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A review of methods used for hazard identification and risk assessment of environmental hazards

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ABSTRACT

Background: Approximately one quarter of all deaths globally are attributed to living or working in an unhealthy environment, with household and ambient air pollution, along with exposures to ultraviolet radiation and chemicals amongst the leading causes. At present there are no international standards for assessing the risks of these environmental hazards. The use of heterogeneous methods to identify health risks from environmental hazards may reduce the level of confidence the public has in the conclusions that are made.

Objectives: To describe and compare the processes and methods used by national and international organisations that conduct hazard identification and/or risk assessment (HI/RA) of environmental hazards and to identify knowledge gaps to inform the development of future methods.

Methods: We searched the websites of 19 organisations (ten national, five international and four World Health Organization (WHO) units) and extracted data from all relevant, publicly available resources which described the processes and methods used in HI/RA of environmental hazards. We contacted each organisation for any additional information.

Results: Five organisations were excluded from further analysis: three made recommendations but did not conduct HI/RA; one used heterogenous methods across their reviews for HI; and one WHO unit did not have any published guidelines. Of the 14 organisations analysed, five (36%) describe the process for establishing the questions to be answered in the assessments. Only one (7%) organisation uses systematic review methods, although five (36%) state that they use such methods. Ten (71%) assess the scientific quality of the included studies, however only three (21%) use explicit criteria. Only three (21%) organisations assess the quality of the body of evidence using explicit criteria. Four (29%) organisations describe the process for making the final HI conclusions and three (38%) the final RA conclusions. Eight (57%) have a conflict of interest policy and seven (50%) organisations describe a process for managing them. The US Office of Health Assessment and Translation and the World Health Organisation meet the most criteria for describing their processes and methods.

Conclusions: The processes and methods used by organisations conducting HI/RA of environmental hazards are inconsistent. There is a need for empirically based tools and methods to be adopted for the evaluation and synthesis of evidence, and the formulation of conclusions across all organisations that conduct HI or RA. These tools and methods will lead to increased transparency, comparability and validity of the assessments.

1. Introduction

Approximately one quarter of all deaths globally are attributed to living or working in an unhealthy environment, with household and ambient air pollution, along with exposures to ultraviolet radiation and chemicals amongst the leading causative risk factors (Prüss-Üstün et al., 2016). While it is estimated that there are approximately 85,000 chemicals in use, the majority of these have not been assessed for toxicity (Judson et al., 2009; United States Environmental Protection Agency (USEPA), 2016).

A hazard is any natural or man-made substance, chemical, physical or biological agent, that is capable of causing an adverse health outcome in certain circumstances. Risk is an estimate of the effect of an adverse health outcome when exposed to a hazard (International Agency for Research on Cancer (IARC), 2016). Risk assessment is a multi-step process, which includes: hazard identification (can a

Abbreviations: HI, Hazard Identification; HC, Hazard Characterisation; RA, Risk Assessment; WHO, World Health Organization

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substance lead to an adverse health outcome in any circumstance?); hazard characterisation (what is the probability of an adverse health outcome at various exposure levels?); exposure assessment (what is the extent of exposure of a substance in a population?); and finally risk characterisation (the integration of both hazard characterisation and exposure assessment to estimate the level of risk of an adverse health outcome in the most sensitive populations). Risk assessment informs the development of risk management options for environmental hazards.

There are a number of challenges in conducting hazard identification (HI) and risk assessment (RA) of environmental hazards that are distinct from assessments of the effectiveness of clinical interventions. The causal chain linking harmful substances with adverse outcomes is complex, with various interactions and often considerable time periods between exposure and effects. Hazardous substances may be comprised of many toxic components, with various interactions amongst them, making it difficult to identify the precise toxic component that causes an adverse health outcome. There is no one single measurement to assess the association of a harmful substance and an adverse outcome. For example, in assessing the toxicity of triclosan in non-human mammalian evidence, over 100 unique outcome measures were identified (Johnson et al., 2016). Several factors must be considered when assessing the risk of a hazard, including populations that are most susceptible (due to intrinsic biological factors), vulnerable (due to environmental factors), and sensitive (both susceptible and vulnerable) (enHealth, 2012). Data required for HI and RA are rarely derived from randomized, controlled trials and usually come from human observational, animal and mechanistic studies, making assessments and synthesis of the evidence challenging. Confounding and selection bias in observational studies make establishing causal links between exposure and effect difficult. Finally, the methods to assess the quality of the evidence from these studies are not well established (Rooney et al., 2016; Mandrioli and Silbergeld, 2016; Morgan et al., 2016).

