GRADE: Assessing the quality of evidence in environmental and occupational health

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A B S T R A C T

There is high demand in environmental health for adoption of a structured process that evaluates and integrates evidence while making decisions and recommendations transparent. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework holds promise to address this demand. For over a decade, GRADE has been applied successfully to areas of clinical medicine, public health, and health policy, but experience with GRADE in environmental and occupational health is just beginning. Environmental and occupational health questions focus on understanding whether an exposure is a potential health hazard or risk, assessing the exposure to understand the extent and magnitude of risk, and exploring interventions to mitigate exposure or risk. Although GRADE offers many advantages, including its flexibility and methodological rigor, there are features of the different sources of evidence used in environmental and occupational health that will require further consideration to assess the need for method refinement. An issue that requires particular attention is the evaluation and integration of evidence from human, animal, in vitro, and in silico (computer modeling) studies when determining whether an environmental factor represents a potential health hazard or risk.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ASTDR, Agency for Toxic Substances and Disease Registry; CDC, Centers for Disease Control and Prevention; CiE, certainty in the evidence; ESSA, European Food Safety Authority; EPA, Environmental Protection Agency; EtD, evidence-to-decision; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; OHAT, Office of Health Assessment and Translation; PECO, Population, Exposure, Comparator, Outcome; PICO, Population, Intervention, Comparator, Outcome; NRC, National Research Council; NTP, National Toxicology Program; RoB, risk of bias; SYRCLE, Systematic Review Center for Laboratory animal Experimentation; WHO, World Health Organization.

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1. Introduction

There is high demand in environmental and occupational health for using systematic review methodology and structured frameworks to evaluate and integrate evidence to support evidence-based and transparent decisions and recommendations (Agency for Toxic Substances and Disease Registry (ATSDR), 2012; Bruce et al., 2014; EFSA, 2010; Johnson et al., 2014; Koustas et al., 2014; Lam et al., 2014; Mandrioli and Silbergeld, 2015; Mandrioli et al., 2014; Murray and Thayer, 2014; NRC, 2007, 2014a, 2014b; Silbergeld and Scherer, 2013; Whaley et al., 2016; Woodruff and Sutton, 2011; Woodruff and Sutton, 2014). Environmental health, which includes occupational health, is a broad field in which data address all the physical, chemical, and biological factors external to a person, and all the related factors impacting behaviors (WHO, 2015). Environmental health questions focus on understanding whether an exposure is a potential health hazard or risk using exposure assessments to recognize the extent and magnitude of exposure, and interventions to prevent or mitigate exposure or risk.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach has the potential to improve transparency in addressing these questions in environmental health assessments. GRADE represents a rigorous, structured, and transparent process to inform decision-making beginning with well-defined questions, followed by an assessment of the certainty in the evidence (also called confidence in the effect or other estimates, or quality of the evidence) (Guyatt et al., 2011d; Schünemann et al., 2003), and leading to development of recommendations and decisions.

GRADE is widely used internationally to address topics related to clinical medicine, public health, and health policy (Atkins et al., 2004; Guyatt et al., 2011d, 2008; Schünemann et al., 2008), including by programs within the U.S. Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), the U.S. Agency for Healthcare Research and Quality (AHRQ), and National Institute for Health and Clinical Excellence (NICE) in the United Kingdom and the National Health and Medical Research Council in Australia (Ahmed et al., 2011; National Health and Medical Research Council, 2011; Thornton et al., 2013; Viswanathan et al., 2012; WHO, 2014b). The Cochrane Collaboration, which prepares, maintains, and promotes the accessibility of systematic reviews, uses the GRADE system for reporting on the quality of evidence for outcomes in systematic reviews (Higgins et al., 2011; Schünemann et al., 2011b). Formed in 2000, the GRADE Working Group now includes over 500 active members from 40 countries and serves as a think tank for advancing evidence-based decision-making in multiple disciplines (Schünemann et al., 2003)(see also http://www.gradeworkinggroup.org/).

