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Instruments for assessing risk of bias and other methodological criteria: Krauth et al. respond

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Authors
Krauth, D
Woodruff, TJ
Bero, L

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In response to the systematic review by Krauth et al. (2013) of instruments for assessing animal toxicology studies for risk of bias and other aspects of quality, we propose the need for a broader perspective when appraising—and hopefully improving—such studies.

Krauth et al. (2013) reviewed 30 instruments, 4 of which were designed for environmental toxicology studies used to evaluate human and ecological health hazards. The authors noted that these instruments were derived from preclinical pharmacological research in animal models. Many of these instruments focus on efficacy and not toxicity, and—as acknowledged by the authors—they may have limited potential application in environmental health research because they often have criteria that are not relevant to hazard and risk assessments.

Based on these 30 instruments, Krauth et al. concluded that a limited number of risk of bias assessment criteria have been empirically tested for animal research, including randomization, concealment of allocation, blinding, and accounting for all animals. However, the authors did not discuss which elements of risk of bias criteria have been empirically tested, nor did they discuss how they were tested, leaving the reader with no information on their reliability or usefulness.

We would like to bring the readers’ attention to several other important publications in environmental chemical health hazard assessment that are pertinent to this topic (Ägerström et al. 2011; Hulzebos et al. 2010; Schneider et al. 2009), along with a U.S. Environmental Protection Agency (EPA) approach developed under the High Production Volume Challenge (U.S. EPA 1999b) as well as relevant and potentially eligible guidance developed by the U.S. EPA (1999a) and the Food and Drug Administration (FDA 2003). In addition, the majority of the procedures specified in Good Laboratory Practices and regulatory in vivo toxicity test guidelines (e.g., U.S. EPA 2013; Organisation for Economic Co-operation and Development 1999) were specifically developed to minimize systematic errors, assure high quality data and produce scientifically reliable studies.

These additional publications describe design, conduct, and reporting criteria that form the basis of the methodologies employed globally to assure quality and reliability of in vivo toxicological investigations for regulatory assessment of human and ecological health hazards. Because the application of systematic review and related evidence-based approaches in toxicology is still in its infancy, it is especially important at this time to recognize the contributions of these publications.

The omission of these publications by Krauth et al. could have major science policy implications. The National Toxicology Program (NTP) (whose parent organization, the National Institute of Environmental Health Sciences, funded the research of Krauth et al.) has begun relying on Krauth et al. (2013) to identify elements of risk of bias in evaluating animal studies of environmental agents as part of its systematic reviews for assessing health effects (NTP 2013a, 2013b). The reliance on criteria that have not been transparently empirically tested instead of well-established methodological criteria developed by authoritative national and international organizations could result in biased systematic reviews that ultimately lead to regulations or classifications not supported by the science.

We suggest that further work is warranted in pulling together published perspectives on how to evaluate study quality in animal toxicology studies. Issues in appraising such studies for evaluating environmental hazards to humans and wildlife go well beyond those of human clinical trials, and would benefit from collaboration of experts in animal toxicology with experts in human clinical trials of medical interventions and human epidemiology.

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None of the authors received specific financial support or honorarium as compensation for developing this letter. Several authors are members of the Evidence-Based Toxicology Collaboration (EBTC), and M.L. Stephens and S. Hoffmann serve as the secretariats for the North American and European EBTC Steering Committees, respectively, for which they are compensated for their time. The EBTC’s overall aims are to improve toxicological decision making, facilitate the modernization of the toxicological toolbox, and reinvigorate the safety sciences (see http://www.ebtox.com). S. Hoffmann, J.R. Fowle III, and J. Goodman are consultants and have worked on a range of toxicity and risk assessment issues for a wide variety of clients. R.A. Becker and N.B. Beck are employed by the American Chemistry Council, a trade association of chemical manufacturers, A. Boobis, D. Ferguson, M. Lalu, and M. Leist are employed by institutes of higher education. All authors contributed equally and are listed in alphabetical order.

