure above a zero threshold (Agathokleous et al., 2018a). It should be also considered that average concentrations can be more effective predictors of the response than the duration of exposure (or total exposure), especially at higher exposure levels (Forberg et al., 1987; Saitanis et al., 2014).

To protect vegetation against O_3-induced adverse effects, O_3 exposure indices/metrics with no thresholds in the concentrations (e.g. AOT40) are needed (De Marco et al., 2015; Anav et al., 2016; Sicard et al., 2016a; Agathokleous et al., 2018a). The resulting dose-response relationship, where the O_3 metric is the predictor of biological response, should be examined whether it follows a non-linear pattern with thresholds (Figs. 1, 4) or a linear one with no thresholds (Fig. 4).

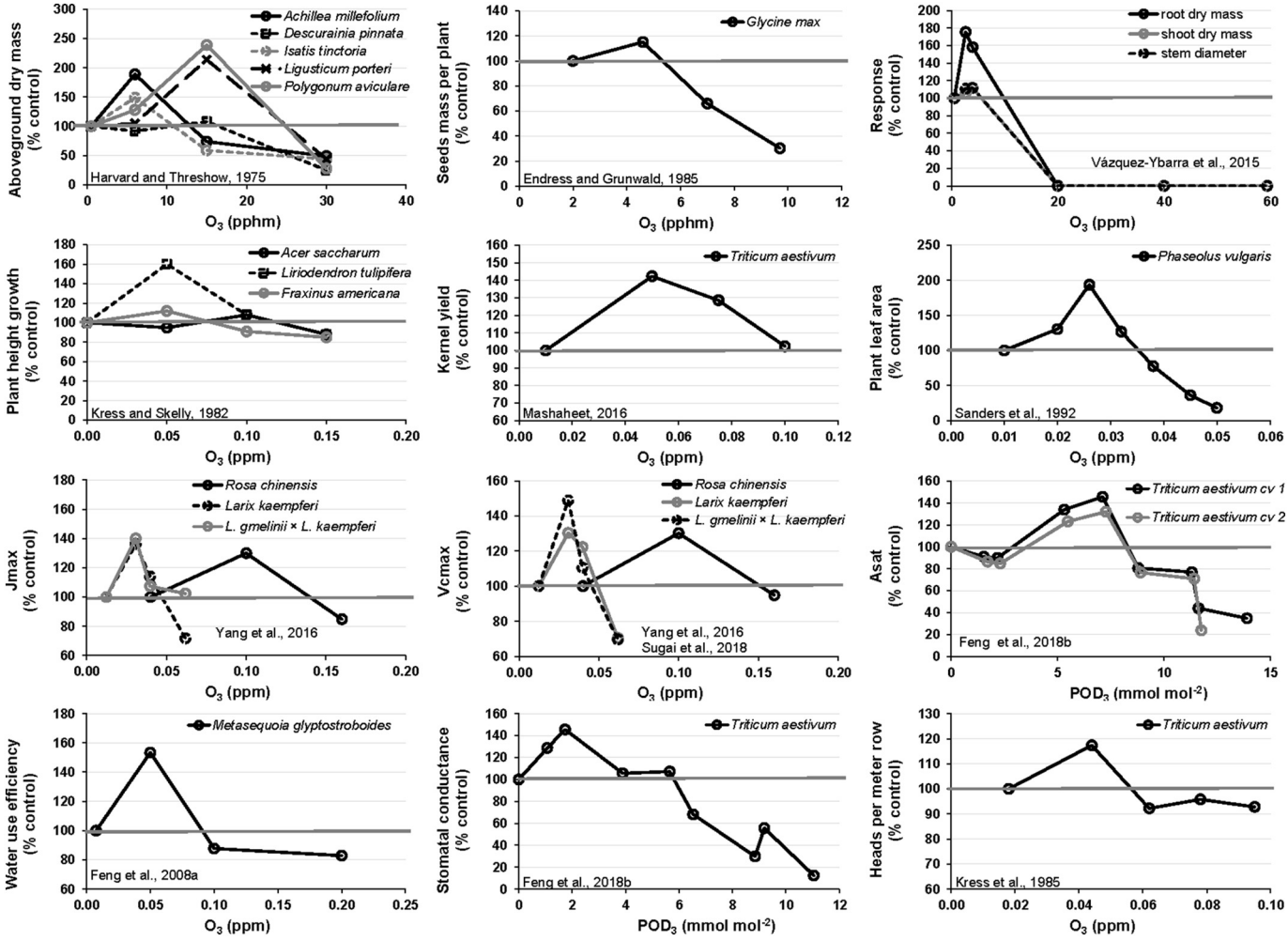

Fig. 1. Examples of hormetic-like dose responses from published literature. When needed, dose levels and response data were estimated from figures using an image analysis software (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA, USA). The estimates were corrected by taking into account the estimation error. Details on the experiments can be found in Supplementary materials 2, Table 1S.

3. What is missing: the hormesis paradigm

3.1. Hormesis

Hormesis is described by a non-monotonic or biphasic dose-response curve (Fig. 1), in contrast to a monotonically increasing dose-response curve. The biphasic dose response may be represented by an inverted *U*-shaped or a *J*-shaped dose-response curve, depending on the endpoint. In the case of cell proliferation, growth and longevity, hormetic responses are typically graphed as inverted *U*-shaped. In the case of mutation or various disease incidences hormetic responses are typically graphed as *J*-shaped. The hormetic dose response has been reported to occur in short-term and chronic studies, both being affected by the pharmacokinetic/dynamic factors. It is widely reported that a low-level dose often induces stimulatory effects whereas a high-level dose leads to inhibitory and/or adverse effects (Calabrese and Baldwin, 2001a; Calabrese, 2014; Calabrese et al., 2007).