At present there are no international standards for conducting HI or RA. Use of heterogeneous methods to identify health risks posed by environmental hazards may reduce the level of confidence the public has in the assessments and hinder the decision-making process. Different pronouncements on the harms of environmental hazards, such as those surrounding glyphosate (The Guardian, 2016; European Food Safety Authority (EFSA), 2017) and bisphenol-A (BPA) (European Food Safety Authority (EFSA), 2015; French Agency for Food Environmental and Occupational Health & Safety (ANSES), 2014) by national and international organisations, leave both the public and policy-makers confused.

Several groups have begun developing methods and frameworks to address environmental health questions, including the assessment of environmental exposures and human health, by extending methods from clinical medicine (Woodruff and Sutton, 2014; Rooney et al., 2014). It has been proposed that well-structured, flexible approaches that are not too prescriptive and account for scientific issues in the design, conduct and analysis of environmental epidemiological and animal toxicology studies may increase transparency and prevent the introduction of a systematic bias when drawing conclusions on environmental hazards (Rooney et al., 2016). The use of scientifically robust and transparent methods to evaluate the evidence also allows the reasons for conflicting conclusions and opinions to be readily identified (Whaley et al., 2016).

The objectives of this study were to:

- describe the processes and methods used by national and international organisations, including World Health Organization (WHO) technical units that conduct HI and/or RA of environmental hazards;
- compare these processes and methods; and
- identify knowledge gaps to inform the development of standardised tools and processes for the evaluation and synthesis of evidence and the formulation of conclusions in HI/RA.

2. Methods

We conducted a cross-sectional content analyses of all publicly available relevant resources of selected national and international organisations that perform HI and/or RA of environmental hazards. We use the term 'organisation' to refer to each organisation, agency, office, unit or department included in our study.

2.1. Selection of organisations

We included organisations that assessed environmental hazards that were categorised as:

- chemical agents, both organic (made with carbon and hydrogen) and inorganic (without carbon);
- radioactive agents, including ionizing and non-ionizing radiation and waste products from the production of nuclear weapons and energy; and
- complex exposures, which include multiple hazardous agents.

If an organisation performed HI/RA for a mixture of agents, including biological and physical, we included the organisation. If a WHO unit had conducted any stage of the HI/RA process in forming a guideline, we included it. Included organisations had to have published at least one assessment or guideline in English.

We excluded organisations that assessed environmental hazards that were categorised as physical agents (including noise, force and light), or biological agents (including mould, bacteria and pollen), even if they were part of complex exposures, such as water quality and air pollution. We excluded voluntary exposures including medications, diet and active smoking. Chemicals ingested through food sources, such as pesticides and food additives were considered involuntary. We also excluded organisations that published conclusions based on assessments provided by other organisations, but did not perform their own HI or RA.

We categorised each included organisation based on the assessments they performed, defined as:

Hazard Identification -whether a substance may lead to key adverse health outcomes at any level of exposure; *Hazard Characterisation* (*HC*) - a quantitative assessment of the dose/exposure-response relationship between a hazardous substance and an adverse health outcome; *Exposure Assessment* - the measurement of the magnitude, frequency and duration of exposure to a hazardous substance in the environment on a specified population; *Risk Characterisation* - the approximation of the incidence and severity of health outcomes, following exposure to the hazardous substance(s); and *Risk Assessment* – the process of completing each of the previous steps.

We initially identified five key organisations that produce HI and/or RA of environmental hazards of the types of interest to us, then consulted those organisations and other experts to identify other organisations for potential inclusion.

2.2. Data sources

Between May and September 2017, we conducted an initial search of the web-sites of identified organisations for publicly available resources which described the processes and methods used in HI and RA of environmental hazards. We also contacted organisation officials via email for guidance on relevant resources.

We examined written guidance documents, assessments, guidelines and websites that described the processes and methods used by an organisation in HI/RA of environmental hazards on any health outcome. If guidance documents were not available, we tried to identify the most recent assessments or guidelines produced by the organisation to identify the processes and methods used in HI/RA.

