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Review

Hormetic dose–responses in nanotechnology studies

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HIGHLIGHTS

- Nanoparticles induce hormetic-like biphasic dose-responses in biological models.
- Nanoparticle-induced hormetic response can depend on physico-chemical properties.
- The maximum stimulatory responses of the hormetic curves were generally modest.
- Hormesis induced by NPs is quantitatively similar to the induced by other agents.

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ABSTRACT

While exposure to nanoparticles is a growing concern, research into their toxicological impact and possible hazard for human health is limited. There remains a lack of information concerning the nature of the dose–response relationship especially at low level exposures. The present paper assesses the occurrence of hormetic-like biphasic dose responses within the nanotoxicology literature. The findings indicate that nanoparticles may induce hormetic-like biphasic dose responses in a wide range of biological cell types, and that these responses can be highly dependent upon the physical and chemical properties of the agent. While the mechanistic foundations of hormetic dose responses induced by chemicals and pharmaceuticals have markedly advanced over the past decade, this remains an important data need for nanotoxicology.

Contents

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1. Introduction

Over the past two decades hormesis has become more broadly and consistently observed as toxicologists and pharmacologists have explored possible biological responses in the low-dose range. Such information has now become integrated into leading textbooks of pharmacology (Calabrese, 2009a) and toxicology (Eaton and Klaassen, 2003; Beck et al., 2007; Calabrese, in press). In 2013 the term hormesis or hormetic was cited over 5700 times in the Web of Knowledge/Science database. Detailed assessments of these developments suggest that the hormetic dose–response model is broadly generalizable, being independent of endpoint measured as well as chemical class and physical agent (Calabrese, 2005, 2009b, 2010, 2011; Calabrese and Baldwin, 2002; Calabrese et al., 2012, 2013; Martins et al., 2011; Maynard, 2011; Vaiserman, 2011). Of particular toxicological significance has been the growing documentation that hundreds of hormetic-like biphasic dose responses are mediated by specific receptor and/or cell signaling pathways (Calabrese, 2008, 2013) and that the quantitative features of the hormetic dose response are independent of mechanism.

In recent years, the increasing industrial applications of nanoparticles (NPs) and their consequent worldwide distribution caused an increased likelihood of environmental and human exposure. In this regard, Gottschalk and Nowack (2011) and Gottschalk et al. (2013), employing both modeling and analytical studies, demonstrated an environmental release and accumulation of NPs as a result of their production, use and disposal. These results raised concerns regarding the potential environmental impact and the adverse health effects of NPs on general and occupational exposed population (Ling et al., 2011; Borm et al., 2006). In particular, the issue of the nature of the dose–response in the low dose zone has become a growing concern for NPs. In fact, numerous examples of hormetic-like biphasic dose responses have been reported for a wide range of nanoparticles (Iavicoli et al., 2010, 2013a,b; Nascarella and Calabrese, 2012). The present paper extents these earlier publications by assessing how physico-chemical parameters (e.g. chemical structure, size, surface area) of nanoparticles may affect hazard assessment, especially with respect to the nature of the dose response in the low dose zone.

1.1. Nanoparticles, toxicological profiles and the dose response: overview

Nanotechnology is the manipulation of matter on a near atomic scale to produce new structures, materials, and devices with unique physico-chemical properties. It has rapidly grown worldwide becoming an important industry (NIOSH, 2009). The essence of nanotechnology is the synthesis and the production of engineered NPs that range in size from approximately 1 to 100 nm (ISO, 2008). NPs exhibit characteristics, such as small size, large surface area to mass ratio, shape, crystallinity, surface charge, reactive surface groups, dissolution rate, state of agglomeration or dispersal that confer properties and a toxicological profile that substantially differ from those of the bulk particles of the same chemical composition (Oberdörster et al., 2005; Handy and Shaw, 2007; Ling et al., 2011; Li and Nel, 2011). However, the same physico-chemical properties that provide a wide industrial use of NPs also affect interactions with biological systems. For example, at the cell level NPs can enhance the formation of reactive oxygen species (ROS), disrupt the electron/ion cell membrane transport activity, and induce oxidative damage and lipid peroxidation. At the organism level NPs may induce adverse effects on respiratory, cardiovascular and nervous systems (Landsiedel et al., 2012; NIOSH, 2012). Therefore, NPs, with their increasing industrial applications and worldwide distribution, have raised concerns regarding their potential for human exposure and adverse health effects on the general public and occupationally exposed workers (Ling et al., 2011; Borm et al., 2006). Nevertheless, current understandings of the health aspects of NPs are still largely underdeveloped (Li and Nel, 2011; Yokel and MacPhail, 2011; Clift et al., 2011; Nel et al., 2006).

1.2. Assessing the dose response from a hormetic perspective

Hormetic dose responses are biphasic dose responses with specific quantitative features with respect to the amplitude and width of response and the relationship of the magnitude of the low dose stimulation to the observed threshold. In order to assess properly whether a dose response displays hormesis it is necessary that the dose response satisfies a priori entry and evaluative criteria. These criteria have been applied to multiple independent data sets in order to estimate the frequency of hormetic dose responses in multiple biological models and for diverse endpoints, with possible consideration also for the generalization of its frequency within the domains of toxicology and pharmacology (Calabrese and Bladwin, 2001, 2003; Calabrese et al., 2006, 2008, 2010). An evaluation of the Hormesis Database indicates that hormetic dose responses display a modest stimulatory response in the low dose zone with the maximum response typically being about 30–60% greater than the control group value (Calabrese and Blain, 2005, 2009, 2011) (Fig. 1). About 80% of hormetic dose responses in the Hormesis Database have their maximum stimulatory response being less than twice the control value. The width of the stimulatory response zone is typically about 5–20-fold, starting immediately below the estimated threshold and/or zero response equivalent point. These dose response features generally require that the agent be tested