Review Article

Progress in the studies on hormesis of low-dose pollutants

Junyi Shi, Mitchell Huber[1], Ting Wang[2], Wang Dali[2], Zhifen Lin[2], Yin Chun-Sheng

Department of Environmental Science, Shanghai Ocean University, Shanghai - 201306, [2]State Key Laboratory of Pollution Control and Resource Reuse, College of Environmental Science and Engineering, Tongji University, Shanghai - 200092, China, [1]Department of Neurosurgery, Wayne State University School of Medicine, Detroit, MI, USA

Abstract

Hormesis can be defined as a biphasic dose-response relationship characterized by low-dose simulation and high-dose inhibition. Given that environmental pollutants are more often found at lower doses, hormesis research has become a recent hot spot in toxicology. This study summarizes current progress on hormesis research, which can be discussed in three contexts: The universality of hormesis, hormesis mechanisms, and the quantification of hormetic responses. The universality of hormesis has been verified, but the degree to which hormesis should be taken into risk assessments and risk management plans remains controversial. Regarding mechanisms, we discuss how our mechanistic understanding of hormesis has come a long way but still lacks strong experimental support, which leads to uncertainty as to the exact underlying causes of hormesis. This study also describes the hormesis quantitative research process and points out that due to an incomplete mechanistic understanding of hormesis, quantitative research has progressed slowly and lacks accurate quantitative characterization parameters and prediction models. Finally, we discuss that a future trend may be to investigate hormesis quantitative characterization parameters based on toxicity mechanism and to establish a quantitative prediction model of hormesis that incorporates those parameters.

Key Words: Hormesis, mechanism, progress, quantification, universality

INTRODUCTION

Modern toxicology is based on the proposition of the 16th-century toxicologist, Paracelsus, that "dose decides toxicity (The dose makes the poison)." This principle has inspired the threshold model and linear nonthreshold model, which have become the central dogma of contemporary toxicology. It is surprising, then, that these principles may be strikingly inadequate to accurately quantify biological responses to a large number of stimuli. In 1887, Hugo Schulz discovered that for many toxic substances, while high-dose exposures attenuated metabolism in yeast, low-dose exposures actually enhanced metabolic rate.[1] When Southam[2] made the same observations in a study on the influence of red cedar extract on fungus, the phenomenon was termed "hormesis," a dose-response phenomenon characterized by low-dose metabolic stimulation and high-dose metabolic inhibition.[3] Unfortunately, the concept was described in homeopathic literature around the same time and consequently became incorrectly associated with homeopathic pseudoscience and fell

Address for correspondence:
Prof. Zhifen Lin,
State Key Laboratory of Pollution Control and Resource Reuse,
College of Environmental Science and Engineering,
Tongji University, Shanghai 200092, China.
E-mail: lzhifen@tongji.edu.cn

Received: 05-06-2016, **Accepted:** 15-06-2016

Access this article online	
Quick Response Code:	Website: www.environmentmed.org
	DOI: 10.4103/2468-5690.185296

How to cite this article: Shi J, Huber M, Wang T, Dali W, Lin Z, Chun-Sheng Y. Progress in the studies on hormesis of low-dose pollutants. Environ Dis 2016;1:58-64.

into relative obscurity. However, the concept has seen a recent resurgence, largely due to the work of Edward Calabrese, who is either named or heavily cited in the majority of central papers on the topic. Calabrese's 2003 Nature article "Toxicology rethinks its central belief"[3] was a pioneering work as it challenged the traditional threshold model and linear threshold model. In this article, Calabrese put forth the more predictive hormetic dose-response model, thereby bringing hormesis back into the consciousness of the toxicology community. Since then, *Science* has published numerous commentaries on hormesis,[4] which has contributed to its recent popularity.

Although many papers discuss hormesis as a beneficial concept, it is important to note that hormesis can also have negative implications; stimulatory effects have been observed in bacteria and neoplastic cells following low-dose administration of antibiotics and chemotherapy, among others. As such, this study is not attempting to portray hormesis as a silver lining to toxin exposure. The purpose of this review is simply to put forth the concept of hormesis as a legitimate, widely applicable toxicological model that may allow the scientific community to more accurately assess the consequences of toxin exposure at a variety of concentrations.

