



## Preface

# Assuring high-quality evidence reviews for chemical risk assessment: Five lessons from guest editing the first environmental health journal special issue dedicated to systematic review



While systematic review (SR), the rigorous methodology for selecting, appraising and synthesising existing evidence in order to answer a research question, may not yet be mainstream among environmental scientists and toxicologists, interest in the methods and what they may bring to chemical risk research is growing rapidly and is evident in an exponential increase in publications over the last 20 years (Fig. 1).

Mirroring the rapid growth of a nascent literature is the proliferation of initiatives, many of which are collaborative, seeking to extend the conduct of systematic reviews to pre-clinical research and laboratory animal experimentation. These include the Systematic Review Centre for Laboratory animal Experimentation<sup>1</sup> (SYRCLE) and the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies<sup>2</sup> (CAMARADES), while efforts to apply SR methods to the toxicological sciences are now coalescing in the form of networks such as the Navigation Guide<sup>3</sup> and the Evidence Based Toxicology Collaboration<sup>4</sup> (EBTC), among others. These initiatives are identifiable by a shared view that SR methods are a vital area of research in their own right, have the potential to greatly improve the scientific quality of reviews of existing evidence, and will facilitate the translation of pre-clinical and toxicological research into evidence-based medical, public health and environmental policy-making.

The purpose of this Special Issue is to contribute to this agenda by promoting interest in and discussion of how SR methods can advance the transparency and scientific rigour of chemical risk assessment (CRA). We have brought together assorted commentaries on the prospects and potential benefits of SR methods for CRA, methods papers explaining how SR methods can be adapted or refined for the CRA context, and a set of full-blown systematic reviews, each of which functions as a case study of how SR methods can apply in practice as well as being valuable pieces of environmental health research in their own right.

The increase in the number of toxicology journal papers with “systematic review” in the title is an encouraging indicator of the regard with which SRs are held in the scientific community. However, proven quality assurance procedures for SRs in environmental health research are limited. This risks a proliferation of publications of variable quality, potentially blunting the influence of SRs as powerful

tools for evidence-based decision-making and undermining the case for using SR methods to synthesise evidence in CRA. With the issue of quality assurance in mind we have drawn up a number of lessons which, while perhaps common knowledge in other fields, have been reinforced for us while editing this Special Issue. The lessons are aimed at SR authors, reviewers and, importantly, journal editors who are being faced with an increasing number of manuscripts that purport to be systematic reviews.

We believe this is the first Special Issue dedicated to systematic review published by an environmental health journal. In spite of the inevitable imperfections this entails, we hope the reader agrees this Special Issue has been a success. We would like to thank all the authors, peer reviewers and funders who contributed to this Special Issue and our initial workshop organised through the Royal Society of Chemistry, of which this Special Issue was one output (detailed in Whaley et al., 2015). We also hope the reader will share our enthusiasm for SR methods and recognise the potential for their uptake and effectiveness in shaping the future of chemical risk assessment.

## Lesson 1: Submitting authors should be provided with detailed guidance about how to report systematic reviews and encouraged to describe how they fulfilled it

Uneven understanding from authors as to the precise requirements of conducting and reporting CRA-related SRs in a comprehensive and transparent fashion is unsurprising given the novelty of the methods. We received a number of SR submissions which, while of high potential scientific value, were obscured by poor write-up. In order to avoid rejecting good research for want of adequate reporting, the editors and peer-reviewers ended up with a substantial workload in providing the authors with guidance as to how their SRs should have been reported. The authors themselves had the burden of making substantial revisions to their manuscripts.

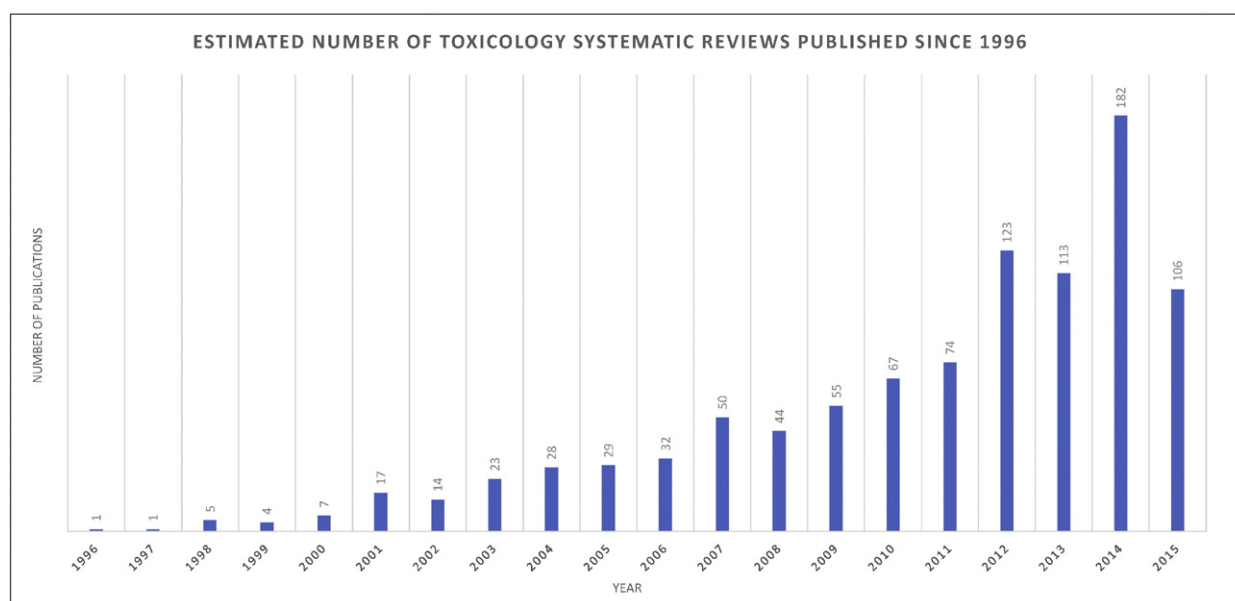
With hindsight, we believe we could have saved probably one revision round for several of the submitted SRs by insisting in advance that they conform at least to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), a relatively straightforward checklist of items to report in a systematic review or meta-analysis already widely endorsed by medical journals (Moher et al., 2009). One review (Joca et al., 2016), unprompted by us, even went so far as to explain in supplementary information how they had fulfilled each PRISMA requirement. This was extremely helpful in providing a clear