If a unit or office within an organisation referenced general guidance documents used by the organisation for various stages of the HI/

RA process but did not clearly describe how this guidance was applied for a particular HI or RA, we did not include it in our extraction. We excluded hazard safety cards, facts sheets and safety guides, as well as documents and web-sites that were not written in English.

2.3. Data collection and analysis

A data extraction sheet was developed to characterise the processes and methods used in HI/RA by the included organisations. One author (NC) performed data extraction independently and data were then tabulated and coded in MS Excel (Microsoft, Redmond WA, USA, 2016 MSO). Each included organisation was contacted by email and given the opportunity to review the extracted data and provide additional information. Following this initial revision, we made further amendments to the extraction and therefore offered those organisations that had edited the original data the opportunity to review the data extraction again.

We extracted data according to 22 criteria addressing the following areas: planning or protocol development, evidence review, evidence integration, establishing reference values, making a final determination or conclusion, peer review and identifying and managing conflicts of interest. We used a modified version of AMSTAR (A Measurement Tool to Assess Systematic Reviews) (AMSTAR; Shea et al., 2009) to assess the evidence review methods; the other criteria were based on recommendations made by the United States National Academies of Science to improve toxicological assessments of environmental contaminants (National Research Council, 2014).

We coded our data extraction into four categories: yes, no, N/A (not applicable) and unclear. We coded 'yes' if the content was identified. If an organisation did not provide any publicly available information on request and if it was clear that a criterion was not completed by an organisation, we coded it as a 'no'. 'N/A' was coded if a criterion was not applicable to an organisation (e.g. 'Use a process and method to select the evidence in establishing reference values' is not applicable to organisations only conducting HI). If we were unable to make a clear 'yes' or 'no' categorisation even after contacting the organisation, we classified it as 'unclear'.

3. Results

3.1. Characteristics of included organisations

We identified 19 organisations that perform HI and/or RA of the types of environmental hazards of interest to us. However, five of these organisations did not fulfil our inclusions criteria: three did not conduct their own HI or HC but rather used other organisations' HI and HC to set reference values (United States Environmental Protection Agency (USEPA); International Commission on Non-Ionizing Radiation Protection (ICNIRP), 2002; World Health Organization, 2017a); one WHO unit used heterogeneous methods in the various reviews relevant to HI and HC to develop a single guideline (World Health Organization, 2014) and another WHO unit had no published guidelines, with one guideline under development (World Health Organization Regional Office for Europe). See Supplementary File A for information on the excluded organisations.

We thus included 14 organisations in our final analysis (Fig. 1). The verbatim descriptions of the type of assessment conducted by each organisation are found in Supplementary File B. One of the included organisations was a WHO unit that assessed harms of hazardous exposures to inform guideline recommendations that make it comparable to the national and international organisations that completed HI/RA. See Supplementary File C for additional information on this guideline.

Eight (57%) of the 14 included organisations had publicly available guidance documents outlining the steps they used in the HI/RA process. The remainder did not have any specific guidance documents available: one (7%) had an outline of their methods in a preamble within a completed assessment (United States Environmental Protection Agency (USEPA), 2017); and four (29%) organisations had descriptions of the processes and methods used in RA on their websites and in completed assessments (United States Environmental Protection Agency (USEPA); United States Environmental Protection Agency (USEPA); National Institute for Occupational Safety and Health (NIOSH), 2017; National Industrial Chemicals Notification and Assessment Scheme (NICNAS)). One (7%) organisation did not have any publicly available resources outlining the processes and methods they used in RA and was therefore coded as 'no' for every criterion. Twelve (86%) organisations required review of three or more resources to complete the data extraction. Supplementary File D lists the resources used in data extraction.

Seven (50%) of the 14 organisations reviewed and edited the data extraction. Of the seven organisations that did not edit the extraction, one (7%) did not reply to this request (European Commission), three (21%) recommended further resources (United States Environmental Protection Agency (USEPA); United States Environmental Protection Agency (USEPA); National Industrial Chemicals Notification and Assessment Scheme (NICNAS)), two (14%) stated that their processes and methods were currently under revision (United States Environmental Protection Agency (USEPA); European Commission), and one (7%) organisation confirmed that they did not have any publicly available resources describing their methods used in RA (Australian Pesticides and Veterinary Medicines Authority (APVMA), 2018).

3.2. Processes and methods used by the organisations

Table 1 summarises the number of organisations that described specific aspects of the methods and processes used in HI/RA according to 22 criteria.