THE UNIVERSALITY OF HORMESIS

A growing number of studies show that hormesis exists in a multitude of organisms (including animals, plants, and microorganisms), poisons (including carcinogens and noncarcinogens), and biological phenomena (including tumor formation, reproduction, growth, metabolism, etc.).[5] Its scope covers a large number of toxic substances, including heavy metal compounds, cyanide, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, organic arsenic, and some pesticides and antibiotics. Furthermore, the hormetic model is believed to occur with a significantly greater frequency than the traditional threshold model.[6] For this reason, hormesis has been put forth as a universal biological principle.[7]

Controversy

While there is no question about the legitimacy of hormesis as a biological principle in general, there has been recent controversy centered on the role that hormesis should play in public health decisions. Calabrese has proposed that given its universality, in the absence of contradictory information, the hormesis model should be utilized as the default model for dose-response evaluations, rather than the currently utilized linear or threshold models.[7] Opponents of this transition have questioned whether the strength of research on the topic warrants such a drastic shift. Thayer *et al*.[8] and Mushak[9] recently, independently evaluated the merits and limitations of hormesis research as a basis for the proposed transition, and in doing so, identified several weaknesses in current research: (1) Most studies on the topic pertain to hormesis as a phenomenon, rather than its underlying mechanisms, and those that do investigate mechanistic underpinnings are largely presumptive and descriptive, rather than data-driven. Before hormesis can be included in risk assessments and management plans, it is necessary to ensure that there is a sufficient understanding of its biological basis and potential consequences. (2) Laboratory testing usually involves discrete administration of individual xenobiotics at controlled doses to a single model. Outside of a laboratory, however, organisms are composed of a wide variety of cell types that are exposed to mixtures of compounds in variable doses. As such, it is likely that the hormetic effects observed in laboratory settings fail to adequately replicate the experience of humans in a complex, uncontrolled environment. (3) Different individuals and species can exhibit variable endurance capacities for the same compound, and identical doses of a compound may stimulate metabolism in some organisms while inhibiting it in others. As such, it is difficult to accurately delineate beneficial from detrimental dosing for a population. (4) The statistical basis of several highly cited claims has been called into question, which implies that hormesis may not be as universal as Calabrese proposes. All of these problems limit the inclusion of hormesis in risk assessments, and the lack of research on hormesis mechanisms and mixture hormesis is an urgent problem to be solved. However, to the best of our knowledge, no criticisms have questioned the validity of hormesis as a general phenomenon, and as such, it seems that further research is all that is needed to satisfy cynics.

In summary, hormesis challenges the traditional school of toxicological thought and could fundamentally change risk evaluation models. While its role in public health policy remains to be seen, its legitimacy is not, and if nothing else, research on the topic provides a wider and potentially more accurate array of risk assessment models for regulatory organizations to utilize.

Past and present barriers to mainstream acceptance of hormesis

Despite its relevance, applicability, and overall legitimacy as a biological phenomenon, hormesis has been plagued with systemic obstacles preventing its widespread acceptance. Chiefly, hormesis as a concept is counterintuitive and could easily be judged as misleading propaganda commissioned by big business to influence public opinion, much like the prosmoking advertisements in the mid-20th century American culture. Second, the agenda of the toxicological community are largely driven by the desires of regulatory agencies, which have always been almost exclusively concerned with risk assessment. As such, there is little monetary or professional incentive to stray from the mainstream

fields of research to something more theoretical. Third, hormesis is logistically difficult to investigate; to adequately evaluate hormesis for a compound, studies must be specifically and methodically designed, including a large number of doses in a large number of trials, and include a temporal component. In a review of over 20,000 toxicology articles spanning from the mid-1960s to early 1990s, only 1.5–2% utilized designs that could adequately evaluate hormesis as a hypothesis. However, of those 1.5–2%, 40% identified evidence of hormesis.[10] Finally, hormesis has historically been associated with homeopathy and has thus been assumed to be a pseudoscience.[11] After identifying the phenomenon of hormesis in 1887, Hugo Schulz became aware of similar reports in homeopathic literature, and proceeded to identify hormesis as the basis for these homeopathic claims. Despite its validity, this work came at a time of heated division between homeopathy and modern medicine, and by associating hormesis with homeopathic literature, Schulz and his ideas were rejected by the medical community.[12]

However, a retrospective evaluation of hormesis research and opinion is scant with scientific evidence refuting its validity. Thus, it is imperative that historical paradigms on the topic be cast aside if an honest evaluation of hormesis is to be conducted.

