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REVIEW ARTICLE

A 21st century roadmap for human health risk assessment

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Abstract

The Health and Environmental Sciences Institute (HESI)-coordinated Risk Assessment in the 21st Century (RISK21) project was initiated to develop a scientific, transparent, and efficient approach to the evolving world of human health risk assessment, and involved over 120 participants from 12 countries, 15 government institutions, 20 universities, 2 non-governmental organizations, and 12 corporations. This paper provides a brief overview of the tiered RISK21 framework called the roadmap and risk visualization matrix, and articulates the core principles derived by RISK21 participants that guided its development. Subsequent papers describe the roadmap and matrix in greater detail. RISK21 principles include focusing on problem formulation, utilizing existing information, starting with exposure assessment (rather than toxicity), and using a tiered process for data development. Bringing estimates of exposure and toxicity together on a two-dimensional matrix provides a clear rendition of human safety and risk. The value of the roadmap is its capacity to chronicle the stepwise acquisition of scientific information and display it in a clear and concise fashion. Furthermore, the tiered approach and transparent display of information will contribute to greater efficiencies by calling for data only as needed (enough precision to make a decision), thus conserving animals and other resources.

Abbreviations: HESI, Health and Environmental Sciences Institute; ILSI, International Life Sciences Institute; NAS, US National Academy of Sciences

Keywords

exposure, framework, hazard, problem formulation, risk, risk assessment, risk policy, tiered

History

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Introduction

For almost half a century, human health risk assessment has relied on a paradigm that depends heavily on animal testing to identify the dose–response for adverse effects. Although originally a sound approach that proved to be effective, in today's world that is increasingly dependent on chemical tools for therapeutics, consumer products, food additives, pest control, etc., this approach needs to evolve to take advantage of scientific advances commensurate with the complex problems that need to be addressed. For example, the dependence on traditional animal testing cannot adequately or efficiently accommodate the thousands of chemicals currently in the marketplace that need testing, the societal and ethical demand to reduce the use of animals for toxicity testing, and calls for greater clarity and transparency in determining and communicating human safety. In addition, uncertainty remains as to how results from animals apply to humans because of genomic, physiological, and behavioral differences. Recognition of these species

differences and other factors has resulted in the assignment of large, non-chemical–specific safety factors to ensure public health is protected. In addition, current risk assessment approaches often conduct hazard and exposure assessment independently, usually without adequate human exposure data, but instead, relying on high-dose studies in animal models for which the exposures may be of questionable relevance to humans.

Of all reasons why the current testing paradigm must evolve, perhaps the most pressing is the many thousands of chemicals that require assessment, and the resources needed to undertake the full battery of traditional testing and evaluation of these chemicals. Such resources are simply not available, despite attempts to apply integrated approaches. Furthermore, there is increasing recognition from all sectors that there is an opportunity to improve the clarity and transparency of information leading to any decision on chemical safety. Rendering the complex information contained in risk assessments in transparent ways, including approaches to portraying alternative hypotheses and extrapolation methods, will facilitate improved understanding and resolution of discrepancies in data interpretation that can plague the risk assessment process.

In recognition of the above concerns, as well as the opportunities provided by new technologies and scientific advances, several influential reports by the U.S. National Academy of Sciences (NAS), the Canadian Academies, and the European Union, have called for a marked change in exposure assessment, toxicity testing, and human health risk assessment (National Research Council 1996, 2007, 2008, 2009, 2012, Council of Canadian Academies 2012, European Commission 2012).

The 1996 NAS publication, "Understanding Risk" stated that, "… it is necessary to reconceive risk characterization in order to increase the likelihood of achieving sound and acceptable decisions" and proposed seven principles for improving risk assessment, including "decision-driven activity" and "early and explicit attention to *problem formulation*". Toxicology Testing in the 21st Century (NRC 2007) states that there is a "… need for efficient testing of all chemicals in a timely, cost-effective fashion". Science and Decisions (NRC 2009) calls for "… a coherent, consistent, and transparent process that would provide [risk assessments] that are relevant to the problems and decisions at hand and that would be sufficiently comprehensive to ensure that the best available options for managing risks were considered". These reports, amongst others, clearly ask for change that will bring greater efficiency and transparency to human health risk assessments.