Table 2 summarises the specific methods and processes used in HI/RA described by each individual organisation. Details of all criteria assessed are available in Supplementary File F.

4. Discussion

Divergent methods are used in HI and RA of environmental hazards by the organisations included in this analysis. Less than half of the organisations met all the criteria for synthesising evidence streams, establishing reference values, and formulating recommendations. Organisations that conduct RA meet the fewest number of criteria (no organisation met even half of the criteria), while organisations that conduct HI meet the most criteria for describing their processes and methods. The US Office of Health Assessment and Translation (National Toxicology Program (NTP), 2015; National Toxicology Program (NTP)) and the World Health Organisation unit meet the greatest number of criteria in describing their processes and methods. Overall, the organisations that reviewed and edited our data extraction also meet the greatest number of criteria.

Our assessment of the processes and methods used in HI/RA by organisations was very difficult to complete: we had to examine multiple documents, undertake time-intensive searching to identify the relevant information, and initiate multiple email communications with most of the organisations. In addition, organisations did not use consistent terminology to describe their methods. Lack of easily identifiable processes and methods used in HI/RA makes it more difficult to determine the reliability and validity of the organisations' assessments, even when systematic and reproducible methods are used.

Reasons for the inconsistencies in methods across organisations may be due to lack of an internationally accepted "gold standard" and the ongoing evolution of methods for RA. Some variation in the methods used by the organisations may be justified depending on the resources available to the organisation (Haddaway and Bilotta, 2016), type of assessment being made or the intended audience. However, to produce reliable and valid answers to environmental health questions,

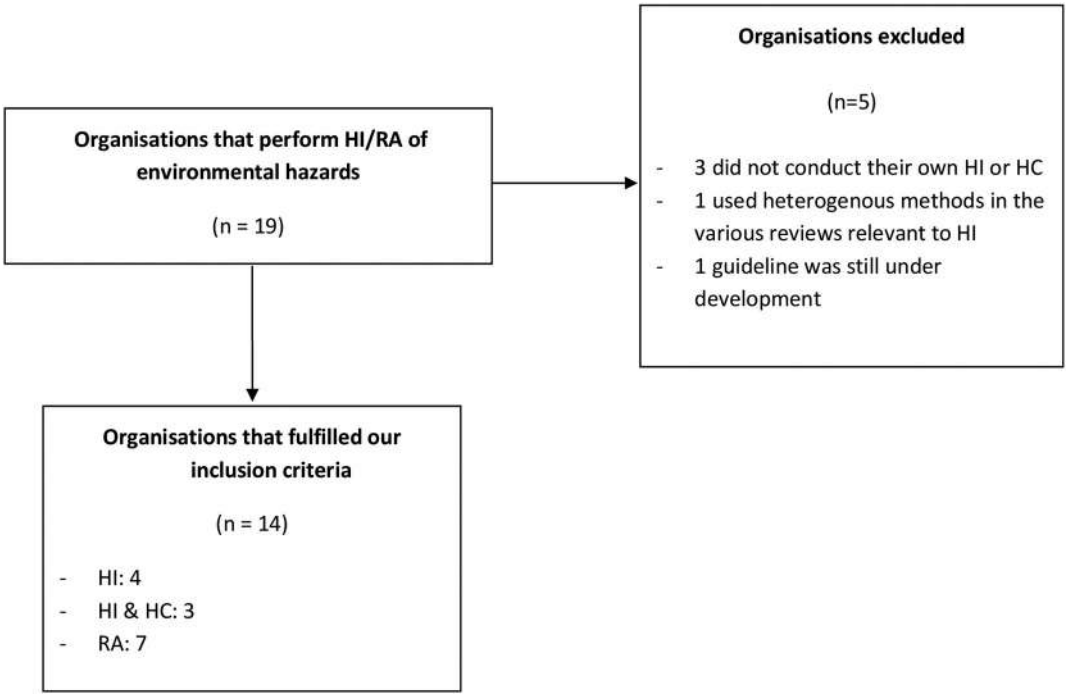

Fig. 1. Flow diagram of the included organisations and the assessments they completed.
HC, hazard characterisation; HI, hazard identification; RA, Risk Assessment.

improvements are required in the processes used to formulate questions, search for evidence, assess quality at the individual study level and the overall body of evidence, integrate evidence streams, and make final recommendations.