HORMESIS MECHANISM

Current mechanistic studies on hormesis lack depth, and it seems that no single mechanism can be credited for the phenomenon. However, the mechanistic investigations that have been conducted usually produce encouraging results. Proposed mechanisms all center on the idea of homeostatic overcompensation; following homeostasis-disturbing low-dose exposure to toxins, the body has a tendency to overcompensate in its attempt to return to homeostatic set points, thereby strengthening normal homeostatic functions in preparation for further toxin exposure. This overcompensation has been proposed as the cause of the hormetic phenomenon, and Townsend and Calabrese[11] have both independently cited many instances to support the excessive compensation hypothesis.

Under the umbrella of the overcompensation hypothesis, several theoretical explanations of hormesis have been put forth, including the receptor mechanism, DNA damage repair, the oxidative stress mechanism, immune function enhancement, and alteration of gene expression.

Receptor subtypes of varying affinities and effects

The leading hypothesis regarding the mechanism of hormesis asserts that the observed phenomenon is due to the same agonist interacting with different receptor subtypes, each with different ligand affinities and effects. It is plausible that higher affinity receptor subtypes stimulate one change in metabolism while lower affinity subtypes stimulate an opposite change; at low ligand concentrations, only the high affinity (stimulatory) receptors would be occupied, while at higher concentrations, the lower affinity (inhibitory) receptors would be filled as well. This hypothesis has been confirmed experimentally; Gao *et al*.,[13] identified this mechanism as the cause of the hormetic response of bisphenol A and other phenolic compounds on *in vitro* lymphocyte proliferation rates in Crucian carp. At low doses, the estrogen receptor played a major role in promoting lymphocyte proliferation, while at higher doses, acute toxicity mechanisms seemed to be activated that inhibit lymphocyte proliferation. In addition, a 2005 study found that steroidogenesis is stimulated in Leydig cells by low-dose administration of histamine while inhibited by higher doses. In line with the two-receptor hypothesis, the opposing effects were mediated by subtypes of the same receptor; low-dose administration only allowed for ligand interaction with the stimulatory HRH2 receptor while high-dose administration allowed for ligand interaction with the inhibitory HRH1 receptor.[14]

However, other studies have yielded inconsistent results. A recent investigation from Zhang *et al*. found that in estrogen receptor-knockout cells transfected with a modified estrogen receptor, administration of E2 β at low dose stimulated cell growth by mediating phosphorylation of an activation site on the Src transcription factor, while administration of E2 β at high dose prevented cell growth by mediating phosphorylation of an inhibitory site on Src.[15] While nonmonotonic effects came from administration of different doses of estrogen, these effects seemed to be facilitated by the same receptor. However, this investigation did not to investigate the role of other receptors in the observed phenomenon, which does not rule out the possibility that the two-receptor mechanism may be responsible for the given results.

DNA generation

DNA damage is a significant mechanism by which toxic substance damage organisms, but it seems that a reversal of this effect may be one of the mechanisms underlying hormesis. Von Zglinicki *et al*. reported that cadmium administered at <100 pmol/L can stimulate DNA synthesis in rat bone marrow cells,[16] and another report claimed that some individuals exposed to low doses of poison can experience reductions in the degree of DNA damage. In addition, mercury is able to stimulate synthesis of metallothionein, which can clear toxic metals from the body, thereby protecting cells from free radical damage generated by normal metabolism.[17]

Oxidative stress mechanism

Reactive oxygen species (ROS) are well-known to play vital roles in signal transduction at low levels, and even better known

for their role in tissue damage at higher levels. Under normal circumstances, the generation and removal of ROS in the body are tightly regulated, which allow them to serve beneficial roles while avoiding their deleterious effects. However, if ROS cannot be removed quickly, they will accumulate, which can be damaging to the body. Thus, moderate levels of ROS seem to exert a stimulatory effect on the body. Yamaoka *et al*. reported that low-dose radiation can activate the activity of GSH-Px and SOD in the liver tissue and argued that these enzymes expedite the process of eliminating free radicals, which protects the body from harm.[18] A more recent study found that cells exposed to oxidized-free DNA suppressed NF-kB activity and stimulated NRF2 activity while those exposed to nonoxidized-free DNA failed to stimulate NF-kB and stimulated NRF2 activity to a lesser degree.[19] It is thought that under oxidative stress, apoptotic cells release oxidized DNA which neighboring cells interpret as a stress signal, thereby inducing expression of antioxidant and prosurvival genes. However, it is well-known that high levels of ROS stimulate apoptosis or necrosis in all cells. Thus, it seems that hormetic effects can be mediated by mechanisms other than the two-receptor hypothesis.

