Available online at www.sciencedirect.com
SCIENCE DIRECT®
Environmental Pollution 138 (2005) 378–411
ENVIRONMENTAL POLLUTION
www.elsevier.com/locate/envpol

Invited paper

Paradigm lost, paradigm found: The re-emergence of hormesis as a fundamental dose response model in the toxicological sciences

Edward J. Calabrese*

Environmental Health Sciences, School of Public Health, Morrill I, N344, University of Massachusetts, Amherst, MA 01003, USA

Received 1 September 2004; accepted 5 October 2004

The quantitative features of the hormetic dose/response are described and placed within the context of toxicology.

Abstract

This paper provides an assessment of the toxicological basis of the hormetic dose–response relationship including issues relating to its reproducibility, frequency, and generalizability across biological models, endpoints measured and chemical class/physical stressors and implications for risk assessment. The quantitative features of the hormetic dose response are described and placed within toxicological context that considers study design, temporal assessment, mechanism, and experimental model/population heterogeneity. Particular emphasis is placed on an historical evaluation of why the field of toxicology rejected hormesis in favor of dose response models such as the threshold model for assessing non-carcinogens and linear no threshold (LNT) models for assessing carcinogens. The paper argues that such decisions were principally based on complex historical factors that emerged from the intense and protracted conflict between what is now called traditional medicine and homeopathy and the overly dominating influence of regulatory agencies on the toxicological intellectual agenda. Such regulatory agency influence emphasized hazard/risk assessment goals such as the derivation of no observed adverse effect levels (NOAELs) and the lowest observed adverse effect levels (LOAELs) which were derived principally from high dose studies using few doses, a feature which restricted perceptions and distorted judgments of several generations of toxicologists concerning the nature of the dose–response continuum. Such historical and technical blind spots lead the field of toxicology to not only reject an established dose–response model (hormesis), but also the model that was more common and fundamental than those that the field accepted.

Keywords: Hormesis; U-shaped; J-shaped; Homeopathy; Dose–response; Biphasic; Risk assessment; Threshold; Linearity; History of science; History of medicine; Toxicology

1. Introduction

Over the past seven years our group has published a substantial body of literature on the topic of hormesis, a dose–response phenomenon characterized by a low dose stimulation and a high dose inhibition. These articles have included 1) a detailed definition of hormesis (Calabrese and Baldwin, 2002a); 2) methodologies for evaluating possible hormetic dose response relationships (Calabrese and Baldwin, 1997a,b, 1998; Calabrese et al., 1999); 3) historical foundations of chemical (Calabrese and Baldwin, 2000a,b) and radiation hormesis (Calabrese and Baldwin, 2000c–e); 4) a description of databases (a) one of which permits an assessment of the generalizability of the hormetic dose response and its quantitative dose–response characteristics (Calabrese and Blain, 2004a), while the (b) second database enabled an estimation of the frequency of hormesis in the toxicological literature (Calabrese and Baldwin, 2001a), the

* Tel.: +1 413 545 3164; fax: +1 413 545 4692.
E-mail address: edwardc@schoolph.umass.edu

0269-7491/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.envpol.2004.10.001