The basis for hormesis dates approximately 130 years back, when Schulz reported that numerous disinfectants stimulated the metabolism and the survival of yeast at low doses, while being harmful at high doses (Schulz, 1887, 1888). These findings were extended to bacteria by Hueppe (1899) and by others (see Calabrese and Baldwin, 2000a, 2000b, 2000c, 2000d, for this early history). Hormesis, as a term, was introduced later, in the framework of experiments assessing the effects of chemical extracts from cedar wood on fungi (Southam and Erlich, 1943). As has now been well documented, hormesis was marginalized due to misconceptions in the scientific community mostly due to its becoming part of the dispute between traditional medicine and homeopathy (Calabrese and Baldwin, 2000a, 2000b, 2000c, 2000d; Calabrese, 2011, 2016a).

Significant research efforts were made mainly during the last two decades which led to mainstreaming hormesis (Calabrese and Baldwin, 2001a; Calabrese, 2004, 2005a, 2005b, 2011, 2016a; Hayes, 2008; Calabrese and Blain, 2011; Cutler, 2013; Hashmi et al., 2014; Linning and Eck, 2018). As a result, hundreds of agents and mixtures were found to induce hormesis across various experimental models, including plants (Calabrese, 2015a; Calabrese and Baldwin, 2001a, 2001b, 2003b; Cedergreen et al., 2007; Cutler, 2013; Agathokleous, 2018). Hormesis was observed in many endpoints, such as behavior, growth, physiology, reproduction, and survival, and across the spectrum of biological organization levels ranging from the cell level to individual and community levels (Calabrese, 2015a; Calabrese and Baldwin, 2001a, 2001b, 2003b; Hayes, 2008; Agathokleous, 2018).

Of particular importance is that the quantitative features of the hormetic dose response were independent of biological model, endpoint, inducing agent and mechanism, suggesting that hormesis is a fundamental feature of biological plasticity. The hormetic stimulation is typically modest with a maximum amplitude only about 30–60% greater than the control group (Calabrese, 2013).

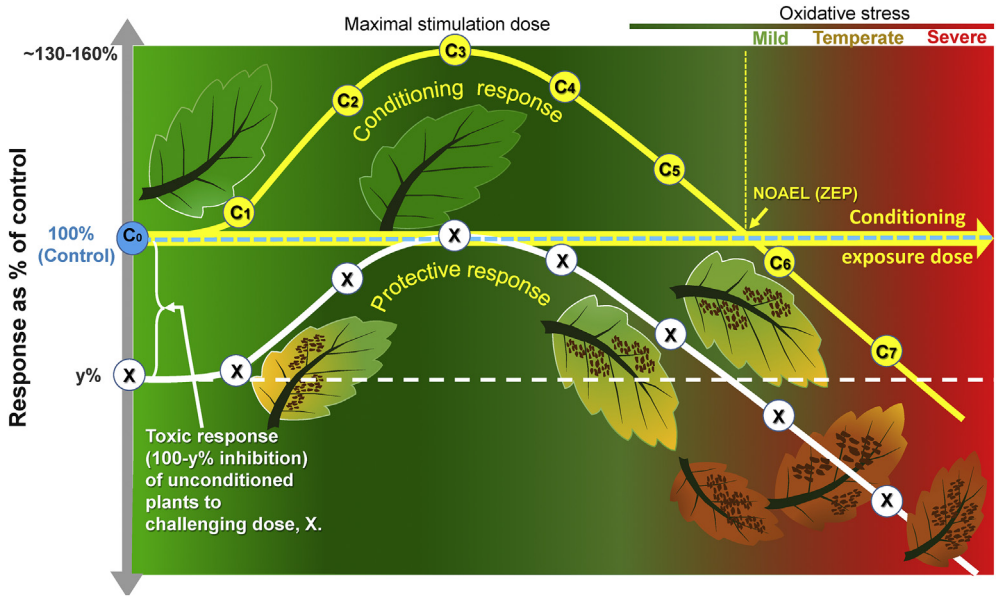

Fig. 2. Hypothetical scheme of pre-exposure (*conditioning*) hormesis. When different plants are exposed either to theoretically zero (C_0, blue) or to a variety of ozone (O_3) levels which are narrowly spaced up to a higher nonlethal level (e.g. C_1–C_7, yellow), the defensive capacity of the O_3 treated plants will be stimulated and a typical hormetic exposure-response curve will likely appear (solid-yellow line). Two parts can be distinguished on this curve: (a) one part at the left of the no-observed-adverse-effect level (NOAEL; or ZEP), which shows stimulation with potential beneficial effects of the conditioning doses on the plant, and (b) one part at the right of NOAEL, which shows adverse effects on the plant. At any re-exposure (later in life) of the same, already conditioned plants to a massive, highly injurious and challenging O_3 exposure of level X (white line), the adverse effects are expected to be mitigated in plants preconditioned with doses <NOAEL. The highest mitigation is expected to appear in plants pre-exposed to the maximal stimulation dose (C_3). The scheme is created based on Calabrese (2016c) and the classification of oxidative stress based on the intensity of stress of Lushchak (2014). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Plant hormesis

In plants, indications for hormesis have a long history, as irradiation from various sources (Calabrese and Baldwin, 2000c) and several chemicals (Calabrese and Baldwin, 2000d) were found to stimulate plant growth.