Enhancement of immune function

Arinaga *et al*.[20] reported that exposure to MMC in low doses can activate the body's immune system, increase interleukin-2 (IL-2) production, induce LAK cells, and strengthen the body's resistance to exogenous chemicals. Moreover, animal experimental data show that low-dose stimulation may enhance the body's immune function by: (1) Enhancing T-cell proliferative response to mitogen stimulation, (2) promoting the activation of interferon-γ and IL-2, (3) increasing the expression of IL-2 receptors in T-cell membranes, and (4) increasing the content of catecholamines in the spleen and reducing serum corticosterone levels.

Gene expression and regulation

Research shows that hormesis is closely related to expression and regulation of genes involved in DNA repair, stress protein production, growth, transcription factors, transcriptional promoters, and apoptosis. Some studies have shown that low-dose radiation can trigger SRF, AP-1, ATFZ, and NF-KB transcription factors by a variety of signal transduction pathways.[21]

QUANTITATIVE STUDY OF HORMESIS

The hormesis quantitative characterization method is roughly divided into two categories according to the different points of concern. One class of hormesis research is only concerned with the quantitative characterization of hormetic stimulation and its parameters, including the width and breadth of the stimulatory range as shown in Figure 1. To this end. , Calabrese and Baldwin reviewe thousands of research papers on the hormetic dose response and found that in the vast majority of cases, low-dose exposure stimulated metabolic rate by a modest 30–60% above control. It was also determined that in ~95% of cases, the width of the low-dose stimulatory range was within 100-fold, and usually within the 10–20 fold range.[22,23]

The other branch of hormesis research is concerned with the quantitative prediction of the hormesis response as a whole. Over the past few decades, scholars have put forth a variety of dose-response models to characterize the hormesis phenomenon, including the biphasic dose-response model[24] [Equation 1] and Brain-Cousens model[25] [Equation 2].

$$Y = \frac{y_0 + f \times x}{1 + e^{b \times (-logEC50)} \times x^b} \quad (1)$$

$$Y = \delta + \frac{\alpha - \delta + y \times x}{1 + \left(1 + \frac{2y \times EC50}{\alpha - \delta}\right) \times \exp\left(\beta \ln\left(\frac{x}{EC50}\right)\right)} \quad (2)$$

Where α indicates the effect of the highest exposure concentration; δ, the effect of the control group; γ, the effect of low-dose range increase trend, and β, the change rate of half the inhibition effect of concentration (EC50).

In the field of mixed hormesis quantitative study, researchers have put forth the corresponding hybrid hormesis quantitative method based on the quantitative study of single-compound hormesis and supplemented by traditional quantitative methods for determining toxicity for interactive mixtures. For example, Ge *et al*.[26] correctly predicted the toxicity effect of an ionic liquid mixture on luminescent bacteria using the concentration addition model; an iteration of this hybrid quantitative method as shown in Figure 2.

As an alternative, a novel model, the "six-point" model was proposed for predicting the hormetic effects of mixtures