Advantages of using the GRADE approach have already been recognized by some within the environmental health field. The Navigation Guide proposed adapting GRADE for an environmental health context (Woodruff and Sutton, 2011) and followed-up with a series of case studies to demonstrate the feasibility of applying GRADE to epidemiological and animal studies (Johnson et al., 2014; Koustas et al., 2014; Lam et al., 2014; Vesterinen et al., 2014). In 2013, the National Toxicology Program’s (NTP) Office of Health Assessment and Translation (OHAT) at the National Institute of Environmental Health Sciences announced plans to use GRADE in its evaluations to assess the evidence for associations between environmental exposures and non-cancer health effects (NTP, 2013, 2015; Rooney et al., 2014). The SYstematic Review Center for Laboratory animal Experimentation (SYRCLE), is currently applying the GRADE approach to assess the quality of evidence from preclinical animal intervention studies (Hooijmans et al., 2014). GRADE has also been used in recent systematic reviews of epidemiological studies of shift work and breast cancer risk (Ijaz et al., 2013), shift work and cardiovascular disease (Vyas et al., 2012), and adverse effects related to reduced indoor air quality related to household fuel use (Bruce et al., 2013; WHO, 2014a). GRADE, including its adoption by NTP/OHAT and the Navigation Guide, was specifically identified in the National Academy of Sciences’ National Research Council (NRC) review of the U.S. Environmental Protection Agency’s (EPA) Integrated Risk Information System as an approach that would increase the transparency of evaluating evidence (NRC, 2014a). Use of GRADE in environmental health is likely to grow as systematic reviews become more common in the field and the limitations of expert-based narrative review methods are increasingly recognized (Aiasa et al., 2015; EFSA, 2010; EPA, 2013; Mandrioli and Silbergeld, 2015; NRC, 2014b; Woodruff and Sutton, 2014).

An additional advantage of GRADE is the GRADE Working Group’s commitment to ongoing methods development and assessment of applicability to different areas of research. This is critical because experience with GRADE in the environmental health context is limited. Work to-date from the Navigation Guide, NTP, and WHO show the GRADE framework is sufficiently flexible to support use now (Johnson et al., 2013, 2014; Kouistas et al., 2014; Lam et al., 2014; NTP, 2015; WHO, 2014a); however, areas for further method assessment have been identified. In this respect, the GRADE Working Group serves as a vehicle to leverage transdisciplinary skills, knowledge, and resources to bridge the fields of clinical and environmental health. The objectives of this article are to provide an overview of the GRADE framework, discuss applicability of GRADE to environmental and occupational health, and identify priority areas for method development.

2. GRADE approach

2.1. Formulating the research question

GRADE requires that decision-makers specify key-elements to formulate a relevant and focused question for decision-making (e.g., to inform clinical and public health guidelines, formulate scientific consensus statements, etc.) (Aiasa et al., 2015; Guyatt et al., 2011b). The key elements are the components of the question that identify what information must be provided in a primary study to evaluate the intervention under assessment and hence answer the question (Aiasa et al., 2015). For instance, for questions aimed at evaluating interventions, the key elements are the Population, Intervention, Comparator, and Outcome (PICO) (Guyatt et al., 2011b; Richardson et al., 1995). Both beneficial and harmful outcomes that the target population may experience as a result of the intervention should be considered. At present, GRADE focuses on answering decision-making (i.e., actionable) questions about interventions (including diagnostic tests and strategies), though the GRADE framework has been expanded to diagnostic questions (Iorio et al., 2015; Spencer et al., 2012).
2.2. Quality of the evidence

GRADE uses a structured framework to determine overall certainty in the evidence (CiE) for outcomes across a collection of research studies or body of evidence (Fig. 1) (Schünemann et al., 2013). The GRADE approach does not remove judgment from decision-making; however, the approach provides a framework of critical components to assess, guidance on the consideration of empirical evidence, and emphasizes transparency throughout the process. An initial evaluation of the CiE is conducted based on whether or not the research studies used randomized allocation. In the current GRADE approach, the CiE from randomized controlled trials (RCT) receives an initial rating of “high”, whereas the CiE from observational (i.e., non-randomized) studies starts at “low”. After this initial evaluation of randomization, other aspects of risk of bias (RoB), i.e., internal validity, are assessed. GRADE does not recommend the use of a specific RoB tool, but suggests specific criteria that should be considered when assessing a body of randomized or non-randomized studies that address risk of bias (Guyatt et al., 2011e). In addition to RoB, the certainty in a body of evidence can be rated down for inconsistency, indirectness, imprecision, or publication bias, or rated up for the magnitude of the effect, dose–response gradient, or direction and impact of residual plausible confounding. Different terminology may be used to describe these elements as long as the concepts are identical (GRADE Working Group, 2010; Schünemann et al., 2013). Like RCTs, randomized experimental studies in animals would start as “high” and typically be downgraded for indirectness due to differences in the population (Guyatt et al., 2011c). The evidence is assessed and presented in an evidence summary table separately for each critical or important outcome and expressed using four levels of certainty ratings (i.e., “high”, “moderate”, “low”, or “very low”) (Balshe et al., 2011; Guyatt et al., 2011a). This table, called a GRADE Evidence Profile or Summary of Findings table, requires transparent descriptions of the reasons for rating down and rating up (WHO, 2014a).

