ARTICLE IN PRESS
EI-03128; No of Pages 9
Environment International xxx (2015) xxx–xxx
Contents lists available at ScienceDirect
Environment International
journal homepage: www.elsevier.com/locate/envint

Implementing systematic review techniques in chemical risk assessment: Challenges, opportunities and recommendations

Paul Whaley [a], Crispin Halsall [a,*], Marlene Ågerstrand [b], Elisa Aiassa [d], Diane Benford [c], Gary Bilotta [e], David Coggon [f], Chris Collins [w], Ciara Dempsey [n], Raquel Duarte-Davidson [g], Rex FitzGerald [h], Malyka Galay-Burgos [x], David Gee [i], Sebastian Hoffmann [j], Juleen Lam [k], Toby Lasserson [l], Len Levy [m], Steven Lipworth [n], Sarah Mackenzie Ross [o], Olwenn Martin [i], Catherine Meads [p], Monika Meyer-Baron [q], James Miller [r], Camilla Pease [s], Andrew Rooney [t], Alison Sapiets [u], Gavin Stewart [v], David Taylor [n]

[a] Lancaster Environment Centre, Lancaster University, Lancaster LA1 4YQ, UK
[b] Department of Environmental Science and Analytical Chemistry, Stockholm University, SE-106 91, Stockholm, Sweden
[c] Food Standards Agency, Aviation House, 125 Kingsway, London WC2B 6NH, UK
[d] Assessment and Methodological Support Unit, European Food Safety Authority, Via Carlo Magno 1/a 43126, Parma, Italy
[e] Aquatic Research Centre, University of Brighton, Lewes Road, Brighton BN2 4GJ, UK
[f] MRC Lifecourse Epidemiology Unit, University of Southampton, MRC Lifecourse Epidemiology Unit, Southampton General Hospital, Southampton SO16 6YD, UK
[g] Centre for Radiation, Chemicals and Environmental Hazards, Public Health England, Harwell Science and Innovation Campus, Didcot, Oxfordshire OX11 0RQ, UK
[h] Swiss Centre for Applied Human Toxicology, University of Basel, Missionsstrasse 64, 4055 Basel, Switzerland
[i] Institute for the Environment, Health and Societies, Brunel University London, Kingston Lane, Uxbridge UB8 3PH, UK
[j] Evidence-Based Toxicology Collaboration (EBTC), Stembergring 15, 33106 Paderborn, Germany
[k] University of California San Francisco, Program on Reproductive Health and the Environment, San Francisco, CA, USA
[l] Cochrane Editorial Unit, Cochrane Central Executive, St Albans House, 57-9 Haymarket, London SW1Y 4QX, UK
[m] Institute of Environment, Health, Risks and Futures, School of Energy, Environment and Agrifood, Cranfield University, Cranfield, Bedfordshire MK43 0AL, UK
[n] Royal Society of Chemistry, Burlington House, Piccadilly, London W1J 0BA, UK
[o] Research Department of Clinical, Educational and Health Psychology, University College London, Gower Street, London WC1E 6BT, UK
[p] Health Economics Research Group, Brunel University London, Kingston Lane, Uxbridge UB8 3PH, UK
[q] Leibniz Research Centre for Working Environment and Human Factors (IfADo), Neurobehavioural Toxicology, Ardeystr 67, D-44139 Dortmund, Germany
[r] Centre for Ecology and Hydrology, Wallingford, Oxfordshire 0X10 8BB, UK
[s] Ramboll Environ, 1 Broad Gate, The Headrow, Leeds LS1 8EQ, UK
[t] National Institute of Environmental Sciences (NIEHS), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), Research Triangle Park, NC, USA
[u] Syngenta Ltd., Jealott's Hill International Research Centre, Bracknell RG42 6EY, UK
[v] Centre for Rural Economy, School of Agriculture, Food and Rural Development, University of Newcastle upon Tyne, UK
[w] Department of Geography and Environmental Science, School of Archaeology, Geography and Environmental Science, University of Reading, Reading, RG6 6DW, United Kingdom
[x] European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Avenue Edmond Van Nieuwenhuyse 2 Bte 8B-1160 Brussels, Belgium

ARTICLE INFO

Article history:
Received 8 August 2015
Accepted 2 November 2015
Available online xxxx

