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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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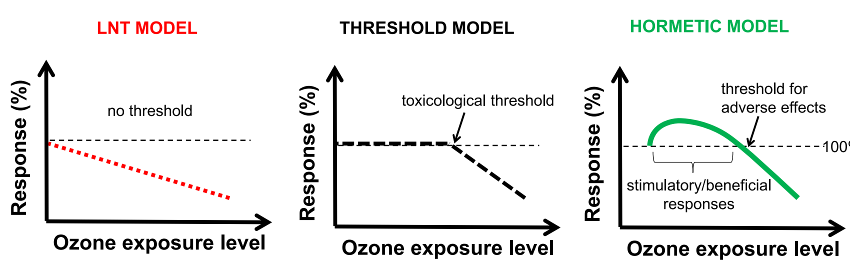
HIGHLIGHTS

- 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* (AOTX) 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 AOTX-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 AOTX 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 AOTX(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 AOTX 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.