"Nancy B. Beck,1 Richard A. Beck,2* Alan Boobis,3* Dean Ferguson,3* John R. Fowle III,4* Julie Goodman,5* Sebastian Hoffmann,6* Manoj Lalu,7* Marcel Leist,4* and Martin L. Stephens8,* 1Regulatory and Technical Affairs, American Chemistry Council, Washington, DC, USA; 2Department of Medicine, Imperial College, London, United Kingdom; 3Office of Human and Ecological Risk Assessment, U.S. EPA; 4Science to Inform, LLC, Pittsboro, North Carolina, USA; 5Gradient, Cambridge, Massachusetts, USA; 6Pathology consulting + services, Paderborn, Germany; 7Center for Alternatives to Animal Testing, John Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. E-mail: nancy_beck@americanchemistry.com

*Members of the Evidence-Based Toxicology Collaboration (EBTC), an initiative of scientists in academia, industry, and government who are interested in promoting evidence-based approaches to strengthen decision making in the safety sciences (see http://www.ebtox.com).

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Beck et al. criticize our systematic review (Krauth et al. 2013) because we included instruments derived from preclinical animal research. Assessment instruments developed for preclinical animal models have criteria that are relevant to hazard and risk assessment because risk of bias in animal studies is not dependent on the data stream or the question being asked, but on the design of the study. Many instruments that have been developed (including those for evaluating animal toxicology studies) have criteria that have not been shown to bias research outcomes (see Supplemental Material, Table S1, of Krauth et al. 2013).

Furthermore, Table 1 of our paper (Krauth et al. 2013) lists the criteria found in most instruments we identified. In the “Discussion,” we described the empirical evidence supporting the use of some of these criteria and cited the relevant references with the empirical data. By empirical evidence, we mean that a criterion (e.g., randomization) has been shown to be associated with overestimation or underestimation of effect (this could be an efficacy or harm outcome).

Beck et al. note several publications in environmental chemical health hazard assessment [Ågerstrand et al. 2011; Food and Drug Administration (FDA) 2003; Hulzebos et al. 2010; Organisation for Economic Co-operation and Development (OECD) 1998; Schneider et al. 2009; U.S. Environmental Protection Agency (EPA) 1999a, 1999b, 2013]. All of these publications, except OECD (1998), were identified in our search; however, they did not meet the a priori inclusion criteria for our systematic review. As noted in our “Methods” (Krauth et al. 2013), we included the earliest publication of an instrument when it was used in subsequent reports. The article by Ågerstrand et al. (2011) was based on four earlier published papers (i.e., Durda and Preziosi 2000; Hobbs et al. 2005; Klimisch et al. 1997; Schneider et al. 2009). We cited three of these in our review, but excluded Schneider et al. (2009) because it appeared to be a description of software that could be used to operationalize the Klimisch criteria. After reviewing the criteria described by Schneider et al. (2009) in their supplemental file, we found no unique additional criteria that were not already included in our Table 1 and Supplemental Material, Table S1. The reports from the U.S. EPA (1999a, 1999b) and FDA (2003) were neither indexed in Medline nor found in screening of bibliographies. In addition, U.S. EPA (2013) was published after we ended our study. Because we did not find the OECD document (OECD 1998), we cannot conclude whether or not it should have been included in our study.

The comment by Beck et al. that the National Toxicology Program is relying on criteria that have not been “transparently empirically tested” is not correct. In our paper (Krauth et al. 2013), we recommended the use of empirically tested criteria and we pointed out criteria that have been shown to be a risk of bias.

We caution against gathering judgments on how to assess study quality and propose that evidence should guide such evaluations. We propose an empirically based approach—as opposed to consensus-based opinion of experts—as this would provide a more unbiased evaluation of the data.

The authors declare they have no actual or potential competing financial interests.

David Krauth,1 Tracey J. Woodruff,2,3 and Lisa Bero1,4

1Department of Clinical Pharmacy, and 2Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco, California, USA; 3Program on Reproductive Health and the Environment, Oakland, California, USA; 4Institute for Health Policy Studies, University of California, San Francisco, San Francisco, California, USA

E-mail: bero@pharmacy.ucsf.edu

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