While most of the organisations describe how substances are selected for assessment, few describe how the questions that are to be answered in the assessment process are established. The formation and use of answerable questions in a PECO (Population, Exposure, Comparator and Outcome) format has been recommended and implemented by various organisations conducting assessments in environmental health (Woodruff and Sutton, 2014; Rooney et al., 2014). The use of PECO statements systematises review objectives and the methods that will be used to answer the defined questions (Whaley et al., 2016).

Only one organisation that conducts RA states that they use systematic reviews to search for, select and evaluate the evidence (United States Environmental Protection Agency (USEPA)). There has been increasing discussion on the limitations around the use of narrative reviews based on expert judgement (Mandrioli and Silbergeld, 2016; Woodruff and Sutton, 2014; Aiassa et al., 2015; U.S. Environmental Protection Agency, 2013), and the need for systematic review methods in the assessment of environmental and occupational health to improve transparency and comparability amongst the assessments (Woodruff and Sutton, 2014). Only one organisation (National Toxicology Program (NTP); National Toxicology Program (NTP), 2015) uses systematic review methods that meet all of the AMSTAR (A Measurement Tool to Assess Systematic Reviews) items that were assessed. Although AMSTAR has limitations (Burda et al., 2016), it has been demonstrated to be a reliable and valid tool to assess the methodological quality of systematic reviews (Shea et al., 2009).

Approximately three quarters of organisations assess the quality of individual studies. However, less than one quarter of the organisations use or adapt their assessment of study quality from an existing tool or use well-defined, reproducible criteria. Several organisations state that they used the Organisation for Economic Co-operation and Development's Test Guidelines and Good Laboratory Practice (GLP) standards to assess study quality. These standards are preferred by chemical industry scientists and consultants (Borgert et al., 2016). Although GLP standards have improved the record keeping of many commercial laboratories, they are not an accurate measure of study quality and should not be relied upon to make public health decisions (Myers et al., 2009).

To assess the body of evidence, less than one quarter of the organisations use well-defined and reproducible methods. Several organisations state that they use 'weight-of-evidence' methods in the assessment process. However, the steps involved in this process and how it is described vary considerably across organisations (National Industrial Chemical Notification and Assessment Scheme (NICNAS), 2017; Scientific Committee on Occupational Exposure Limits (SCOEL), 2013; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)). Formal procedures and consistent nomenclature for weight-of-evidence methods are lacking, (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)). The 2014 National Academy of Science (NAS) review of the Environmental Protection Agency's Integrated Risk Information System (IRIS) process found the weight-of evidence process to be judgement-based and of little scientific use (National Research Council, 2014).

Less than half of the organisations describe the processes used for making final determinations or recommendations. While there is an element of subjectivity in the process, the use of objective processes versus expert judgement and opinion alone may be an important influence in how accurately the evidence is interpreted (Whaley et al., 2016). Further, when expert opinions are conflicting and undocumented, it is difficult to establish the most valid evaluation and synthesis of all the evidence (Whaley et al., 2016).

While approximately two thirds of organisations have a policy on disclosure of funding of the assessment or guideline, half do not have a policy on declaring or managing conflicts of interest. Lack of policies around conflicts interest in guideline development is cause for concern (Sox, 2017).

4.1. Limitations of this study

We only had one assessor and extractor. Because we experienced

Table 1
Description of specific aspects of methods and processes used for hazard identification (HI) and risk assessment (RA).

Method or process	Number[a] (%)
Planning/protocol stage (n = 14)	
Use a process for identifying the substances	12 (86)
Use a process for establishing the questions	5 (36)
Participants involved in the decision-making process for identifying the substances	8 (57)
Participants involved in the decision-making process for establishing the questions	3 (21)
Use a process for how the review/working group is established	7 (50)
Evidence review methods (n = 14)	
Use systematic reviews	5 (36)
Use systematic review methods that meet 11 out of 11 AMSTAR items[b]	1 (7)
Conduct an assessment of individual study quality	10 (71)
Use well-defined, reproducible methods to assess study quality[c]	3 (21)
Use well-defined, reproducible methods to assess quality of the body of evidence[d]	3 (21)
Rate the overall confidence in the body of evidence	4 (29)
Integrating evidence streams (n = 13)[e]	
Use well-defined methods to integrate evidence streams	3 (23)
Hazard identification (n = 14)	
Use a process and method for making final HI conclusions	4 (29)
Rate the strength of the recommendation	5 (36)
Establishing reference values (n = 10)[f]	
Have a separation between identification and synthesis of the scientific evidence used in HI and the formulation of reference values	3 (30)
Use a process and method to select the evidence in establishing reference values	3 (30)
Risk assessment conclusions (n = 8)[g]	
Use a process and method for making final RA conclusions or guideline recommendations	3 (38)
Rate the strength of the recommendation	3 (38)
Review process (n = 14)	
Include external peer review process of the assessment or guideline	6 (43)
Conflicts of interest and funding (n = 14)	
Have a policy on conflicts of interest	8 (57)
Use a process for managing conflicts of interest	7 (50)
Disclose funders[h]	11 (79)