Re-examination of previously published data along with additional contemporary evidence indicates that hormesis appears widely in plants as a result of exposure to chemical agents or environmental stimuli (Calabrese and Baldwin, 2000d; Cedergreen et al., 2005, 2007, 2009; Belz et al., 2008; Calabrese and Blain, 2009; Hadacek et al., 2010; Belz and Cedergreen, 2010; Cedergreen and Olesen, 2010; Poschenrieder et al., 2013; Hashmi et al., 2014; Agathokleous, 2017, 2018; Vargas-Hernandez et al., 2017). The maximum stimulatory response is commonly <2-fold that of controls and the width of the stimulatory dose range is <20-fold, independent of the endpoint, while the quantitative features are similar to those in invertebrate and vertebrate animals and micro-organisms (Calabrese and Blain, 2009; Agathokleous, 2018; Agathokleous and Kitao, 2018; Agathokleous et al., 2018c).

3.3. Ozone – plant hormesis

Stimulation of plant growth by low levels of O_3 was initially reported by Bennett et al. (1974) and later summarized in a book chapter (Jaeger and Krupa, 2009). That literature review revealed some studies which indicated O_3-induced hormesis in growth or yield endpoints of 13 unique species, by finding a statistically significant responses or with responses ≥110% relative to the control (Neil et al., 1973; Bennett et al., 1974; Harward and Treshow, 1975; Bennett and Runeckles, 1977; Endress and Grunwald, 1985; Rajput and Ormrod, 1986; Adaros et al., 1991; Sanders et al., 1992; Finnan et al., 1996). Jaeger and Krupa (2009) presented also a photo from the European Biostress Program of the Agricultural University of Wageningen, The Netherlands, where purple moor-grass displayed growth stimulation to increasing O_3 levels (3, 34, 54 and 77 ppb). Hormesis has also been reported by other studies (Percy et al., 2009; Vázquez-Ybarra et al., 2015; Mashaheet, 2016; Sugai et al., 2018; details in Supplementary materials 2, Table 1S). More recently, it was shown that hormesis can be induced by a variety of abiotic factors, including O_3 (Agathokleous, 2018).

An expanded literature assessment reveals significant evidence from nearly 100 examples supporting the occurrence of O_3-induced hormesis (Supplementary materials 2, Tables 1S, 2S). These examples come from 28 unique studies[2] and provide evidence for either O_3-induced hormesis with both stimulation and no-observed-adverse-effect level (NOAEL) (Supplementary materials 2, Table 1S; Fig. 2) or significant O_3-induced stimulation without NOAEL (Supplementary materials 2, Table 2S) in 39 unique endpoints, from at least 33 taxa and several cultivars or genotypes. From the 39 endpoints, 66.7% are growth or production, 28.2% physiological and 5.1% nutritional endpoints. In about 60% of the studies, O_3 exposure lasted for at least one growing season, i.e. about three or more months.

It is important to note that hormesis is endpoint specific. Low doses can negatively affect plant productivity when plants are under competition for resources (Sugai et al., 2018). Furthermore, while stimulation can be observed in some endpoints, inhibition can be observed in others (Kam et al., 2015). These suggest that care should be exercised when selecting endpoints for conducting risk assessment; production endpoints can shed light on the question whether the low-dose effects are beneficial.

A meta-analysis has shown no evidence for stimulatory response of photosynthesis to O_3 across diverse angiosperm and gymnosperm trees

[2] The studies including this evidence are: Adaros et al. (1991), Bennett (1975), Bennett and Runeckles (1977), Bennett et al. (1974, 1979); Eamus et al. (1990), Endress and Grunwald (1985), Finnan et al. (1996), Feng et al. (2008a, 2018b), Harward and Treshow (1975), Hiraoka et al. (2017), Hoshika et al. (2013), Juknys et al. (2008), Kam et al. (2015), Kitao et al. (2015), Kress et al. (1985), Kress and Skelly (1982), Leone and Brennan (1975), Mashaheet (2016), Neil et al. (1973), Percy et al. (2009), Pleijel and Danielsson (1997), Rajput and Ormrod (1986), Sanders et al. (1992), Sugai et al. (2018), Vázquez-Ybarra et al. (2015), Williamson et al. (2016), and Yang et al. (2016).