Risk Assessment in the 21st Century (RISK21) was formed in response to the opportunity to change the way data are acquired and evaluated for human health risk assessment. The purpose of this paper is to outline the principles that led to the formation of a highly transparent methodology that when employed, will result in a more efficient derivation, interpretation, integration, and application of modern, often high throughput exposure and toxicological data to the risk assessment process.

The HESI RISK21 project

To address and catalyze the improvements in human health risk assessment, the Health and Environmental Sciences Institute (HESI) created the RISK21 Project. RISK21 provides a conceptual framework whereby both exposure and hazard are evaluated effectively and transparently, using all relevant and reliable sources of information. It realizes the vision of the recent U.S. National Academy of Sciences reports by suggesting ways to reduce unnecessary resource utilization, while providing sufficient precision and accuracy to enable decisions that protect human health, and represents an improvement to current risk assessment guidance and methodology.

RISK21 is coordinated by HESI, a global branch of the International Life Sciences Institute (ILSI), and is a multi-sector program, with participants from government agencies, academia, industry, and others (www.hesiglobal.org). The project has engaged over 120 participants from 12 countries, 15 government institutions, 20 universities, and 2 non-government organizations since it was formed in 2010.

The project is based on the premise that risk assessment should be fit for purpose: each step of the proposed process is directed at obtaining or deriving information that addresses the problem at hand. RISK21 provides a method to synthesize current knowledge and approaches using evolving science and technology, a vision shared by the U.S. National Academy of Sciences reports and numerous other publications by forward-thinking scientists.

RISK21 principles

RISK21 methodology provides a flexible framework for bringing together knowledge to enable effective decision making. It is a problem formulation-based, exposure-driven, tiered data acquisition approach that supports human health safety decisions as soon as sufficient evidence is acquired to address the specific problem formulation. It provides a transparent framework that incorporates exposure and toxicity estimates and their attendant uncertainty, which will guide informed decision making.

Focus on problem formulation

Various sources have described the need and approach of incorporating problem formulation into human health risk assessment (NAS 2009, Dourson et al. 2013, Meek et al. 2013). RISK21 seeks to change the inefficient use of resources by starting with problem formulation. This step establishes purpose, scope, and a plan for collecting and evaluating information that will guide the effective use of resources at each stage of the assessment process. Too often, data are collected with no clear sense of how they will be used. Risk assessments should begin with the end in mind by considering physical/chemical properties, use characteristics, existing exposure and toxicological data, and the risk management context. By starting with these disciplined and transparent steps, there is greater likelihood that appropriate and necessary data are developed without unnecessary commitment of resources.

Problem formulation is built around the fundamental question: "What do you need to know?" or, alternatively, "What decision do you need to make?" For example, for priority setting, the problem formulation would limit the scope of the assessment to the chemicals that are of greatest concern. For a full human health risk assessment, the problem formulation would focus on identifying sufficient information

on use, exposure, and toxicity to establish a margin of exposure (MOE) and a decision as to whether or not that MOE provides reasonable certainty of no harm.

Problem formulation should define how precise the exposure and toxicity data must be to make a decision about human safety. Data acquisition can stop when there is enough precision to make a decision. "Precision" is used here to represent the degree of exactness in the data, which is usually an estimate bounded by a confidence interval or range, the size of which is typically proportional to the quality and quantity of knowledge used to generate the estimate.

Usually, greater investment of resources is rewarded with narrower ranges of estimates, and hence greater precision. In some cases, a broad estimate of exposure or toxicity may be sufficient, while in other cases, more precision will be necessary. Problem formulation must clearly state these considerations, which will define the quantity and quality of data that are needed. A subsequent paper that details the RISK21 roadmap will also describe more fully the concepts of precision, accuracy, and uncertainty.

Problem formulation is often iterative, particularly when using a tiered approach to risk assessment. As questions are answered, the problem often becomes clearer, leading to a restatement of the problem.

