



Contents lists available at ScienceDirect

Toxicology

journal homepage: [www.elsevier.com/locate/toxicol](http://www.elsevier.com/locate/toxicol)



## Review

# Cross-species coherence in effects and modes of action in support of causality determinations in the U.S. Environmental Protection Agency's integrated science assessment for lead

Meredith Gooding Lassiter<sup>a,\*</sup>, Elizabeth Oesterling Owens<sup>a</sup>, Molini M. Patel<sup>a</sup>, Ellen Kिरrane<sup>a</sup>, Meagan Madden<sup>b</sup>, Jennifer Richmond-Bryant<sup>a</sup>, Erin Hines<sup>a</sup>, Allen Davis<sup>a</sup>, Lisa Vinikoor-Imler<sup>a</sup>, Jean-Jacques Dubois<sup>c</sup>

<sup>a</sup> National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, USA

<sup>b</sup> Oak Ridge Institute for Science and Education Research Participation Program, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, USA

<sup>c</sup> Southern Region Integrated Pest Management Center, North Carolina State University, 1730 Varsity Drive, Suite 110, Raleigh, NC 27606, USA

## ARTICLE INFO

### Article history:

Received 24 September 2014

Received in revised form 24 December 2014

Accepted 26 January 2015

Available online xxx

### Keywords:

Cross-species

Mode of action

Lead

Biological plausibility

Causality

Coherence

## ABSTRACT

The peer-reviewed literature on the health and ecological effects of lead (Pb) indicates common effects and underlying modes of action across multiple organisms for several endpoints. Based on such observations, the United States (U.S.) Environmental Protection Agency (EPA) applied a cross-species approach in the 2013 Integrated Science Assessment (ISA) for lead for evaluating the causality of relationships between Pb exposure and specific endpoints that are shared by humans, laboratory animals, and ecological receptors (i.e., hematological effects, reproductive and developmental effects, and nervous system effects). Other effects of Pb (i.e., cardiovascular, renal, and inflammatory responses) are less commonly assessed in aquatic and terrestrial wildlife limiting the application of cross-species comparisons. Determinations of causality in ISAs are guided by a framework for classifying the weight of evidence across scientific disciplines and across related effects by considering aspects such as biological plausibility and coherence. As illustrated for effects of Pb where evidence across species exists, the integration of coherent effects and common underlying modes of action can serve as a means to substantiate conclusions regarding the causal nature of the health and ecological effects of environmental toxicants.

© 2015 Published by Elsevier Ireland Ltd.

## Contents

1. Introduction	00
2. Methods	00
3. Coherence of mode of action and effects	00
3.1. Hematological effects	00
3.1.1. Pb effects on heme synthesis	00
3.1.2. MOA for hematological effects	00

**Abbreviations:** δ-ALA, delta aminolevulinic acid; ALAD, aminolevulinic acid dehydratase; AOP, adverse outcome pathway; BW, body weight; CASAC, Clean Air Scientific Advisory Committee; DNA, deoxyribonucleic acid; EPA, Environmental Protection Agency; FSH, follicle stimulating hormone; GABA, gamma aminobutyric acid; GnRH, gonadotropin releasing hormone; Hb, hemoglobin; HERO, Health and Environmental Research Online; HPG, hypothalamic–pituitary–gonadal; IGF-1, insulin-like growth factor; ISA, Integrated Science Assessment; LH, luteinizing hormone; MOA(s), mode(s) of action; NAAQS, National Ambient Air Quality Standards; Pb, lead; ROS, reactive oxygen species; U.S., United States; ZPP, zinc–protoporphyrin production.

\* Corresponding author. Tel.: +1 919 541 3200; fax: +1 919 541 2985.

E-mail addresses: [lassiter.meredith@epa.gov](mailto:lassiter.meredith@epa.gov) (M.G. Lassiter), [owens.beth@epa.gov](mailto:owens.beth@epa.gov) (E.O. Owens), [patel.molini@epa.gov](mailto:patel.molini@epa.gov) (M.M. Patel), [kirrane.ellen@epa.gov](mailto:kirrane.ellen@epa.gov) (E. Kिरrane), [meagankmadden@gmail.com](mailto:meagankmadden@gmail.com) (M. Madden), [richmond-bryant.jennifer@epa.gov](mailto:richmond-bryant.jennifer@epa.gov) (J. Richmond-Bryant), [hines.erin@epa.gov](mailto:hines.erin@epa.gov) (E. Hines), [davis.allen@epa.gov](mailto:davis.allen@epa.gov) (A. Davis), [vinikoor-impler.lisa@epa.gov](mailto:vinikoor-impler.lisa@epa.gov) (L. Vinikoor-Imler), [jjbdubois@ncsu.edu](mailto:jjbdubois@ncsu.edu) (J.-J. Dubois).

<http://dx.doi.org/10.1016/j.tox.2015.01.015>

0300-483X/© 2015 Published by Elsevier Ireland Ltd.