<sup>1</sup> Website: <https://www.radboudumc.nl/Research/Organisationofresearch/Departments/cdl/SYRCLE/Pages/default.aspx>.

<sup>2</sup> Website: <http://www.dcn.ed.ac.uk/camarades/>.

<sup>3</sup> Website: <http://prhe.ucsf.edu/prhe/navigationguide.html>.

<sup>4</sup> Website: <http://www.ebtox.com/>.



**Fig. 1.** Papers indexed in Web of Science (WoS) with the term “Systematic Review” in the publication title, filtered for “Toxicology” as topic, excluding topic of “Pharmacology Pharmacy”. WoS database search excludes Biosis Citation Index (not subscribed). Date of search: 4 April 2016.

picture of the strengths and limitations of the SR methods employed and we would strongly encourage other SR authors to do the same.

The PRISMA checklist is not exhaustive and there may be room for developing detailed reporting guidance specifically for toxicology SRs. While editing the Special Issue we became aware of initiatives such as the Methodological Expectations of Cochrane Intervention Reviews (MECIR, 2012), which provide a lengthy and detailed checklist of “must-haves” and “should-haves” for conduct and reporting of SRs adapted for different medical disciplines. As editors, we would like to flag the potential for adapting MECIR standards to the current research context.

## **Lesson 2: Editors need to invest in developing a balanced peer-review group and cultivate a network of interdisciplinary expertise in the review pool**

In principle, peer-review of an SR is straightforward: each submission should be attended by two content experts and a SR methods expert. The problem is, this is easier said than done. One SR submission spent 111 days between first reviewer accepting invitation to review the manuscript and the three required reviews finally being completed. Although as editors we bear full responsibility for this, it is indicative of several challenges we faced in securing peer-review for SRs, insofar as they are often lengthy, complex, and require a breadth of interdisciplinary expertise to be reviewed fairly. While content experts were relatively easy to find, experts in SR methods were much harder to secure and we ended up leaning heavily on a relatively small group of SR experts, to whom we are extremely grateful for their commitment and patience.

Of course, access to a comprehensive peer-review pool of interdisciplinary expertise is not something which can be secured overnight, but efforts need to be made by journals to help editors identify and keep track of reliable reviewers who can handle the specific demands of systematic reviews. Databases to help editors identify peer-reviewers do exist, and we used them in editing the Special Issue, but it was very difficult to filter appropriate reviewers from the long lists of those identified as potentially suitable. In particular, being able to quickly identify reviewers with specific SR experience (either as researchers or as reviewers) would have been very helpful.

Reviewers initially brought in as content experts will quickly acquire relevant SR experience in the course of reviewing SRs. With the right guidance and training (as we touch on in [Lesson 3](#) below), we anticipate

that content experts can therefore be cultivated into a pool of competent SR reviewers. To be effective, editors need to treat this cultivation as an active process and should be supported by easy access to more detailed information about the review histories of individual peer-reviewers and, for example, relevant training they might have received.

## **Lesson 3: Peer-reviewers should be provided with detailed guidance and ideally training in how to critically appraise systematic reviews**

There is a major challenge in ensuring that even an experienced SR researcher provides a sufficiently thorough critical appraisal of a submitted SR, such that all the important methodological features of the submission have been given due consideration. For less experienced SR reviewers, the challenge multiplies. For example, we found that reviewers without significant experience in SR were often bemused by the level of detail presented in the SRs they were reviewing and/or the value of an additional review in a field in which literature reviews might already be plentiful. We also found many reviewers were insufficiently alert to obvious flaws in conduct or reporting of a review. The best reviews came from experienced SR researchers with substantial field expertise; however, these researchers are currently limited in number and present an unsustainably small pool of reviewers from which to draw. As editors with experience in SR methods we were able to compensate for some of the shortcomings of the review process but such a hands-on approach, spending as much as eight hours on some submissions, is likely to be too time-consuming to become standard practice.