Utilize existing information

There are few chemicals that are so isolated in their properties, effects, or exposure characteristics that their potential toxicity, mode of action, or human exposure cannot be estimated from similar chemicals or class members. By collating and mining the extensive knowledge that now exists on chemistry, fate, use characteristics, and toxicity, chemicals can be grouped by similar characteristics. Doing so may provide sufficient estimates for a decision about the risk of a particular chemical based on its assignment to such a group without additional testing and given the decision context. Clearly, a chemical that is first in class, whether based on its chemical structure or its biologic target (such as occurs with new classes of pharmaceuticals), will require more extensive evaluation than subsequent members (nth in class) of the class.

One example of using existing knowledge is the threshold for toxicological concern. By collecting and organizing toxicological information on hundreds of chemicals, Kroes et al. (2000, 2004) categorized chemicals by class and endpoint and derived safe exposure levels. Likewise, over the last 40 years, exposure scientists have characterized the way in which physicochemical properties and use patterns can predict human exposure. Models are available to generate estimates of exposure ranging from, for example, personal use of household materials to the transport of chemicals into drinking water.

Decades of data generation, now available in online databases, can be utilized to provide estimates of exposure and toxicity that may be sufficient to make a decision or, alternatively, to guide focused data generation.

Start with exposure rather than toxicity

Human safety depends on exposure and toxicity. Indeed, the 2012 European Commission report on addressing the New Challenges for Risk Assessment states, "A paradigm shift is likely from a hazard-driven process to one that is exposure driven" (EC 2012). Starting with exposure means that problem formulation must focus on the exposure scenarios of greatest concern. As a result, an early estimate of potential human exposure in relevant populations, including susceptible populations, will characterize the degree of specific toxicological data needs. For example, chemicals with exceedingly low potential exposure should lead to less allocation of toxicological resources than those with higher exposures, which could call for a more extensive toxicological database to inform risk assessment.

RISK21 participants also realized that highly toxic (potent) substances may need careful consideration because of the potential for adverse effects at low exposure levels. In such a case (e.g., botulinum toxin, sodium fluoroacetate, nitroso compounds, etc.), exposure estimates are critical in characterizing, monitoring, and mitigating human safety and risk.

Whether high potency or low, RISK21 emphasizes the crucial role of estimating human exposure as early as possible in risk assessment. Exposure estimates guide the development of toxicity information and characterize human safety for substances with a toxicological dataset. In any case, risk cannot be properly assessed without adequate knowledge of potential exposure and the populations potentially exposed.

Using a tiered approach to data development and decision making

RISK21 utilizes a tiered structure for both exposure and hazard assessment. This leads to the optimization of limited resources and establishes a value of information approach for decision making. Obtaining as much information as possible before making a decision about human safety may be desirable, but can waste resources and delay decision making. A more rational approach is to acquire additional data only if necessary and when they add value. Guided by problem formulation and taking advantage of existing information, both exposure and toxicity estimates can be generated at a very basic level that may be sufficient for a decision about human safety. If not sufficient, greater commitment of resources will inform the safety decision as needed. Lastly, this tiered approach is flexible, such that a higher tier hazard assessment approach can be coupled with a lower tier exposure approach, and vice-versa, with the ability to enter and exit the strategy at any point when sufficient data have been generated to make a decision.

One example of integrating data from new high-throughput and high data content technologies into a tiered chemical testing framework has been recently proposed by Thomas et al. (2013). The framework is consistent with the RISK21 principles and invokes successive tiers of testing where MOE is the primary metric determining appropriate next steps.

The RISK21 roadmap

Based on these principles, RISK21 organized the above principles into a transparent and tiered framework called the RISK21 roadmap. The roadmap is problem formulation-based, exposure driven, and expresses the intersection of exposure and toxicity on a matrix that clearly identifies the degree of human risk and safety (Figure 1). This highly visual