3.1.3.	The cross-species approach: conclusions for hematological effects of Pb	00
3.2.	Reproductive and developmental effects	00
3.2.1.	Delayed maturation	00
3.2.2.	Male reproductive function	00
3.2.3.	MOA for reproductive effects	00
3.2.4.	The cross-species approach: conclusions for reproductive and developmental effects of Pb	00
3.3.	Nervous system effects	00
3.3.1.	Cognitive function	00
3.3.2.	Externalizing behaviors	00
3.3.3.	Neurotransmitter function to support effects on cognitive function, externalizing behaviors, internalizing behaviors, and motor function	00
3.3.4.	MOA for nervous system effects	00
3.3.5.	The cross-species approach: conclusions for nervous system effects of Pb	00
3.4.	Biological systems with less evidence for coherence	00
4.	Conclusions	00
	Disclaimer	00
	Conflict of interest	00
	Transparency document	00
	Uncited references	00
	Acknowledgements	00
	References	00

## 1. Introduction

There is increasing recognition in the scientific community of the potential value of integrating scientific information across human and ecological receptors to improve characterization of the risk posed by environmental exposures (Munns et al., 2003; U.S. EPA, 2005a; Vermeire et al., 2007). A cross-species and transdisciplinary approach was proposed for characterization of the effects of Pb to humans and wildlife (Pokras et al., 2009; Pokras and Kneeland, 2008). Consistent with these developments, the United States (U.S.) Environmental Protection Agency (EPA) used a novel cross-disciplinary approach, drawing upon the coherence of the effects of Pb across human and animal species, to form causal determinations for relationships of Pb exposure with health and ecological effects. These causal determinations are described in the recent Integrated Science Assessment (ISA) for Pb (U.S. EPA, 2013a), which is the comprehensive review, synthesis, and evaluation of the most policy-relevant science and serves as the scientific foundation for the review of the National Ambient Air Quality Standards (NAAQS) for Pb in the U.S (U.S. EPA, 2013a). Pb is one of six criteria pollutants for which the U.S. EPA establishes primary and secondary standards for the level of pollutant in the air. The primary NAAQS are established to provide an adequate margin of safety that is requisite to protect public health from air pollution. Secondary standards for Pb provide public welfare protection, including damage to animals, wildlife, soils, crops, and vegetation. The Clean Air Act requires periodic review of the scientific evidence upon which the standards are based and the adequacy of the standards themselves.

In order to determine the causal nature of air pollution-related health or ecological effects, ISAs apply a well-defined framework to integrate scientific evidence and evaluate the overall weight of evidence. This framework, described in detail in the preamble to the ISA, includes several factors to guide the evaluation of the evidence across all disciplines: consistency, coherence, strength, biological plausibility, temporality, specificity, analogy, and experimental evidence (U.S. EPA, 2013a). These various aspects of the available scientific information, based on the criteria first articulated by Sir Austin Bradford Hill (Hill, 1965), have been widely applied for hazard identification when evaluating human health evidence for the purpose of judging causality (IOM, 2008; IARC, 2006; U.S. EPA, 2005b; CDC, 2004). Although, originally developed for interpretation of epidemiologic results, the Hill aspects have been modified for use with a broader array of data, i.e.,

epidemiologic, controlled human exposure, ecological, and animal toxicological studies as well as in vitro data (U.S. EPA, 2013a).

Causal inference can be strengthened by the integration of evidence across disciplines. A weak inference from one line of evidence can be addressed by other lines of evidence and their coherence across disciplines can add support to a cause–effect interpretation of the association. For example, for any effect identified in one scientific discipline, other lines of evidence that elucidate the sequence of key events that lead to that effect can add to the weight of evidence by providing biological plausibility for effects. Where effects of Pb observed in humans can support conclusions regarding effects in wildlife and vice-versa (Pokras et al., 2009), consideration of common underlying mechanisms of Pb toxicity across species can provide an additional basis for integration. While human health and ecological effects are typically assessed through the consideration of distinct discipline-specific bodies of literature, both human and ecological toxicology have recently moved toward characterization of underlying pathways conserved across taxa (Perkins et al., 2013; Ankley et al., 2010). Both the mode of action (MOA) approach and the adverse outcome pathway (AOP) approach are based on shared molecular pathways and key initiating events (Meek et al., 2014). An AOP examines the linkages between molecular initiating events and adverse outcomes at higher levels of biological organization that are relevant to risk assessment (Ankley et al., 2010). MOA is defined as a series of causally linked biochemical or biological key events that are empirically observable, measurable, reproducible and necessary steps of a MOA leading to an effect. The MOA approach typically uses a chemical-specific focus to characterize key events while the AOP approach uses an endpoint specific focus for the same purpose (Ankley et al., 2010; Meek et al., 2014). Although the MOA construct has historically been used in human toxicology and the AOP in ecological contexts, both facilitate characterizing the effects of toxicants on humans and wildlife. Both approaches support the identification of key events that are conserved across taxa and may in turn inform the other for a range chemicals or outcomes.

As noted by Munns et al. (2003), joint examination of health and ecological effects of environmental stressors in risk-based decision-making is supported by shared exposure pathways and commonalities in biological responses across species, including those characterizing potential underlying mechanisms. In the case of Pb, human and ecological receptors share pathways of exposure due to the non-specificity of multiple sources, including current

Download English Version:

<https://daneshyari.com/en/article/5859100>

Download Persian Version:

<https://daneshyari.com/article/5859100>

[Daneshyari.com](https://daneshyari.com)