Keywords:
Risk assessment
Research synthesis
Environment
Chemicals
Systematic review
Toxicology

ABSTRACT

Systematic review (SR) is a rigorous, protocol-driven approach designed to minimise error and bias when summarising the body of research evidence relevant to a specific scientific question. Taking as a comparator the use of SR in synthesising research in healthcare, we argue that SR methods could also pave the way for a "step change" in the transparency, objectivity and communication of chemical risk assessments (CRA) in Europe and elsewhere. We suggest that current controversies around the safety of certain chemicals are partly due to limitations in current CRA procedures which have contributed to ambiguity about the health risks posed by these substances. We present an overview of how SR methods can be applied to the assessment of risks from chemicals, and indicate how challenges in adapting SR methods from healthcare research to the CRA context might be overcome. Regarding the latter, we report the outcomes from a workshop exploring how to increase uptake of SR methods, attended by experts representing a wide range of fields related to chemical toxicology, risk analysis and SR. Priorities which were identified include: the conduct of CRA-focused prototype SRs; the development of a recognised standard of reporting and conduct for SRs in toxicology and CRA; and establishing a network to facilitate research, communication and training in SR methods. We see this paper as a milestone in the creation of a research climate that fosters communication between experts in CRA and SR and facilitates wider uptake of SR methods into CRA.

* Corresponding author.
E-mail address: c.halsall@lancaster.ac.uk (C. Halsall).

http://dx.doi.org/10.1016/j.envint.2015.11.002

1. Introduction

Systematic review (SR) is a rigorous, protocol-driven approach to minimising error and bias[1] in the aggregation and appraisal of evidence relevant to answering a research question. SR techniques were initially developed in the fields of psychology, social science and health care and have, since the 1980s, provided a valuable tool for evidence-informed decision-making across many domains (Lau et al., 2013). In medicine, SRs have provided a valuable response to the need for consistent, transparent and scientifically-robust interpretations of the results of increasing numbers of often conflicting studies of the efficacy of healthcare interventions. SRs have taken on an increasingly fundamental role both in supporting decision-making in healthcare and, by channelling resources towards questions for which the answers are not yet known, reducing waste in research (Chalmers and Glasziou, 2009; Salman et al., 2014). It is now accepted practice in healthcare to use SR methods to assess evidence not only for the efficacy of interventions, but also on diagnostic tests, prognostics and adverse outcomes.

The extension of SR techniques to other fields is based on a mutual need across disciplines to make the best use of existing evidence when making decisions, a move for which momentum has been growing for several decades. For example, the What Works Clearinghouse was established in 2002 to apply SR techniques in support of American educational policy (US Institute of Education Sciences, 2015), and in 2000 the international Campbell Collaboration research network was convened to undertake and disseminate systematic reviews on the effects of social interventions in diverse fields such as crime and justice, education, international development and social welfare (Campbell Collaboration, 2015). Meta-analysis and SR in ecology have contributed to evidence-based environmental policy since the mid-1990s (Stewart, 2010); more recently, the Collaboration for Environmental Evidence (CEE) has been established to encourage conduct of SRs on a wide range of environmental topics (Collaboration for Environmental Evidence, 2015).

The potential advantages of adapting SR methodology to the field of chemical risk assessment (CRA) have also been recognised, with multiple research groups and organisations either developing and adopting (Woodruff and Sutton, 2014; Birnbaum et al., 2013; European Food Safety Authority, 2010; Rooney et al., 2014; Aiassa et al., 2015) or recommending (US National Research Council, 2014a, 2014b; US Environmental Protection Agency, 2013; Silbergeld and Scherer, 2013; Hoffmann and Hartung, 2006; Zoeller et al., 2015) the use of SR methods for evaluating the association between health effects and chemical exposures to inform decision-making. There are, however, a number of recognised challenges in extending SR methods to CRA, many of which derive from key differences in the evidence base between the healthcare and toxicological sciences.