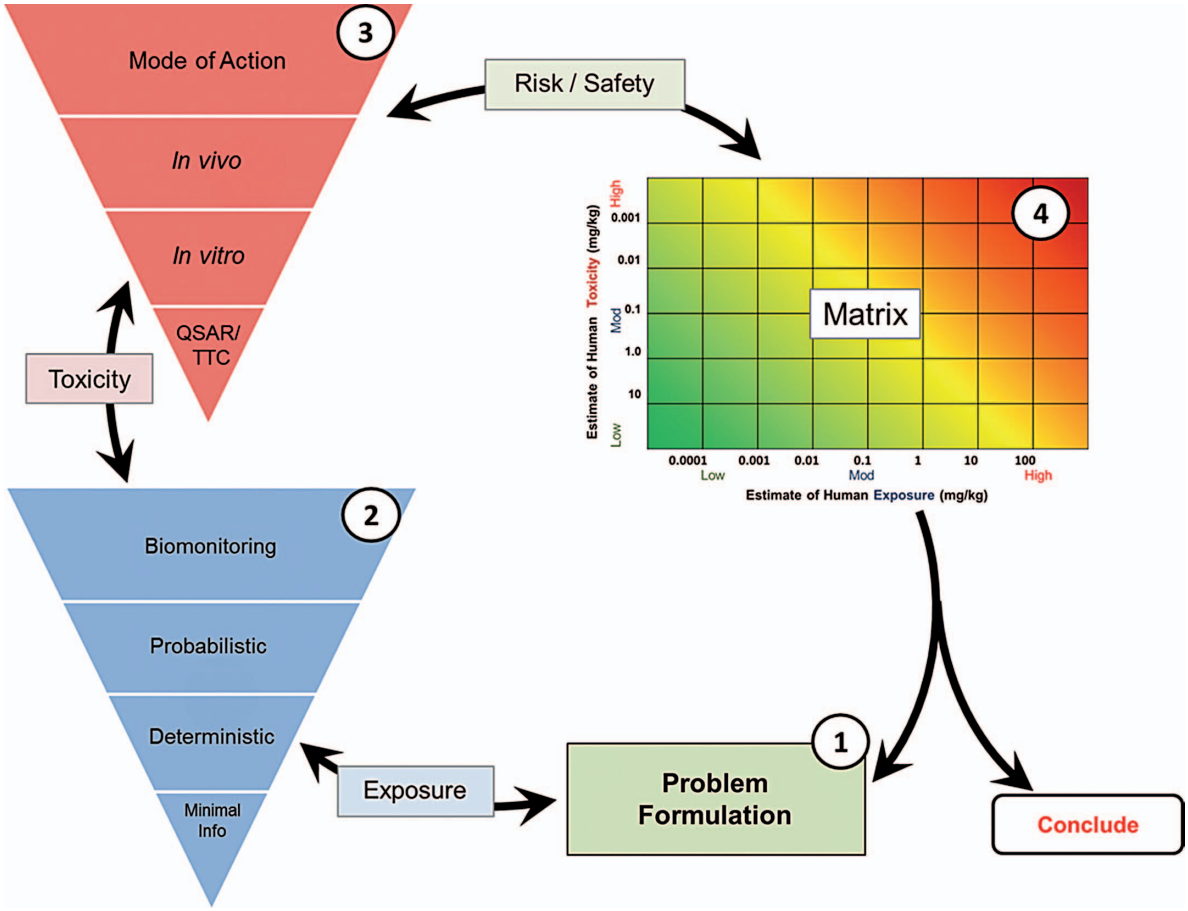

Figure 1. The RISK21 roadmap. This diagram is a schematic representation of a multifunctional tool that provides a transparent process for obtaining rational risk-related decision points. The inverted triangles for exposure and toxicity represent the proportional investment of resources needed for each tier. The following steps describe the use of the roadmap and are described in additional detail in Embry et al. (2014): 1) *Problem formulation*: Define problem. This initial step is reevaluated throughout the iterative process; 2) *Exposure estimate*: Obtain tiered estimate of exposure BEFORE assessing toxicity. Use existing knowledge. Express as range; 3) *Toxicity estimate*: Obtain tiered estimate of toxicity. Use existing knowledge. Develop data only as needed. Express as range; 4) *Matrix*: Intersect exposure and toxicity estimates on the matrix.

methodology clearly identifies problem formulation, stepwise progression of data acquisition, and the degree of precision obtained in the safety evaluation in a transparent and reproducible manner. Estimates of exposure and toxicity are plotted on the RISK21 matrix, with an estimate of their respective bounds of uncertainty. Use of this matrix allows dynamic illustration of the impact of moving through the respective assessment tiers (exposure and toxicity) and the consequences of reducing uncertainty in the estimates. The axes can be any suitable dose metric, from external exposure to target tissue concentration, as long as it is the same on both.