2.3. Recommendations and the Evidence-to-Decision framework

In addition to assessing the CiE across outcomes, the GRADE EtD framework explicitly considers the balance of benefits and harms, values and preferences, resource implications, feasibility, equity, and acceptability to determine the strength of the recommendation (strong or weak), and the direction (for or against) to make a final recommendation or decision (Andrews et al., 2013; Schünemann et al., 2012; Treweek et al., 2013). The elements of the framework's structure transparently display the important criteria for deliberation (including relevant research evidence, judgments from decision makers, and other considerations) to inform the balance about the desirable and undesirable consequences of the options or interventions considered. A judgment is needed for making decisions during all steps. However, the GRADE EtD framework provides a structure to maximize transparency and limit subjectivity throughout the process: in fact CiE is a key determinant for making a strong GRADE guidelines recommendation (Djulbegovic et al., 2015).

3. Considerations for environmental health

3.1. Formulating the research question

The GRADE approach has been utilized predominantly to answer questions on interventions in health care, like “what is the impact of an intervention (including diagnostic tests and strategies) compared with an alternative on patient or population important outcomes?” or “should intervention A or B be used for X?” In the context of decision-making in environmental health, the term intervention has somewhat different connotations. First, an intervention can be thought of as a specific environmental factor (i.e., exposure) that is being evaluated in human, animal, in vitro, or in silico studies as a risk factor or causative agent for an undesirable health outcome. In this scenario, the PICO question can be rephrased as a PECO question, where the term “intervention” is replaced with “Exposure” (Collaboration for Environmental Evidence, 2013; NTP, 2015; Woodruff and Sutton, 2014). The complexity of the exposure questions will vary, ranging from a single well-defined chemical to complex scenarios like wind farms, agricultural run-off, etc. To address the benefits and harms to humans from wind farms, PECO questions were developed to look at the exposure of physical emissions produced by wind farms or wind turbines (e.g., noise, infrasound, shadow flicker, and electromagnetic radiation), as compared with no exposure to the physical emissions produced by wind farms or turbines (Merlin et al., 2015). Questions assessing exposures as risk factors or causative agents are used in risk assessments, which have several sub-questions (EPA, 2012; Schünemann et al., 2011a):

![Fig. 1. GRADE's approach to developing certainty ratings across a body of evidence for each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision-making).](image-url)
Second, an environmental intervention question could be formulated to evaluate the impact of interventions that prevent or mitigate an exposure or risk. Environmental exposure-related interventions typically address chemical or physical agents in the environment, such as air, soil, water, or food, in a public or occupational setting, with the goal of trying to prevent, remove, or reduce exposure levels (e.g., reduction at source, improved ventilation, ingredient reformulation) through regulatory, technical, or behavioral interventions. Questions assessing the effects of an intervention to prevent or reduce exposure should be based on an established relationship between the exposure and health outcome(s). For example, since the relationship between noise exposure and noise-induced hearing loss has been established, showing that an intervention reduces noise exposure is sufficient to also conclude that the intervention decreases noise-induced hearing loss (Verbeek et al., 2012). In studies of environmental health, such questions have the ability to compare the desirable consequences of reducing an exposure with potentially undesirable consequences of removing an exposure (e.g., costs, use of alternatives with unknown toxicity). While these types of questions are very similar to the clinical or public health intervention PICO questions, GRADE was designed to assess, some challenges have been identified, such as how to assess complex interventions, use non-epidemiological evidence, and choosing outcomes and outcome measures (Rehfuess and Akl, 2013). Methodological research has continued to address concerns with applying GRADE to studies of interventions (Guyatt et al., 2011b; Schünemann, 2013).