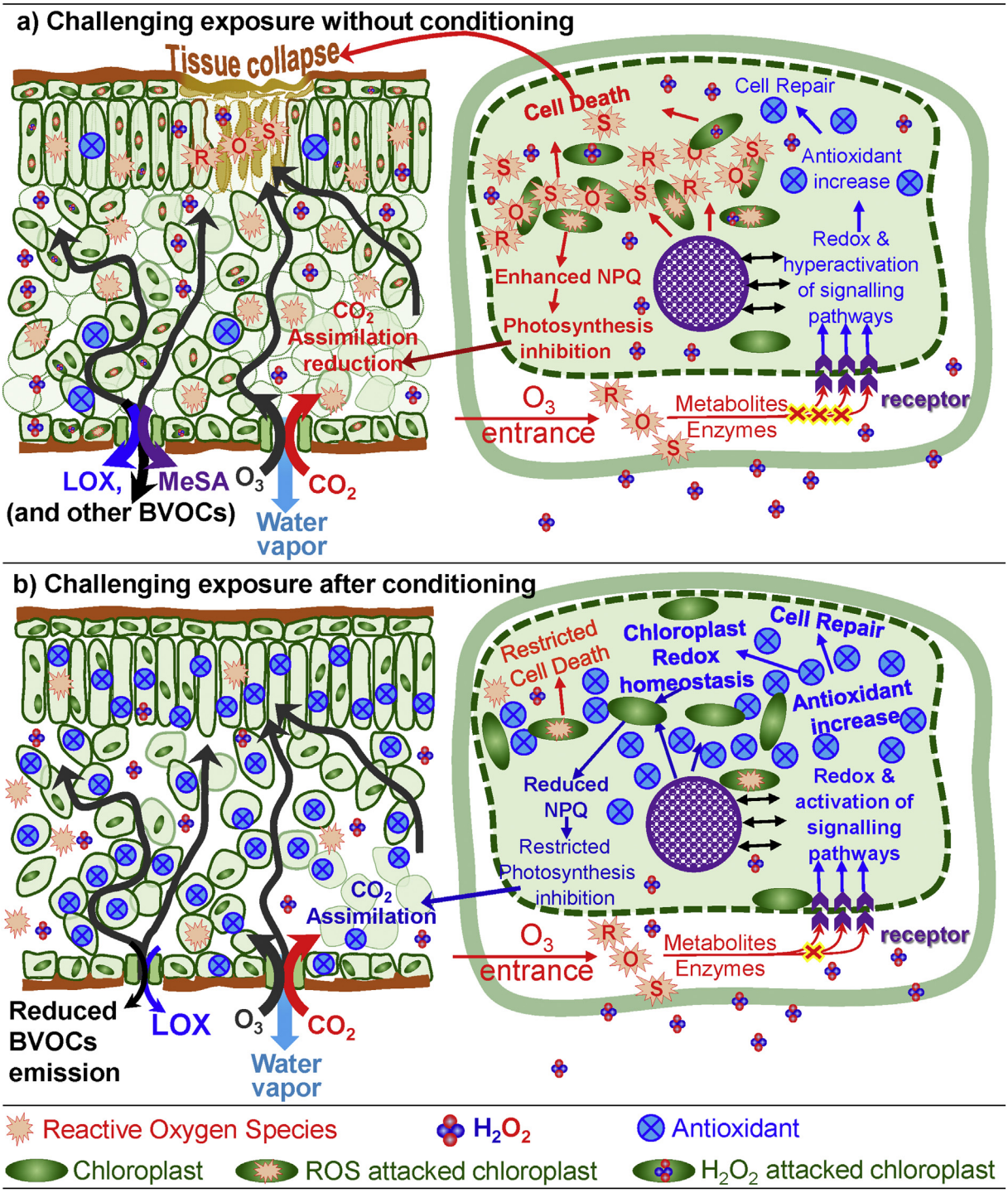

Fig. 3. Conceptual depiction of the major biological processes involved at cell (right) and tissue (left) level in the response of plants to O_3 exposure (a) without or (b) after (low-dose) pre-exposure (conditioning). a) **Without conditioning**: O_3 triggers the reactive oxygen species (ROS) formation, the overaccumulation of which leads to enhanced non-photochemical quenching of chlorophyll fluorescence (NPQ), photosynthesis inhibition, cell death, and tissue collapse. Biogenic volatile organic compounds, BVOCs (methyl salicylate (MeSA) and especially lipoxygenase (LOX)), are emitted from leaves. H_2O_2 is over-accumulated and expanded from the cell wall to the plasma membrane, cytosol, and chloroplasts. b) **With conditioning**: Pre-exposure stimulates antioxidants formation preventing cell death and photosynthesis inhibition. LOX emission is restricted; MeSA emission is eliminated. H_2O_2 is restricted to the apoplast without adverse effects to the cells. The concept is drawn based on preliminary evidence discussed in Section 3.4 "Ozone – Plant conditioning."

(Wittig et al., 2007, 2009). A similar analysis suggests the same for soybean (Morgan et al., 2003) and wheat (Feng et al., 2008b). However, the total biomass of angiosperms was about 110% of control when O_3 was <40 ppb (average = 29 ppb), but with large variance as there were only 9 degrees of freedom (Wittig et al., 2009). These studies may indicate that, as a general response, plants are not stimulated by low O_3 doses (Morgan et al., 2003; Wittig et al., 2007, 2009; Feng et al., 2008b). However, these meta-analyses do not support such an assumption because (i) they lack data from the low-dose zone (the entire toxicological literature suffers from satisfied requirements for evidence of hormesis; see Calabrese and Baldwin (2001a) and Calabrese and Blain (2011)), and (ii) every experiment under all conditions is not expected to show hormesis. Furthermore, a meta-analysis may fail to detect effects when studies have contrasting effects. For example, when half of

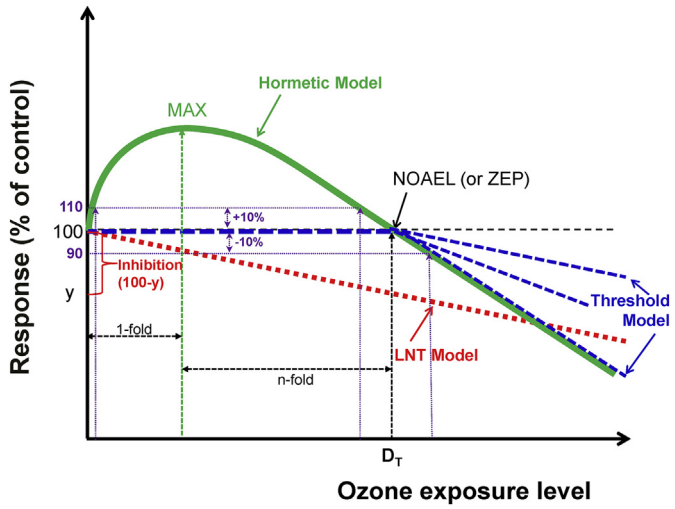

Fig. 4. Intercomparison of the linear no-threshold (LNT), threshold and hormetic models. D_T stands for the Threshold Dose at which the minimum statistically detectable inhibition (100-y %) is predicted by LNT; D_T corresponds to the zero equivalent point (ZEP) and no-observed-adverse-effect level (NOAEL) points; and MAX is the expected maximum stimulation point. The concept is developed based on an application to carcinogen risk assessment (Calabrese et al., 2015). ZEP is the highest exposure level yielding a response equal to the control response, and is supposed to be same with the NOAEL.

the studies report stimulation whereas the other half report inhibition, there would be a neutral or a likely inhibitory effect because the stimulation is usually small/modest whereas the inhibition is stronger.