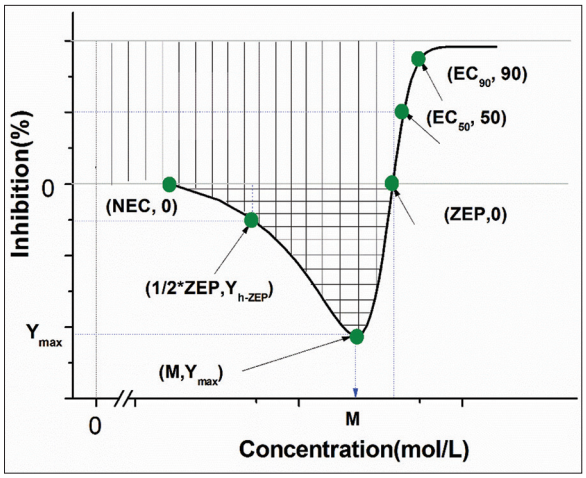

Figure 1: Quantitative characterization parameters of hormesis curve

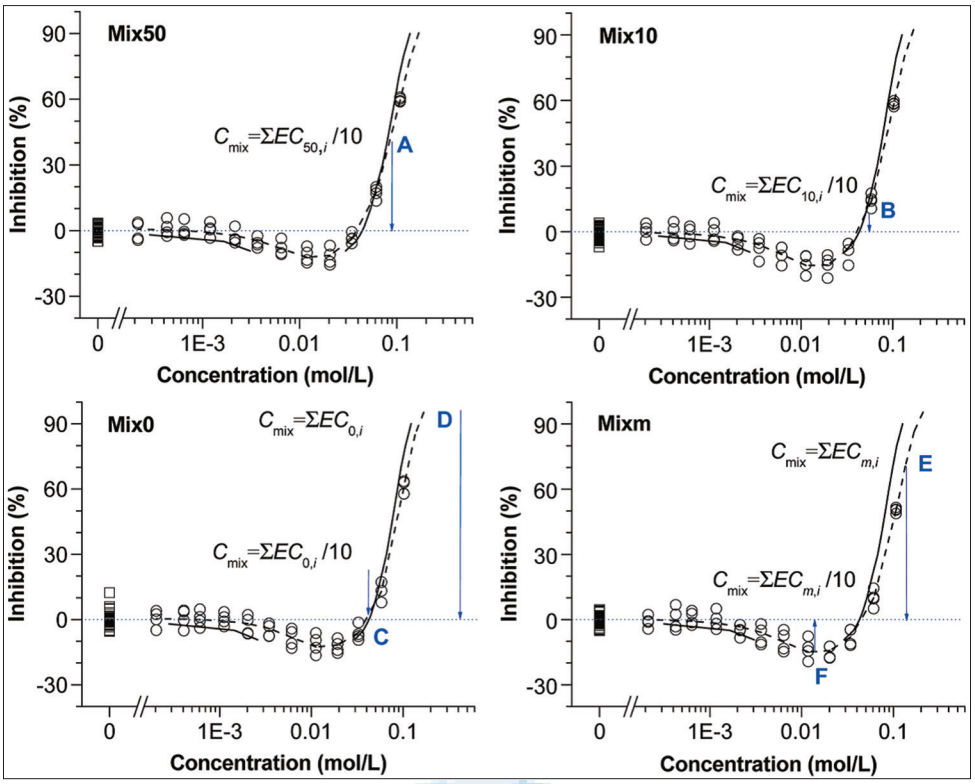

Figure 2: Hormesis of ionic liquid mixture on the luminescent bacteria

in low dose. The six-point model was developed based on the quantitative structure-activity relationship approach and the quantitative features in the determined dose-response curve. Zou *et al*.[27] found six representative dose-effect points on the hormesis curve (NEC, 0), (1/2*ZEP, $Y_{1/2ZEP}$), (M, ZEP), (ZEP, 0), (EC50, 50), (EC90, 90), and according to a single compound's contribution to the toxicity of mixture, established a relationship between six representative single dose-response points and mixed dose-response points, culminating in successful prediction of the hormetic response of a mixture. The results indicated that this model can accurately predict the hormetic effects of mixtures in low dose not only for noninteractive mixtures but also for interactive mixtures as well. Therefore, the "six-point" model is a powerful tool to predict the hormetic effects of mixtures at low doses and may serve as a more accurate tool for assessing the environmental risk of toxin mixtures.

Despite these recent advances, current research on hormesis for both single and combined quantitative characterization parameters according to the dose-response curve for external characteristics lacks an understanding of chemical toxicity mechanisms and fails to provide support to its specific biological significance. Thus, it is necessary to investigate these areas of ambiguity if we hope to accurately assess the risk of toxin exposure.

APPLICATIONS

Hormesis will significantly influence the current risk assessment process

Two basic models are generally used in toxicology: Threshold model and linear nonthreshold model. The former is used to assess the risk of noncarcinogens and the latter is extrapolated for the risk of carcinogenic substances at very low concentrations. Compared with these two traditional models, hormesis is better able to predict the toxic behavior of compounds at low dose.[28] Thus, in an effort to more accurately forecast the toxicological behavior of these compounds, Calabrese *et al*.[29] have proposed that hormesis be used as the default model of dose response. This default dose-response model would be used for risk assessments in the absence of convincing reason to employ a different model.[28] Risk assessment agencies should incorporate hormetic concepts into risk assessment procedures for a more precise assessment of the physiological risk caused by environmental pollutants. Specifically, in biological experiments and human epidemiological investigations, we should simulate and analyze dose-effect relationships according to the specific characteristics of a given compound and dose, rather than simply extending a linear extrapolation of the traditional risk assessment. In addition, during experimental design, low-concentration groups should be included, as well as a more extensive dose range to investigate

the effect of hormesis. These fundamental changes could radically alter the way modern regulatory agencies assess the danger of a pollutant.[30]