Abbreviations: AMSTAR: A Measurement Tool to Assess Systematic Reviews; HI: Hazard Identification; RA: Risk Assessment.
Legend:
[a] Number of organisations that described the specific methods or processes. We used a modified version of AMSTAR (A Measurement Tool to Assess Systematic Reviews) (AMSTAR; Shea et al., 2009) to assess the evidence review methods; the other criteria were based on recommendations made by the United States National Academies of Science to improve toxicological assessments of environmental contaminants (National Research Council, 2014).
[b] Number and description of the AMSTAR items met by each organisation in conducting evidence reviews are described in Supplementary File E.
[c] We included organisations that referenced a tool or described reproducible criteria and methods to assess study quality. We did not include organisations that used the Organisation for Economic Co-operation and Development's (OECD) Test Guidelines and Good Laboratory Practice (GLP) standards to assess study quality.
[d] We included organisations that described reproducible criteria and methods to assess the quality of the body of evidence. We did not include organisations that stated that they had used the 'Weight of Evidence' approach.
[e] 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials' (World Health Organization, 2017b) is excluded from this summary as in the review relevant to HI by Lee et al. (Lee et al., 2017) it only used animal studies found in OECD dossiers to form classifications and evidence streams could not therefore be integrated.
[f] Four organisations conducted HI only, so they are therefore excluded from this summary. 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials' (World Health Organization, 2017b) was included as the evidence reviews supporting this guideline distinguished between HI and establishing reference/guideline values (HC).
[g] Six organisations conducted HI or HC only and are therefore excluded from this summary. 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials' (World Health Organization, 2017b) is included as they make final guideline recommendations.
[h] Assessments published by the US Government were assumed to have been funded by the US Government. Assessments published by the European Commission were assumed to have been funded by the European Commission.

difficulty identifying the information we needed for our evaluation, we offered each organisation the opportunity to review and revise our data extraction, including the AMSTAR assessments and offer guidance on the location of additional relevant resources. While every organisation responded, not every organisation reviewed the data in detail for accuracy and completeness. We did not cross check the methods outlined in guidance documents with the methods used in completed assessments and it is possible that there may be some discordance.

The criteria that we used to examine the different steps in the HI/RA assessment process are not intended to be equally weighted or counted, thus comparisons of the percentages of organisations that described specific methods and processes should be made with caution. Although we based our criteria on existing, accepted, validated tools (Shea et al., 2009; National Research Council, 2014), different criteria could have been used. In addition, because we used a snowball sampling strategy to identify organisations, we may not have included some important organisations that conduct HI/RA of environmental hazards.

4.2. Implications for policy-makers and future research

The recent different pronouncements on the harms of environmental hazards, such as those surrounding glyphosate (The Guardian, 2016; European Food Safety Authority (EFSA), 2017) and bisphenol-A (BPA) (European Food Safety Authority (EFSA), 2015; French Agency for Food Environmental and Occupational Health & Safety (ANSES), 2014) may be in part due to the limitations in chemical RA methods, including the lack of systematic reviews. Systematic reviews are rigorous evaluations of the literature, using a protocol with pre-defined questions and explicit methods, to search, select, evaluate and synthesise the scientific body of evidence, in order to minimise error and bias (Whaley et al., 2016; Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, 2011). Several organisations and research groups have developed or adopted (Woodruff and Sutton, 2014; Rooney et al., 2014; Birnbaum et al., 2013; National Academies of Sciences, Engineering and Medicine, 2017), or recommended the use (National Research Council, 2014; Zoeller et al., 2014) of systematic reviews in the assessment of chemicals. Using systematic reviews can detect differences in how questions are formulated, searches are conducted, or studies are evaluated. Use of these methods may lead to improved transparency, objectivity and communication of HI/RA of harmful environmental substances (Whaley et al., 2016).