3.4. Ozone – plant conditioning

This section introduces *conditioning* with reference to O_3 in plants, including the concepts of pre- and post-*conditioning*, and discusses why conditioning is an important feature of hormesis. This discussion is based on preliminary evidence which suggests that future research should be directed to O_3 conditioning in plants.

3.4.1. Introduction to conditioning

Conditioning hormesis was proposed to indicate *preconditioning*, *adaptive response* or *autoprotection* in biological organisms (Calabrese et al., 2007). *Preconditioning* is the phenomenon where a prior low-level exposure to a stressor generates adaptive responses, and, thus, protects against a subsequent more massive threat (Murry et al., 1986; Calabrese et al., 2007). Adaptation, or *adaptive response* (Jeggo et al., 1977), is the phenomenon where "a small prior exposure to a mutagen reduces the response to a larger subsequent mutagenic exposure" (Calabrese et al., 2007). It was first reported for the gram-negative bacterium *Escherichia coli* (Jeggo et al., 1977; Samson and Cairns, 1977). The term *autoprotection* was used for the same phenomenon, observed in a non-mutational liver toxicity endpoint in rats (Ugazio et al., 1972). Therefore, *preconditioning*, *adaptive response* and *autoprotection* fall under *conditioning* (Figs. 2, 3). *Preconditioning* would be an appropriate *conditioning* mode for plants, i.e. for utilization before transplantation at the field. Post-exposure *conditioning* hormesis is also a phenomenon where an adapting dose is administered after the larger toxic dose typically within a defined temporal window (Calabrese et al., 2007). Ozone is an agent that is being used within a *conditioning* mode in animal models and for human health enhancement (Hernández et al., 1995; Bocci, 1996, 1999, 2006, Bocci et al., 2009, 2011; Supplementary materials 1).

Preconditioning/priming, a relatively new concept in plant science (Conrath et al., 2002, 2006; Wang et al., 2014; Carmody et al., 2016; Martinez-Medina et al., 2016), can be utilized to protect plants from a subsequent exposure to abiotic stress (Fig. 3) and thus sustain food supplies (Agathokleous, 2017; Vargas-Hernandez et al., 2017). *Preconditioning* has been widely shown in plants, as for example in the case of cold *preconditioning*, where it protected against subsequent exposure to environmental stress (Cvetkovic et al., 2017; Iakovoglou and Halivopoulos, 2016; Pogány et al., 2016; Savvides et al., 2016; Sun et al., 2018; Van Buer et al., 2016; Theerakulpisut et al., 2016). *Conditioning* can occur in plants either endogenously or exogenously (Aranega-Bou et al., 2014; Bandoly et al., 2016; Martinez-Medina et al., 2016; Agathokleous, 2018) and indicates an intelligent achievement of profit from experience through biologically-based learning and memory (Trewavas, 2017).

3.4.2. Plants (pre)conditioning mechanisms with reference to O_3

Ozone can induce *conditioning* in plant defense reactions (Sharma and Davis, 1997; Sandermann et al., 1998). Plants can naturally scavenge O_3, by removing reactive volatile compounds and other antioxidants (Loreto and Fares, 2007). Ozone can alter the non-photochemical quenching (NPQ) of chlorophyll fluorescence (Cardoso-Gustavson et al., 2014), an indicator of photoprotective dissipation of excess absorbed light energy as heat (Moustakas et al., 2017). The production of ROS can be induced by a decrease in NPQ (Shapiguzov et al., 2012). When the O_3 exposure is low, ROS produced as a result of O_3 is unlikely to disturb the reduction–oxidation reaction (redox) state of the chloroplast (Cardoso-Gustavson et al., 2014). With this condition, ROS can upregulate defense mechanisms (Pfannschmidt, 2003; Shapiguzov et al., 2012; Cardoso-Gustavson et al., 2014). The regulation of NPQ was proposed as an "intrinsic component of the plant's defense program" (Goehre et al., 2012). A decrease in NPQ may serve as a *conditioning* mechanism for responding with vigorous ROS burst at later stages (Goehre et al., 2012). This early decrease was observed with different biological models and stressors (Goehre et al., 2012; Shapiguzov et al., 2012; Agathokleous et al., 2016). It occurs at exposures levels exceeding the toxicological threshold early in the exposure (Agathokleous et al., 2016) and is likely to be reversed at later stages of the exposure. However, the opposite phenomenon appears below the toxicological threshold (i.e. hormetic dose zone): an initial increase, with a maximum response (Agathokleous et al., 2016), similar to those of numerous endpoints in multiple biological models (Calabrese, 2015a), followed by a decrease at later stages of the exposure to maintain homeostasis balance. The separated NPQ response mechanisms for the regions of hormesis and adverse effects are biologically dynamic and variable to some extent.

One important component of plant *conditioning* is emission of volatile organic compounds (VOCs) which allows an external plant-to-plant "communication" (Frost et al., 2008). For instance, pretreatment with *cis*-Jasmone or other agents can increase the speed and potency of VOCs emission and thus potentially protect plants against insect herbivores (Oluwafemi et al., 2013). These responses may be driven by Ethylene Response Factor1 (ERF1), or other ERFs, a component in jasmonate and ethylene signaling, as it was found to regulate gene expression responsive to abiotic stress by binding to *cis*-acting elements in response to abiotic stressors (Cheng et al., 2013; Müller and Munné-Bosch, 2015). When undamaged plants receive VOCs from neighboring attacked plants (i.e. a type of *bystander effect*), they undergo an indirect secondary *conditioning* for stronger VOCs emission upon subsequent threat (Giron-Calva et al., 2017). Isoprenoids protect leaves against oxidative stress by reacting with O_3 in the intercellular spaces and limiting O_3 concentration at the cell level. The response of isoprenoid emission under increasing dose of O_3 shows an apparent hormetic dose-response function as well (Calfapietra et al., 2009; Yuan et al., 2016; Tani et al., 2017). A clear biphasic emission of VOCs in response to exogenous agents other than O_3 was also reported (Jiang et al., 2017), in agreement with further studies which indicate biphasic response of biogenic VOCs to O_3 or other environmental stresses (Agathokleous et al., 2018d). Pre-exposure of bean (*Phaseolus vulgaris* L.) leaves to a O_3 (≈200 ppb, 30 min) protected against a subsequent more massive exposure to O_3 (≈600 ppb, +30 min) by modifying the