The application of hormesis in radiation assessments

Hormesis induced by low-dose ionizing radiation has been confirmed in a large number of experiments *in vivo* and *in vitro*. In mouse models, low-dose (75 mGy) radiation has been found to enhance immune function, reduce apoptosis, significantly improve the body's ability to resist tumor formation, and improve the ability of erythrocytes to carry oxygen.[31,32] In early 2015, Kudryasheva and Rozhko reviewed the effect of low-dose particulate (α and β) radiation on luminous marine bacteria[33] and concluded that under low-dose radiation, the adaptive properties of bacteria could be attributed to a hormetic response. In another study investigating the location of nuclear weapon testing, the United States was divided into high and low background exposure states.[34] Surprisingly, the study found that states with higher background radiation had a lower incidence of lung cancer ($P < 0.001$).[35] On the other hand, other studies have shown that low doses of radiation have no influence on, or even inhibit, repair of DNA double-strand breaks. Given the conflicting results, the exact effects of low dose exposure to radiation are not known.[36] However, the dose-dependent nonlinear effects of radiation exposure are evident, and must be addressed.

Although the nonthreshold model is widely accepted, there has been a resurgence of literature investigating radiation hormesis, including epidemiologic studies on the relevance of radiation hormesis in plants, bacteria, fungi, and mammalian cells. This is evident in recent policy decisions. The French Académie des Sciences and Académie Nationale de Médecine recently published several joint reports collectively alleging that the use of the linear nonthreshold model for assessing public health risks for low dose radiation was not based on valid scientific evidence, and that most dose-effect relationships were linear-quadratic or quadratic, rather than linear. Furthermore, a hormetic response was observed in 40% of their experiments.[37] However, the United States National Council on Radiation Protection and Measurements conducted a similar investigation, but found that the linear nonthreshold model was able to adequately assess carcinogenic risks for moderately low-dose radiation.[38] Thus, opposing viewpoints on the matter are not only found in the pages of scientific journals; they have real-world implications that could significantly affect the lives of people. It seems urgent, then, to come to an empirically rooted consensus on the matter.

Applications of hormesis in clinical medicine

Hormesis allows researchers to reexamine the linear efficacy of medications and provides new ideas and methods for the evaluation of dose-dependent side effects.[39] Anticancer drugs are of particular interest to this end. For instance, while resveratrol and doxorubicin have been utilized as anti-neoplastic agents, they have been found to play roles in promoting proliferation of lung cancer cells at low doses.[34-38] Thus, failure to accurately predict the effective dose of a drug can lead to clinical treatment failure and in some cases, be explicitly detrimental. However, while the traditional dose-response model cannot reveal drug action in the low-dose range, the hormetic dose-response model has been investigated for exactly this purpose, allowing it to guide clinicians to more precise, effective medication dosing.[44]

In addition, studies on the efficacy and mechanisms of exercise-induced hormesis have increased in recent years and some studies have found that redox signaling may be one of the most important molecular mechanisms of exercise-induced hormesis.[45] Among the best-known hormetic effects studied to date are upregulation of the antioxidant network, mitochondrial adaptation, cardiac protection against ischemia-reperfusion, heat tolerance, adaptation to low energy substrates (especially blood sugar), and muscle hypertrophy in response to blood flow restriction.[45,46]

PROSPECTS

Research on the toxicity of pollutants in low doses is still in its infancy, so some problems still remain. Chiefly, the mechanisms of hormesis proposed in the present review are explanatory but seem inadequate to characterize the full scope of hormetic responses. Second, there is currently a lack of quantitative characterization parameters based on the established hormesis mechanisms, which makes research progress on the quantitative prediction model of hormesis slow moving. Third, the applications of hormesis models in environmental science need to be more widely publicized in order for them to attain widespread acceptance.