It is vital to the integrity of evidence-based evaluations of environment health hazards that the primary studies that underpin decision-making are assessed with transparent and accepted methods (Rooney et al., 2016). This highlights the need to develop tools to assess the risk of bias and methods for the types of human and animal evidence that is relevant to environmental RA (Mandrioli and Silbergeld, 2016). Further development of empirically-based tools to assess the quality of various types of evidence used within HI/RA is still required (Mandrioli and Silbergeld, 2016).

Well-structured, flexible approaches that are not too prescriptive while accounting for the scientific issues that are present in the design, conduct and analysis of environmental epidemiological and animal toxicology studies may increase the level of transparency in making hazard assessment conclusions and prevent the introduction of a

Table 2
Total number and key specific methods and processes used in hazard identification (HI) and risk assessment (RA) by the individual organisations.

Organisation and program categorised by type of assessment they perform	Country	Total number of criterion completed (%)[a]	Use a process for establishing the questions	Use systematic reviews	Number of AMSTAR criteria met for systematic reviews (n = 11) (%)	Use well-defined, reproducible methods to assess study quality	Use well-defined, reproducible methods to assess quality of the body of evidence	Use well-defined methods to integrate evidence streams	Include an external peer review process	Have a policy on conflicts of interest	Disclose funder(s)
Hazard identification (n = 18 criteria)[b]											
International Agency for Research on Cancer (IARC)	International	12 (67)	Unclear	Yes	4 (36)	No	No	Yes	Unclear	Yes	Yes
Office of the Report on Carcinogens (ROC), Division of the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services	United States	16 (89)	Yes	No	8 (73)	Yes	Yes	Yes	Yes	Yes	Yes
National Centre for Environmental Assessment (NCEA), RTP Division, Office of Research and Development (ORD), U.S. Environmental Protection Agency, Integrated Science Assessment (ISA)	United States	7 (39)	Yes	No	4 (36)	No	No	Unclear	Yes	Unclear	Yes
Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services	United States	18 (100)	Yes	Yes	11 (100)	Yes	Yes	Yes	Yes	Yes	Yes
Hazard identification and characterisation (n = 20)[c]											
Scientific Committee on Occupational Exposure Limits (SCOEL)	International	4 (20)	No	No	1 (9)	No	No	No	No	Yes	Yes
National Centre for Environmental Assessment (NCEA), Office of Research and Development (ORD), U.S. Environmental Protection Agency, Integrated Risk Information System (IRIS)	United States	7 (35)	No	Yes	7 (64)	No	No	Unclear	Yes	No	Yes
Department of Public Health, Environmental and Social Determinants of Health- World Health Organization 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials'	International	20 (95) (21 criteria used)[d]	Yes	Yes	6 (86) (7 criteria used)[e]	Yes	Yes	N/A[f]	Yes	Yes	Yes
Risk assessment (n = 22)[g]											
Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)	International	10 (45)	Yes	No	3 (27)	No	No	Unclear	No	Yes	Yes
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	International	8 (36)	No	No	5 (45)	No	No	No	No	Yes	No

(*continued on next page*)

Table 2 (*continued*)

Organisation and program categorised by type of assessment they perform	Country	Total number of criterion completed (%)[a]	Use a process for establishing the questions	Use systematic reviews	Number of AMSTAR criteria met for systematic reviews (n = 11) (%)	Use well-defined, reproducible methods to assess study quality	Use well-defined, reproducible methods to assess quality of the body of evidence	Use well-defined methods to integrate evidence streams	Include an external peer review process	Have a policy on conflicts of interest	Disclose funder(s)
Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pesticide Programs (OPP), U.S. Environmental Protection Agency, Risk Assessment in the Pesticide Program	United States	2 (9)	No	No	3 (27)	No	No	No	Unclear	No	Yes
Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT), U.S. Environmental Protection Agency, Assessing and Managing Chemicals under TSCA	United States	3 (14)	No	Yes	1 (9)	No	No	No	Unclear	No	Yes
National Institute for Occupational Safety and Health (NIOSH), Department of Health and Human Services, Centres for Disease Control and Prevention	United States	6 (27)	No	No	2 (18)	No	Unclear	Unclear	Yes	Yes	Yes
National Industrial Chemical Notification and Assessment Scheme (NICNAS), Department of Health, Australian Government	Australia	4 (18)	No	No	1 (9)	No	No	No	No	No	No
Australian Pesticides and Veterinary Medicines Authority (APVMA), Australian Government	Australia	0 (0)	No	No	0 (0)	No	No	No	No	No	No