SRs in medicine often focus on direct evidence for benefits and adverse effects of healthcare interventions derived from randomised controlled trials (RCTs) in humans. The evidence base for CRA is generally more complex, with a need to extrapolate from investigations in animals, in vitro and in silico, and then to synthesise findings with those from human studies if available. Furthermore, the human data tend to come from observational studies with greater and more varied potential for bias and confounding than RCTs, and the range of outcomes to be considered is usually much wider than in the assessment of healthcare interventions. Thus, when the various types of toxicological research are combined into a single overall conclusion about the health risks posed by a chemical exposure, reviewers are challenged with integrating the results from a broad and heterogeneous evidence base.

In spite of these differences, there is reason for thinking that SR methods can be applied successfully to CRA. For example, techniques for aggregating the results of different study types are already addressed in various frameworks currently in use in toxicology. These include: International Agency of Research on Cancer (IARC) Monographs (International Agency for Research on Cancer, 2006); the Navigation Guide (Woodruff and Sutton, 2014); and the US Office for Health Assessment and Translation (OHAT) (Rooney et al., 2014; US National Toxicology Panel, 2015) – though it should be noted that none of these approaches have yet applied SR methods to the exposure assessment component of CRA. Heterogeneous sources of evidence are a familiar challenge in all domains including clinical medicine (Lau et al., 1998), and SR of observational studies has a crucial role in identifying complications and side-effects of healthcare interventions (Sterne et al., 2014; Higgins and Green, 2011). The need for SR of pre-clinical animal trials of healthcare interventions, in order to better anticipate benefits and harms to humans, is another area in which methods being developed and implemented by a number of groups including SYRCLE (Hooijmans et al., 2012; van Luijk et al., 2014) and CAMARADES (Macleod et al., 2005; Sena et al., 2014). (Stewart and Schmid, 2015) argue that research synthesis methods (including systematic review) are generic and applicable to any domain if appropriately contextualised.

Given the sometimes controversial outcomes of CRAs and the growing public and media profile of the risks that chemicals may pose to humans and the environment, SR is increasingly viewed as a potentially powerful technique in assessing and communicating how likely it is that a chemical will cause harm. SR methods add transparency, rigour and objectivity to the process of collecting the most relevant scientific evidence with which to inform policy discussions and could provide a critical tool for organising and appraising the evidence on which chemical policy decisions are based.

Consequently, in November 2014 a group of 35 scientists and researchers from the fields of medicine, toxicology, epidemiology, environmental chemistry, ecology, risk assessment, risk management and SR participated in a one-day workshop to consider the application of SR in CRA. The purpose was three-fold:

1. Identify from expert practitioners in risk assessment and SR the obstacles, in terms of practical challenges and knowledge gaps, to implementing SR methods in CRA;
2. Develop a "roadmap" for overcoming those obstacles and expediting the implementation of SR methods, where appropriate, by the various stakeholders involved in CRA;
3. Establish the foundations of a network to co-ordinate research and activities relating to the implementation of SR methods in CRA. The aim would be to support best practise in the application of SR techniques and promote the wider adoption of SR in CRA, both in Europe and elsewhere.

Participants heard seven presentations about recent developments in SR methods, their application to the risk assessment process, and their potential value to policy-makers. There were two break-out sessions in which participants were divided into three facilitated groups, firstly to discuss challenges to implementing SR methods in CRA, and then to suggest ways in which the obstacles could be overcome. These ideas were discussed in plenary before being summarised, circulated for comment, and then published in this paper. The Workshop was conducted under the "Chatham House Rule" such that participants were free to refer to the information presented and discussed, provided they did not attribute it to identifiable individuals or organisations.

[1] It is worth drawing a distinction between three sources of bias in the review process. There is potential for bias in the conduct of a review (e.g. because of inappropriate methods for identifying and selecting evidence for inclusion in the review); bias because the material available for the review is not representative of the evidence base as a whole (due to selective publication); and bias arising from flaws in the design, conduct, analysis and reporting of individual studies included in the review that can cause the effect of an intervention or exposure to be systematically under- or over-estimated. One of the major functions of SRs is to minimise bias in the conduct of a review and, as far as possible, to ensure that potential bias from selective publication and methodological flaws in the evidence are properly taken into account when drawing conclusions in response to a research question.

Please cite this article as: Whaley, P., et al., Implementing systematic review techniques in chemical risk assessment: Challenges, opportunities and recommendations, Environ Int (2015), http://dx.doi.org/10.1016/j.envint.2015.11.002