As to the problems above, follow-up research should include further exploring the mechanisms of hormesis, and to this end, identifying the biological significance of hormesis quantitative characterization parameters, thereby establishing a quantitative prediction model based on the toxicity mechanism of hormesis. Overall, it is important for toxicologists to appreciate the utility of hormetic models for risk assessments and attempt to incorporate them when warranted, not in the interest of employing a novel model, but for the sake of quantifying environmental risks to the best of our abilities.

Financial support and sponsorship

This work was funded by the Foundation of the State Key Laboratory of Pollution Control and Resource Reuse, China (PCRRY 11003), the National Natural Science Foundation of China (21377096, 21577105), the "Climbing" Program

of Tongji University (0400219287), the 111 Project, and the Science& Technology Commission of Shanghai Municipality (14DZ2261100).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Southam J M, Erlich J. Effects of Extract of western red cedar heartwood on certain wood-decaying fungi in culture. Phytopathol 1942:33.
2. Calabrese EJ, Baldwin LA. The marginalization of hormesis. Hum Exp Toxicol 2000;19:32-40.
3. Calabrese EJ, Baldwin LA. Toxicology rethinks its central belief. Nature 2003;421:691-2.
4. Calabrese EJ, Baldwin LA. Applications of hormesis in toxicology, risk assessment and chemotherapeutics. Trends Pharmacol Sci 2002;23:331-7.
5. Geard C, Lavora H. A healthful dab of radiation? Science 2003;302:378.
6. Calabrese EJ, Baldwin LA. The hormetic dose-response model is more common than the threshold model in toxicology. Toxicol Sci 2003;71:246-50.
7. Calabrese EJ. Hormesis is central to toxicology, pharmacology and risk assessment. Hum Exp Toxicol 2010;29:249-61.
8. Thayer KA, Melnick R, Burns K, Davis D, Huff J. Fundamental flaws of hormesis for public health decisions. Environ Health Perspect 2005;113:1271-6.
9. Mushak P. Hormesis and its place in nonmonotonic dose-response relationships: Some scientific reality checks. Environ Health Perspect 2007;115:500-6.
10. Calabrese EJ, Baldwin LA. The frequency of U-shaped dose responses in the toxicological literature. Toxicol Sci 2001;62:330-8.
11. Calabrese EJ. Overcompensation stimulation: A mechanism for hormetic effects. Crit Rev Toxicol 2001;31:425-70.
12. Calabrese EJ. Hormesis: From mainstream to therapy. J Cell Commun Signal 2014;8:289-91.
13. Gao CA, Zhang AQ, Lin Y, Yin DQ, Wang LS. Quantitative structure-activity relationships of selected phenols with non-monotonic dose-response curves. Chin Sci Bull 2009;54:1786-96.
14. Mondillo C, Patrignani Z, Reche C, Rivera E, Pignataro O. Dual role of histamine in modulation of Leydig cell steroidogenesis via HRH1 and HRH2 receptor subtypes. Biol Reprod 2005;73:899-907.
15. Zhang XT, Ding L, Kang LG, Wang ZY. Involvement of ER-a36, Src, EGFR and STAT5 in the biphasic estrogen signaling of ER-negative breast cancer cells. Oncol Rep 2012;27:2057-65.
16. von Zglinicki T, Edwall C, Ostlund E, Lind B, Nordberg M, Ringertz NR, *et al*. Very low cadmium concentrations stimulate DNA synthesis and cell growth. J Cell Sci 1992;103(Pt 4):1073-81.
17. Winters A. Sipping from a poisoned chalice. Science 2003;302:376.
18. Yamaoka K, Edamatsu R, Mori A. Increased SOD activities and decreased lipid peroxide levels induced by low dose X irradiation in rat organs. Free Radic Biol Med 1991;11:299-306.
19. Kostyuk SV, Tabakov VJ, Chestkov VV, Konkova MS, Glebova KV, Baydakova GV, *et al*. Oxidized DNA induces an adaptive response in human fibroblasts. Mutat Res 2013;747-748:6-18.
20. Arinaga S, Karimine N, Takamuku K, Nanbara S, Inoue H, Abe R, *et al*. Correlation of eosinophilia with clinical response in patients with advanced carcinoma treated with low-dose recombinant interleukin-2 and mitomycin C. Cancer Immunol Immunother 1992;35:246-50.