magnitude and kinetics of VOCs emissions such that the emission of methyl salicylate was inhibited, emission of lipoxygenase was decreased and stomata closure was promoted under the subsequent O_3 exposure (Li et al., 2017); VOCs and MeSA are important components of plant defense against O_3 (Kanagendran et al., 2018a,b; Río Segade et al., 2017; Bison et al., 2018).

Ozone *conditioning* is seen also with changes in the antioxidant system (Ranieri et al., 1996) (Fig. 3). Pretreatment of tomato (*Lycopersicon esculentum* cv. PKM1) calli with O_3 (charcoal-filtered air or 100, 200, or 300 ppb O_3, 7 d, 30 min d^{-1}) promoted tolerance of regenerated plantlets against acute O_3 exposure (200 ppb, 2 h) as reflected to modifications in the levels of apoplastic ascorbic acid and dehydroascorbate, ascorbate redox state, glutathione content, and total soluble phenolic content; this was observed in chlorophyll content too (Nagendra-Prasad et al., 2008). The conditioning doses in the latter case show an inverted *U*-shaped dose response, suggestive of hormesis. Ozone pretreatment (200 ppb, 4 d, 6 h d^{-1}) also stimulated the production of salicylic acid and pathogenesis-related proteins in plants and led to resistance to a subsequent threat of a virus introduced 4 d after the first O_3 treatment (Yalpani et al., 1994). Ozone-induced activation of signaling pathways which are regulated by salicylic acid were observed in other studies too, and contribute in *conditioning* plants against stress (Sharma and Davis, 1997). Ozone pre-treatment (70 ppb, 3 d) resulted in stimulation of catalase (*CAT*) and peroxidase activities over time in the field and in rosettes with greater diameter and more leaves in cabbage plants (*Brassica oleracea* var. *capitata f. alba*) after 3 and 7 weeks of field cultivation (Rozpadek et al., 2013). Importantly, there was a direct increase in γ-tocopherol (γ-toc) content after O_3 exposure, returning to the control values later in the field, i.e. homeostasis balance (Rozpadek et al., 2013). In a different experiment, Chinese cabbage (*Brassica pekinensis*) and broccoli (*Brassica oleracea* var. *italica*) experienced O_3 (≈35 ppb, 3 d) pretreatment had inflorescences with greater α-toc and γ-toc content and heads with greater anthocyanin and β-carotene content, respectively, when later grown in the field for about 10 weeks (Rozpadek et al., 2015). The field of both studies (Rozpadek et al., 2013, 2015) was at Krakow Province, southern Poland, where the mean O_3 concentrations can be multi-fold the preindustrial ones and with peaks that can exceed 100 ppb (Godzik, 1997; Choi et al., 2015); nonetheless, in both cases the advantages of O_3-pretreated plants could be upon other stressors occurred under field conditions too. The exposure of this O_3-induced conditioning matches with current O_3 levels presently occurring at the Northern Hemisphere (Akimoto, 2003; Yamaji et al., 2006; Paoletti et al., 2014; Saitanis et al., 2015; Xing et al., 2015; Sicard et al., 2016b; Rasheed et al., 2017), thus suggesting some of the ambient O_3 may also induce *conditioning*, highlighting the need for an hormesis perspective in risk assessment. This assumption is supported by an additional experiment where barley (*Hordeum vulgare* L.) and smartweed (*Polygonum lapathifolium*) plants exposed to O_3 (30 ppb, 12 d) had greater biomass than those exposed to relatively O_3-clean air at 13 weeks after the end of the exposure (Bennett et al., 1974).

In addition to the aforementioned O_3 *conditioning* indications from plants exposed to O_3 (pre-harvest), a great deal of research with fruits and vegetables detached from plants (post-harvest) also suggest that O_3 induces *conditioning* (Horvitz and Cantalejo, 2014; Tzortzakis and Chrysargyris, 2017; Agathokleous, 2018). Pretreatment of tomatoes and grapes with O_3 (50–100 ppb during the daytime) led to protection against a subsequent threat by grey mold (*Botrytis cinerea*), for even two months during storage (Tzortzakis et al., 2011; Feliziani et al., 2014). Protection was found in other studies too where O_3 treatment applied before, during, or after inoculation of fruits with pathogens, suggesting a direct and/or indirect O_3 effect on pathogens, and more resistant fruits/vegetables (Gabler et al., 2010; Minas et al., 2010; Ozkan et al., 2011; Alexopoulos et al., 2013; Ames et al., 2013; Tzortzakis et al., 2013; Yeoh et al., 2014; Mylona et al., 2014; Ong et al., 2014; Ong and Ali, 2015; Glowacz and Rees, 2016).