3.2. Quality of the evidence

3.2.1. Human and experimental animal data

In environmental health, observational human studies and experimental animal studies (where animals are randomly assigned to treatment groups), and observational animal studies (i.e., “wildlife studies” or natural population-based studies) are often the highest quality evidence available to understand whether there is an association (or, if possible, cause–effect relationship) between an exposure and health outcome, as in the case of carcinogens (Pearce et al., 2015). The factors considered in GRADE when making and presenting judgments about the CiE (Fig. 1) translate well to observational human and experimental animal studies, although harmonization of RoB tools and development of additional guidance on when rating down or rating up should be pursued. The WHO considered evidence from both non-randomized experimental and observational studies to inform their Recommendations for Indoor Air Quality (WHO, 2014a). In the report, WHO assessed whether or not coal should be used as a household fuel. The decision to recommend against using unprocessed coal as a household fuel was informed by 1) the results from studies of cancer in humans and experimental animals; 2) systematic reviews of observational studies on particular matter exposure and risk of lung cancer; and 3) population-level studies on the toxicity of coal and the impact of banning coal. While possible confounders of the different study types were recognized, they still provided the best available evidence to inform the recommendations. In addition, on-going methods development for rating the risk of bias (Bilotta et al., 2014; Johnson et al., 2014; Kostas et al., 2014; Lam et al., 2014; Morgan et al., 2015; NTP, 2015; WHO, 2014a) includes searching for observational studies that might be considered equivalent to randomized trials for the initial assessment of the risk of bias (e.g., factors in study design and execution that mitigate the lack of randomization, such as steps taken to fully control or adjust for confounding). Examples, however, are currently lacking.

3.2.2. Mechanistic data

In environmental health, human and experimental animal data are often interpreted in conjunction with evidence from mechanistic data supporting the biological plausibility of an association and/or to prioritize chemicals for additional testing or evaluation. The GRADE framework does not explicitly address mechanistic data, but they may be used to inform judgments about indirectness. There are an estimated 85,000 chemicals in commerce, the vast majority of which have not been tested for toxicity, even though in many cases the evidence available for a chemical will be mechanistic in nature (EPA, 2009; Judson et al., 2009). The lack of toxicity data for most environmental chemicals has led to major initiatives to generate high throughput screening (HTS) data for chemicals. For example, the NTP’s Tox21 HTS program has generated data for ~10,000 chemicals on ~75 biochemical- and cell-based assays that cover a range of activities including overall cellular health (cytotoxicity and apoptosis induction, mitochondrial toxicity, DNA damage), perturbation of cell signaling pathways, inflammatory response induction, agonists/antagonists for 15 nuclear receptors, and drug metabolism (Tice et al., 2013). The US EPA’s ToxCast HTS program currently has mechanistic data on 1860 chemicals tested in up to 821 assay endpoints (Kavlock et al., 2012); however, many chemicals are still untested. Computer-modeling approaches are also being pursued to predict potential hazard and likelihood of significant exposure. For mechanistic data, tools to rate RoB for in vitro and in silico studies need to be developed and their contribution to the stream of evidence for different outcomes should be determined because these data are expected to be used more widely for prioritizing chemicals of concern as well as replacing traditional data in regulatory assessments (Mandrioli and Silbergeld, 2015; NRC, 2007). When assessing the effects of wind farms on human health, both direct and indirect evidence was considered to address the PECO question (Merlin et al., 2015). When assessing the body of evidence across the outcome of shadow flicker, there was low quality direct evidence available; however, available indirect data suggested that shadow flicker can affect health by inducing seizures among persons prone to photosensitive epilepsy. The utility of the GRADE rating down and rating up factors also needs to be assessed, although the concepts should generally apply (e.g., magnitude of effect can be analogous to efficacy and potency in an in vitro system). Analyses to assess the predictive utility of mechanistic data are a high priority in toxicology, and results will inform indirectness ratings within the GRADE framework.