Abbreviations: AMSTAR: A Measurement Tool to Assess Systematic Reviews; HC: Hazard Characterisation; HI: Hazard Identification; N/A: Not Applicable; RA: Risk Assessment.

Legend:

[a] The 22 criteria are listed in Table 1 and Supplementary File F. We used a modified version of AMSTAR (A Measurement Tool to Assess Systematic Reviews) (AMSTAR; Shea et al., 2009) to assess the evidence review methods; the other criteria were based on recommendations made by the United States National Academies of Science to improve toxicological assessments of environmental contaminants (National Research Council, 2014).

[b] Criteria for 'Establishing reference values' and 'Risk assessment conclusions' were not applicable for organisations conducting HI. Total number of criteria is therefore 18.

[c] Criteria for 'Risk assessment conclusions' were not applicable for organisations that conduct HI and HC. Total number of criteria is therefore 20.

[d] Criteria 'Use a process and method for making final RA conclusions or guideline recommendations' and 'Rate the strength of the recommendation' were applicable. Criterion 'Use well-defined methods to integrate evidence streams' was not applicable as the review by Lee et al. (2017) used to assess the HI stage only used animal studies found in OECD dossiers and evidence streams could not therefore be integrated. Total number of criteria is therefore 21.

[e] In the review by Lee et al. (2017), a systematic review of OECD dossiers was conducted to assess hazardous properties of manufactured nanomaterials and assign them according to the GHS (Globally Harmonized System) of classification and labelling. This was used for the evidence review methods included in the HI stage of this assessment. Several AMSTAR criteria for the systematic review process were thus not applicable and the overall rating is out of 7. The criteria that were assessed were: 1. An a priori design was used/will be provided; 2. Duplicate screening and data extraction was/will be conducted; 5. A list of included studies was/will be provided; 7. The characteristics of the included studies was/will be provided; 8. The scientific quality of the included studies was/will be assessed; 10. The methods to combine studies was described and appropriate; and 11. Industry sponsorship/author COI was/will be considered?

[f] To assess the HI stage we used the review by Lee et al. (2017) and it only used animal studies found in OECD dossiers to form classifications and evidence streams could not therefore be integrated. This criterion was therefore not applicable.

[g] Organisations that conducted RA were assessed using all 22 criteria.

systematic bias (Rooney et al., 2016). A structured approach such as GRADE (Grading of Recommendations Assessment, Development and Evaluations) has been recommended for its transparent evaluation of the quality of the evidence and synthesis of evidence into normative guidance for clinical interventions (Balshem et al., 2011; Andrews et al., 2013). While GRADE methods have not been developed to account for all important considerations related to RA in environmental health (Norris and Bero, 2016), the GRADE system is now being modified for use in environmental health assessments (National Toxicology Program (NTP), 2015).

HI and RA of potentially hazardous substances require topic area experts such as toxicologists and epidemiologists. Conflicts of interest of these experts must be identified and managed. Several organisations have extensive policies on how to manage experts with conflicts of interest but whose participation is deemed essential to the development of a guideline (Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, 2011; United States Food and Drug Administration (USFDA)). The consistent use of rigorous and transparent policies on disclosure and management of conflicts of interest is required.

The processes and methods used by organisations conducting HI/RA of environmental hazards are inconsistent. There is therefore a need to develop explicit processes and adopt empirically-based tools and methods for the evaluation and synthesis of evidence, and the formulation of conclusions across all organisations that conduct HI and RA. These processes, tools and methods will lead to increased transparency, comparability and validity of the assessments.

Declaration of interest

SL Norris is an employee of the World Health Organization and she consulted on one of the guidelines evaluated in this study. She is a member of the GRADE Working Group and has published on the GRADE system.

Competing financial interest

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Disclaimer

The authors alone are responsible for the views expressed in this [article][chapter] and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.11.060.

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