third (c) facilitated an assessment of hormesis in the dose-range finding experiments of the NTP bioassay program (Calabrese and Baldwin, 2003a), the fourth (d) permitted an assessment of the occurrence of hormesis in the National Cancer Institute's (NCI) dose response databases dealing with the screening of anti-neoplastic agents in human tumor cell lines and in yeast (Calabrese, 2004e) and (5) numerous articles dealing with pharmacological aspects of hormesis involving endogenous agonists such as adenosine (Calabrese, 2001g), nitric oxide (Calabrese, 2001c), peptides (Calabrese and Baldwin, 2003e), 5-hydroxytryptamine (serotonin) (Calabrese, 2001h), dopamine (Calabrese, 2001i), opiates (Calabrese, 2001j), amyloid β-peptides (Calabrese, 2001k), numerous chemotherapeutic agents (Calabrese and Baldwin, 2003d), estrogens (Calabrese, 2001d), androgens (Calabrese, 2001e), prostaglandins (Calabrese, 2001b), adrenergic agonists (Calabrese, 2001f), alcohol (Calabrese and Baldwin, 2003f), and physiological processes such as chemotaxis (Calabrese, 2001m) and apoptosis (Calabrese, 2001l), chemical carcinogens (Calabrese and Baldwin, 1999), radiation and cancer (Calabrese and Baldwin, 2002b) and lifespan (Calabrese and Baldwin, 2000f), inorganic contaminants (Calabrese and Baldwin, 2003c; Calabrese and Blain, 2004b), immunological responses (Calabrese, 2004b) and cancer cell lines (Calabrese, 2004c). In addition to these developments we have also published a number of general review articles on hormesis in major textbooks (Beck et al., 2000; Calabrese, 2004d), and journals (Calabrese, 2004a, 2002; Calabrese and Baldwin, 2003g–i, 2002c, 2001c, 2001e, 1999; Calabrese et al., 1999). We have also conducted a number of conferences (1992, 1994, 1998, 2000, 2002, 2003, 2004) with several published proceedings on the topic of hormesis (Calabrese, 1992, 1994, 1998; Calabrese and Baldwin, 2003b, 2001b). These collective activities have led to a spate of articles in the scientific [Science (Kaiser, 2003); Scientific American (Renner, 2003); Discover (Hively, 2002); Environmental Science and Technology (Renner, 2004); Chemistry and Industry (Butler, 2004); Chemical & Engineering News (Hogue, 2004)] and general publications [Forbes (Lambert, 2003); Fortune (Stipp, 2003); Wall Street Journal (Begley, 2003); The Boston Globe (Cook, 2003) and a number of others].

Despite this plethora of activity and technical focus there has not been a comprehensive publication of the hormesis hypothesis in the 'environmental sciences' area. While the present paper attempts to achieve this goal some explanation is necessary to account for this apparent lack of focus on environmental sciences. In fact, the principal reason is that hormesis has been a very marginalized hypothesis especially in human oriented chemical toxicology and risk assessment as well as in the field of radiation health (Calabrese and Baldwin, 2000a–2000e). Thus, a decision was made to concentrate our publication efforts where the lack of general acceptance appeared greatest. This is at least in partial contrast to the field of environmental sciences where the hormesis concept was recognized in the early decades of the 20th century in plant, microbiological, and insect models (see Calabrese and Baldwin, 2000a,c), and more broadly expanded and promoted in subsequent publications (Smyth, 1967; Stevenson, 1966; Luckey, 1963, 1959; Luckey and Stone, 1960; Townsend and Luckey, 1960; Stebbing, 1982; Kocan et al., 1985; Laughlin et al., 1981). Recent discussions on various implications of hormesis for ecotoxicology and ecological risk assessment have become even more widespread (Chapman, 2002, 2001; Gentile, 2001, 2000; Gentile and van der Schalie, 2000; Forbes, 2000; Van der Schalie and Gentile, 2000; Parsons, 2000). Nonetheless, even though there appears to have been no obvious general attempt to be dismissive of the concept of hormesis with respect to 'environmental' toxicology, it still has been difficult for this concept to be broadly accepted and integrated within environmental sciences as has been the case with human oriented toxicology and risk assessment. Most texts on environmental toxicology and ecological risk assessment have generally not explored the hormesis concept even to a cursory degree.

While this paper represents a broad and integrative review of the hormetic hypothesis it also extends the efforts of our previous papers in a number of important respects. That is, it provides numerous examples of hormetic dose response relationships of relevance to environmental sciences that have not been presented in our prior publications, assesses historical aspects of statistical procedures and how they affected the acceptance/rejection of hormesis, presents new information on the concept of reproducibility of hormetic dose responses using the NCI yeast database and assesses the critical issue of evaluating multiple possible hormetic endpoints within the context of dose limited studies that have risk assessment application.

2. Definition of hormesis

Hormesis is a dose response phenomenon in search of mechanistic, physiological and evolutionary explanations. The term hormesis (meaning to excite) was coined in 1943 by Southam and Ehrlich (1943) in studies dealing with the effects of red cedar extracts on fungal metabolism. In the early decades of the 20th century the hormesis concept was referred to as the Arndt-Schulz Law and to a lesser extent Hueppe's Rule. Both of these terms have gradually faded from use. The form of this dose–response curve may be either of an inverted U or a J-shape depending on the endpoint measured. In cases of endpoints such as growth, longevity, fecundity and cognitive function the response would be seen as an