Factors other than O_3 may also induce *conditioning* in plants and protect against a subsequent O_3 exposure. For instance, tomato (*Solanum lycopersicum* L.) plants which experienced low turgidity of leaves due to drought stress showed less phytotoxicity after a subsequent exposure to O_3 mainly because of a lower stomatal aperture (Khatamian et al., 1973). Water deficit-induced *conditioning* protected also *Pinus densiflora* Sieb. et Zucc. seedlings against O_3 adverse effects (Hong and Lee, 2001). In addition to this form of *preconditioning*, further studies provide evidence for *preconditioning* by mechanical wounding and exogenous application of substances like jasmonic acid and methyl jasmonate (MeJA) which reduced damage to subsequent acute exposure to O_3, e.g. 250–500 ppb for a few hours (Orvar et al., 1997; Koch et al., 2000; Rao et al., 2000). The MeJA-induced *conditioning* is supported by its capacity to induce biphasic VOCs emissions in plants, hence showing consistency with the concept of hormesis (Jiang et al., 2017). Experimental evidence also reveals that irradiation can induce *preconditioning* in plants (Calabrese, 2016b, 2016c), and, thus, may protect against subsequent high exposures of O_3.

3.5. Ozone – plant acclimation

The current scientific base suggests that plants display pleiotropic *adaptive responses* to O_3 through acquired traits,[3] a biologically plausible assumption as *adaptive responses* to stress, which may even pass to the next generation via epigenetic mechanisms, were shown for a variety of biological models and stressors, and for all biological organization levels.[4] Ozone, and other stressors, induce *adaptive responses*, where ROS hold a core role, and plants display stress "memory" and "carry-over" (Langebartels et al., 1998; Walter et al., 2013; Avramova, 2015; Carmody et al., 2016). Several post-harvest studies also show the induction of adaptive, beneficial responses of numerous fruits/vegetables to O_3 treatment prior to storage, within a hormetic framework (Salvador et al., 2006; Alothman et al., 2010; Ali et al., 2014; Glowacz et al., 2015; Sachadyn-Król et al., 2016; reviewed in Horvitz and Cantalejo, 2014; Tzortzakis and Chrysargyris, 2017). Moreover, there is evidence showing that plants may recover from O_3 injury (Tingey and Blum, 1973; Tenga and Ormrod, 1990; Tenga et al., 1990; Oksanen and Saleem, 1999; Köllner and Krause, 2003; Pasqualini et al., 2003; Francini et al., 2007).

The growth stimulation by low O_3 exposures was interpreted as an *adaptive response* from the early 1990s (Sanders et al., 1992). This interpretation was based on earlier reports which demonstrated acclimation to O_3 through regulation of "stress ethylene" formation (Mehlhorn and Wellburn, 1987; Mehlhorn et al., 1991). It is known that ERFs, part of the ethylene signaling and response pathway, regulate plant response to abiotic stress through integration of ethylene, abscisic acid, jasmonate and redox signaling (Rao et al., 2000, 2002; Cheng et al., 2013; Müller and Munné-Bosch, 2015). The earlier discussion on O_3-induced conditioning along with the understanding about the action of ERFs suggests that plants acclimate to O_3 or other stressors via hormetic mechanisms.

Limited O_3-induced damage found by long-term field surveys, despite O_3 exposures often highly exceed the CL adopted by worldwide regulatory agencies, supports the assumption that plants can acclimate to O_3 (Ferretti et al., 2007, 2018; Gottardini et al., 2014, 2018; Yue et al., 2016; Paoletti et al., 2017). Both cultivated plants and natural vegetation perform satisfactorily and overcome the relatively high ambient O_3 levels (3-, 5-, 10- or even 15-fold above the threshold) as occurring in

[3] Ting and Dugger, 1968; Walmsley et al., 1980; Darrall, 1989; Tenga and Ormrod, 1990; Mehlhorn et al., 1991; Sanders et al., 1992; Eckardt and Pell, 1996; Ranieri et al., 1996; Sharma and Davis, 1997; Sandermann et al., 1998; Carmody et al., 2016; Abeli et al., 2017.

[4] Selye, 1936, 1950; Leshem and Kuiper, 1996; Kaprinski et al., 1999; Leshem et al., 1998; Parsons, 2000; Schulte et al., 2002; Radak et al., 2005; Rattan, 2008; Zhang et al., 2008; Lebaudy et al., 2008; Onoda et al., 2009; Kranner et al., 2010; Rahavi et al., 2011; Bocci, 2012; Tissue and Lewis, 2012; Cheng et al., 2013; Fernandez et al., 2014; Koyama, 2014; Maiuri and Kroemer, 2015; Basu et al., 2016; Sthijns et al., 2016; Davies, 2016; Gradari et al., 2016; Niinemets et al., 2017.

the Mediterranean region and South East Asia (Nali et al., 2001; Riga-Karandinos and Saitanis, 2005; Paoletti et al., 2014; Yamaguchi et al., 2014; Saitanis et al., 2015; Agathokleous et al., 2017, 2018a; Gao et al., 2017; Marzuoli et al., 2017).

Long-term studies on large trees indicate a limited impact of O_3 on perennial vegetation, or much lower than it should be expected based on short-term dose response experiments with juveniles. For instance, at Harvard forest, by using *artificial neural networks* (ANNs) and simulations with a terrestrial biosphere model, it was found that O_3-induced inhibition of the 20-year trend of photosynthesis and gross primary productivity (GPP) was limited (Yue et al., 2016). Further multi-year field surveys for symptoms, chlorophyll-related and volume increment measurements revealed no or only limited evidence of O_3 impact on vegetation, and especially in forest trees, despite O_3 levels and fluxes being several times greater than the current CL (Ferretti et al., 2007, 2018; Gottardini et al., 2014, 2018; Paoletti et al., 2017; details in Supplementary materials 1). Importantly, a recent study reports field evidence for positive effects of aerosols on tree growth (Wang et al., 2018). These high-resolution analyses (Ferretti et al., 2007, 2018; Gottardini et al., 2014, 2018; Yue et al., 2016; Paoletti et al., 2017; Wang et al., 2018) suggest that O_3 risk assessment based on short-term experiments, with constant O_3 exposures, and with juveniles, are likely to overestimate O_3 impacts at ecosystem level.