3.3. Evidence-to-Decision frameworks

Very little work has been done to use structured and transparent decision-making frameworks to guide the development of recommendations in environmental health. The WHO Recommendations for Indoor Air Quality applied the GRADE Etd framework to guide their final recommendations (WHO, 2014a). For their recommendation on household use of coal, in addition to the quality of evidence from studies on carcinogenicity of coal, risk of lung cancer, and population-level studies on toxicity, they also determined that the benefits of replacing unprocessed coal with cleaner alternatives clearly outweigh the harms of replacement, the values and preferences of replacing coal varied among stakeholders, and that there may be some limitations to the feasibility of implementing cleaner alternatives based on affordability and supply. The GRADE Etd framework, which has the capacity to integrate consideration of the CiE of a health hazard with evidence of benefit associated with mitigating exposure, values, preferences, resource implications and other criteria, has great potential for enhancing the transparency of decision-making in environmental and occupational health. The strength of the recommendation may be apparent and actionable, or
application of GRADE may reveal gaps in our knowledge, and thus help efficiently and effectively target the allocation of scarce research funds.

The regulation of diesel is an example of an environmental topic that could be addressed with the GRADE EtD framework. Diesel engine exhaust is carcinogenic to humans and associated with increased hospital admissions, emergency room visits, asthma attacks, and premature death (IARC, 2012; Office of Environmental Health Hazard Assessment, 2007). At the same time, diesel engines have desirable consequences of higher fuel efficiency, lower carbon dioxide emissions, heavy duty hauling capacity, and durability. For example, EPA rule-making for diesel standards included consideration of the composition of diesel, technological feasibility, costs of retrofitting or replacing, cost–benefit analyses that include quantifying human health impacts, overall economic impact and alternatives assessment. Moreover, the rule-making applied to specific scenarios such as vehicles on highways, city streets, construction sites, and ports. These analyses have led to a number of emission standards for diesel fuel and diesel engines (NCDC, 2014). By 2030, EPA estimates that particulate matter and nitrous oxides will be reduced by 380,000 tons/year and 7 million tons/year, respectively. This will result in annual benefits of over $290 billion, at a cost of approximately $15 billion. The GRADE EtD framework could also be applied to alternative assessments that look for safer chemicals by identifying and evaluating the safety of alternative chemicals (EPA, 2011). Although such assessments are often not regulatory, they are used to inform consumer choice and encourage industry to move to safer alternatives and can complement regulatory actions.

The challenges of applying the GRADE EtD framework to environmental health topics are expected to be similar to clinical research, with most findings requiring a careful weighing of the health and other benefits or harms. A challenge specific to decision-making for environmental health is that many regulatory agencies require a determination of an allowable level or threshold of an exposure or risk, while in other cases there is no allowable exposure (for example asbestos ban). In studies where there is not a clear desirable effect of the exposure, the balance may focus on how frequently the undesirable effects occur. Research is also needed to increase understanding and acceptability of the format that desirable and undesirable consequences are presented in to end-users.

4. Future directions

This paper provides an overview of important aspects of adapting GRADE to decision-making in environmental health. In 2014, several project groups were formed within the GRADE Working Group to focus on methods assessment needs that are directly applicable to environmental and occupational health, including project groups for environmental health, observational studies, public health, application of GRADE to laboratory animal research, and non-randomized study risk of bias integration. Priority areas for the environmental and occupational health project group include (1) developing approaches to evaluate and integrate evidence from observational human, animal, in vitro, and in silico (computer modeling) studies to determine whether an association exist between exposure and health outcome(s); (2) applying GRADE to evaluations of interventions to mitigate exposure or reduce risk when an association has been identified; and (3) gaining experience in applying the GRADE frameworks for evidence-to-decision (EtD) and determining the direction and strength of recommendations for environmental and occupational health topics. Critically adapting GRADE to environmental health also requires consideration of how to rate the overall strength of the evidence and to integrate evidence across multiple evidence streams.

5. Conclusions

This paper examines several key components of GRADE as they can be assessed and expanded as a standardized methodology for research and decision-making in environmental and occupational health. Over 90 organizations from 18 countries worldwide have adopted the GRADE framework to assess evidence and inform decision-making. With a focus on rigorous and transparent methods, the GRADE approach has been applied successfully to clinical medicine, public health, diagnostic decision-making, questions about prognosis, and has great potential for the field of environmental and occupational health. In parallel to the methods development that has occurred over the past decades in the clinical and public health field, environmental health scientists have developed topic specific expertise about the evidence that informs how the environment shapes our health and sets the stage for knowledge transfer across disciplines to strengthen the scientific basis of decision-making for public policy. Leveraging this synergy will increase the transparency of, and scientific basis for, decision-making in environmental health, and thus help secure improved health outcomes for individuals and populations.

Conflict of interest

The authors declare they have no financial interests with respect to this manuscript, or its content, or subject matter.

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