21. Canman CE, Kastan MB. Signal transduction. Three paths to stress relief. Nature 1996;384:213-4.
22 Calabrese EJ, Baldwin LA. Defining hormesis. Human & Exp Tox 2002;21:91-7.
23. Calabrese EJ, Baldwin LA. Hormesis: The dose-response revolution. Annu Rev Pharmacol Toxicol 2003;43:175-97.
24. Li W , Tian D, Lin Z, Wang D, Yu H. Study on the variation rules of the joint effects for multicomponent mixtures containing cyanogenic toxicants and aldehydes based on the transition state theory. J Hazard Mater 2014;267:98-108.
25. Belz RG, Cedergreen N, Sørensen H. Hormesis in mixtures – Can it be predicted? Sci Total Environ 2008;404:77-87.
26. Ge HL, Liu SS, Zhu XW , Liu HL, Wang LJ. Predicting hormetic effects of ionic liquid mixtures on luciferase activity using the concentration addition model. Environ Sci Technol 2011;45:1623-9.
27. Zou X, Lin Z, Deng Z, Yin D. Novel approach to predicting hormetic effects of antibiotic mixtures on *Vibrio fischeri*. Chemosphere 2013;90:2070-6.
28. Calabrese EJ. Hormesis: Principles and applications. Homeopathy 2015;104:69-82.
29. Calabrese EJ. Hormesis: From marginalization to mainstream: A case for hormesis as the default dose-response model in risk assessment. Toxicol Appl Pharmacol 2004;197:125-36.
30. Shen KL, Yu J, Lin G, Shen CF, Chen XC. Importance and potential application of hormetic effect in risk assessment of environmental pollutants. J Environ Occup Med 2012;29:183-6.
31. Rithidech KN, Scott BR. Evidence for radiation hormesis after *in vitro* exposure of human lymphocytes to low doses of ionizing radiation. Dose Response 2008;6:252-71.
32. Vaiserman AM. Radiation hormesis: Historical perspective and implications for low-dose cancer risk assessment. Dose Response 2010;8:172-91.
33. Kudryasheva NS, Rozhko TV. Effect of low-dose ionizing radiation on luminous marine bacteria: Radiation hormesis and toxicity. J Environ Radioact 2015;142:68-77.
34. Lehrer S, Rosenzweig KE. Lung cancer hormesis in high impact states where nuclear testing occurred. Clin Lung Cancer 2015;16:152-5.
35. Frigerio NA, Eckerman KF, Stowe RS. Carcinogenic Hazard from Low Level, Low-rate Radiation, Part I. Report ANL/ES 26. Argonne, IL: Argonne National Lab; 1973.
36. Baldwin J, Grantham V. Radiation hormesis: Historical and Current Perspectives. J Nucl Med Technol 2015;43:242-6.
37. Tubiana M. Dose-effect relationship and estimation of the carcinogenic effects of low doses of ionizing radiation: The joint report of the académie des sciences (Paris) and of the académie nationale de médecine. Int J Radiat Oncol Biol Phys 2005;63:317-9.
38. National Council on Radiation Protection and Measurements. Evaluation of the Linear-nonthreshold Dose-response Model for Ionizing Radiation, in NCRP Report No: 136. Bethesda, MD: National Council on Radiation Protection and Measurements; 2001. p. 1. [Online resource (ix, 287 p.)].
39. Borak J, Sirianni G. Hormesis: Implications for cancer risk assessment. Dose Response 2006;3:443-51.
40. Sagan LA. On radiation, paradigms, and hormesis. Science 1989;245:574, 621.
41. Pandey KB, Rizvi SI. Anti-oxidative action of resveratrol: Implications for humanhealth. J Arab J Chem 2011;4:293-8.
42. Calabrese EJ, Mattson MP, Calabrese V. Resveratrol commonly displays hormesis: Occurrence and biomedical significance. Hum Exp Toxicol 2010;29:980-1015.
43. Vichi P, Tritton TR. Stimulation of growth in human and murine cells by adriamycin. Cancer Res 1989;49:2679-82.
44. Zhang C, Chen S, Chengwei HE, Wang Y. Hormesis and neuroprotection. Sci Technol Rev 2015;33:110-3.
45. Ji LL, Kang C, Zhang Y. Exercise-induced hormesis and skeletal muscle health. Free Radic Biol Med 2016. pii: S0891-584900076-9.
46. Peake JM, Markworth JF, Nosaka K, Raastad T, Wadley GD, Coffey VG. Modulating exercise-induced hormesis: Does less equal more? J Appl Physiol 2015;119:172-89.