4. Applicability of linear & hormesis models for public health protection

Acknowledging the practical difficulties for adapting hormetic model (e.g. experimental units and narrow exposure levels spacing), an alternative way would be to integrate hormesis with linear models for endpoints other than visible injury (e.g. biomass, yield, growth). This paper indicates that, in the cases of studies dealing with the plant response to O_3, it is possible to reconcile hormesis with threshold, as it was applied to studies dealing with human cancer (Calabrese, 2015b; Calabrese et al., 2015, 2016). Calabrese and Blain (2011) expanded their original database on the occurrence of hormesis (Calabrese and Blain, 2005) to 8962 dose-response cases occurring in plants and animals, using a priori criteria for inclusion. From the 8962 cases, 3166 dose-responses concern plants with no predominant plant species (although wheat occurred most commonly with 118 dose responses). The most common endpoint types in plants were growth, metabolism and reproduction, with 2197 (69%), 598 (19%) and 179 (6%) dose-response relationships, respectively, totalling to 2974 (94%) dose-response relationships. The NOAEL of a hormetic model is supposed to correspond with the zero equivalent point (ZEP). The probability of the maximum stimulatory response (MAX) to be between 110 and 149% of control is $P_{(110\leq MAX<150)} = 0.59$, independently from the endpoint (Calabrese and Blain, 2011). Considering the 0 to MAX interval as the one fold measure, the NOAEL falls at a distance of x-fold from the MAX (Fig. 4). The probability the NOAEL to have a distance within 5-fold from the MAX is $P_{(1\leq NOAEL<5)} = 0.69$, with a median of 3-folds, independently of the endpoint (Calabrese and Blain, 2011). The probability of the width of the stimulatory dose range (W) to be up to 10-fold is $P_{(1\leq W<10)} = 0.54$ and up to 100-fold is $P_{(1\leq W<100)} = 0.88$, independently of the endpoint (Calabrese and Blain, 2011).

For data that are subjected to dose-response relationship analysis, the point where the hormetic dose-response curve crosses the ZEP is considered as toxicological threshold (D_T) (Fig. 4). If the experiment was not designed to detect hormesis, the data are fitted to a threshold model, and the toxicological threshold is marked, or to an LNT model. The LNT model does not follow a parallel prediction with hormetic model at high exposure levels but also fails to predict stimulation responses at low levels (Fig. 4). Regarding the threshold model, it fails to predict stimulation responses at low exposure levels, but is capable to predict inhibitory responses at high levels, more or less similarly with the hormetic model. Now, considering that the D_T of the LNT model would reflect the NOAEL in a hormetic model, it can be suggested that NOAEL is expected to be n-fold ($1 \leq n < 5$) greater than the MAX, for the majority of the hormetic responses (Calabrese and Blain, 2011). Thus, if the NOAEL is known, MAX can be estimated using the formula: $MAX \approx NOAEL/(1 + n)$.

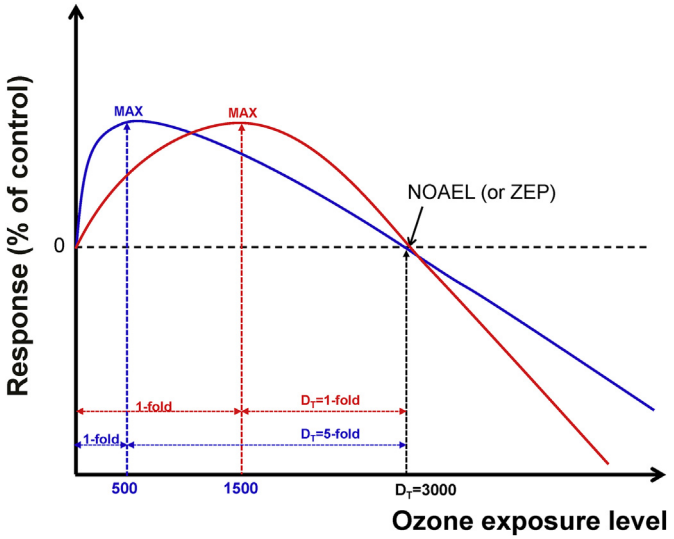

Fig. 5. Estimating the maximum stimulation dose (MAX) response when plants are exposed to ozone. Assuming that NOAEL is a 1 to 5-fold greater than the MAX, and considering the AOT40 (O_3 levels Accumulated Over the Threshold of 40 ppb) threshold of 3000 ppb h as the no-observed-adverse-effect level (NAOEL), the MAX is expected to range between 500 and 1500 ppb h.

In the case of the AOT40 metric (Fuhrer et al., 1997; Mills et al., 2007; Agathokleous et al., 2018a), for example, the D_T (for a 5% injury) for agricultural crops and semi-natural vegetation has been set to 3000 ppb O_3 h and thus the MAX is expected to occur between AOT40 levels of 500 and 1500 ppb O_3 h (Fig. 5). This of course remains to be experimentally confirmed taking, however, into account that it is expected to differ among plant genotypes.

5. Conclusions

Hormetic dose responses have been extensively reported concerning the effects of ozone on plant growth and productivity and other endpoints.

Hormesis represents a fundamental biological process which expresses the quantitative features of *adaptive responses* induced at low doses of stressor agents.

The hormetic dose response is therefore the quantification of induced *adaptive responses* and is a fundamental feature of biology and highly conserved.

The processes of O_3 hazard and risk assessment can be significantly enhanced by incorporating hormesis into their principles and practices.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.08.264.

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