We believe that securing the balance of competence to assess both the scientific content of the systematic review, the limitations in design, conduct and reporting of the SR, and ensuring that the peer-review is sufficiently thorough, would have been significantly facilitated by provision for peer-reviewers of detailed guidance on how to critically appraise a SR (i.e. a structured approach to determining which methodological features need to be present in a SR, and how to distinguish when those features either have or have not been implemented validly). While uneven quality of peer-review comments is a fact of editorial life, editors and journals can do much more to educate and train peer-reviewers, to increase the likelihood that the review process will provide fair, valuable and comprehensive feedback to the submitting authors, and more consistently identify those SRs which should be published.

#### Lesson 4: Journals need to implement a formal-but-flexible standard for publishing SRs

As will quickly become evident to the reader of this Special Issue, we did not implement a standard approach for formatting and structuring reviews or handling supplementary material and appendices. Some papers present structured abstracts, some do not (the former is clearly preferable as it is standard practice in the field of medicine, for example). Similar to guidance for authors on what to report in a SR, publishers should have their own formal but flexible guidance on what they expect to present in a systematic review and how it should be structured. This should cover: basic SR structure; the provision of a structured abstract; the handling of appendices and supplemental material; and so forth.

#### Lesson 5: All systematic reviews should be preceded by formal publication of protocols

Pre-publication of protocols is already considered essential for systematic reviews in other fields (e.g. the Cochrane Collaboration in clinical medicine), in part to prevent methodological choices being influenced by what the reviewers might be learning in the course of conducting a SR. Editing the Special Issue reinforced another aspect of the value of protocols: they provide an opportunity for external appraisal and validation of planned methods before conducting the systematic review, which in turn allows SR authors to minimise effort before risking rejection of an inadequate, completed manuscript.

Rejection of a systematic review because of basic errors such as ineffective search strategies, ambiguously articulated or invalid eligibility criteria, or the use of statistical methods, is a poor return on the large time investment in conducting a review. This is potentially avoidable if a protocol is submitted for peer-review prior to the decision to proceed with conducting the full SR. While disappointing, the cost of rejection of a protocol is only the time spent planning a review, which is far preferable to rejection after completing a SR using flawed methods.

This first-stage peer-review of a submitted protocol may also provide valuable critical appraisal of methodological choices before the full SR process commences. Not only will the SR benefit from this, the preliminary but still substantial work done by the authors in developing a SR protocol can be recognised by citation in the literature. As editors of this Special Issue we were not in a position to insist on pre-publication of protocols, and while it is possible to pre-publish protocols through databases such as PROSPERO<sup>5</sup>, here we urge that consideration be given to the value

of formal publication of protocols in peer-reviewed journals as an important step in the quality assurance of SRs, in particular assuring the validity of methodological choices. This has already been implemented by the journal *Environmental Evidence* (*Collaboration for Environmental Evidence*, 2016) and is a practice which could be adopted elsewhere.

#### References

- Collaboration for Environmental Evidence, 2016. Guidelines for Authors. (accessed 10 April 2016) <http://www.environmentalevidence.org/information-for-authors>.
- Joca, L., Sacks, J.D., Moore, D., Lee, J.S., Sams 2nd, R., Cowden, J., 2016 Feb 18. Systematic review of differential inorganic arsenic exposure in minority, low-income, and indigenous populations in the United States. *Environ. Int.* <http://dx.doi.org/10.1016/j.envint.2016.01.011> (pii: S0160-4120(16)30011-3 [Epub ahead of print] PubMed PMID: 26896853).
- MECIR, 2012. Methodological expectations of cochrane intervention reviews (MECIR) standards for the conduct (version 2.2) and reporting (version 1.1) of new cochrane intervention reviews. (accessed 6 April 2016) <http://www.editorial-unit.cochrane.org/mecir>.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., P.R.I.S.M.A. Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6 (7), e1000097. <http://dx.doi.org/10.1371/journal.pmed.1000097>.
- Whaley, P., Halsall, C., Ågerstrand, M., Aiassa, E., Benford, D., Bilotta, G., Coggon, D., Collins, C., Dempsey, C., Duarte-Davidson, R., FitzGerald, R., Galay-Burgos, M., Gee, D., Hoffmann, S., Lam, J., Lasserson, T., Levy, L., Lipworth, S., Ross, S.M., Martin, O., Meads, C., Meyer-Baron, M., Miller, J., Pease, C., Rooney, A., Sapiets, A., Stewart, G., Taylor, D., 2015 Dec 10. Implementing systematic review techniques in chemical risk assessment: challenges, opportunities and recommendations. *Environ. Int.* <http://dx.doi.org/10.1016/j.envint.2015.11.002> (pii: S0160-4120(15)30086-6 [Epub ahead of print] PubMed PMID: 26687863).

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<sup>5</sup> Website: <http://www.crd.york.ac.uk/PROSPERO/>.