Two case studies were conducted to test the utility of the roadmap. One case study examined a data-rich "nth-in-class" example for a new pesticide. A second case study looked at prioritizing multiple chemicals in drinking water for further evaluation. In each case study, the roadmap and matrix clearly tracked the iterative stages of data acquisition and safety assessment until sufficient precision was obtained. The details for the use of the RISK21 roadmap along with these case studies will be published separately. Additional papers that detail the steps that can be taken for exposure and toxicity data, as well as the application of the RISK21 roadmap approach for cumulative risk assessment are in development.

Benefits of RISK21

Dynamic thinking by a broad range of stakeholders identified stepwise changes in the methodological approaches that will ultimately shape the way risk and safety determinations will be done. This focused attention has identified techniques to improve how human safety can be determined in a science-based, highly transparent, flexible, and efficient way. The value of the roadmap is its capacity to chronicle the stepwise acquisition of scientific information and display it in a clear concise fashion. Pages and pages of detailed exposure and toxicity data can be coalesced into an understandable rendering that can be flexibly revisited as new information is generated. The approach is non-judgmental with regard to the methodological origin of the data, as long as they can be expressed in a common metric. Furthermore, the tiered approach and transparent display of information will contribute to greater efficiencies by calling for data only as needed, thus conserving animals and other resources.

Many publications, most notably the U.S. National Academy reports, have called for a significant progression in toxicology, exposure science and risk assessment. RISK21 is contributing to the strategic vision of these calls by offering a roadmap for data development and assessment that can clearly visualize human health risk assessment.

Conclusions

This paper is the first in the series of papers that describes the work of the HESI-coordinated RISK21 project. This paper summarizes the principles, roadmap, and matrix developed by over 120 participants from 12 countries, 15 government institutions, 20 universities, 2 non-governmental organizations, and 12 corporations.

RISK21 is based on several core principles that led to the development of a transparent roadmap that is a problem formulation-based, exposure-driven, tiered data acquisition risk assessment methodology that utilizes the vast amount of information already available. The RISK21 roadmap has the potential to be a major step forward in human health risk assessment. The exposure-led approach allows one to quickly determine the toxic potency of concern. The concept of enough precision to make a safety decision allows methods to be used that otherwise would be considered not accurate enough. Knowing the degree of precision allows appropriate decisions to be made with confidence, quickly, efficiently, and using fewer resources. As a framework, it will allow new methods to be used as they are developed. The roadmap provides a visual representation of the intersection between exposure and toxicity estimates in a way that fosters transparency, understanding, and communication.

The RISK21 approach will be described in detail in forthcoming publications, including a thorough description of how to utilize the RISK21 roadmap and matrix (Embry et al. 2014); two case studies that test the utility of the RISK21 approach; an expansion of the existing mode of action and Key Events Dose Response Framework (Julien et al. 2009) to quantitatively incorporate dose-response information (Simon et al. 2014); discussion on appropriate extrapolation techniques to express *in vitro* exposure concentrations as an *in vivo* dose; development of a novel, tiered approach for estimating exposure; and a description of how the RISK21 approach can be applied to cumulative risk.

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Declaration of interest

This manuscript was prepared under the auspices of the International Life Sciences Institute Health and Environmental Sciences Institute (ILSI HESI), a non-profit organization aimed at engaging scientists from academia, government, industry, research institutes, and NGOs to identify and resolve global health and environmental issues. ILSI HESI collects funding from member companies to support projects. The authors' affiliations are as shown on the cover page. The authors had sole responsibility for the writing and content of the paper. The views and opinions expressed in the paper are those of the authors, and do not necessarily reflect the views of the authors' employers or the opinions or policies of the US EPA or NIH. Mention of trade names does not constitute endorsement. None of the authors has recently or is currently involved as an expert witness in litigation or formal government rule-making on the subject of this paper. The authors employed by ILSI HESI participated as part of their normal employment. No other authors received financial support or an honorarium in the preparation of this paper. The authors declare that there are no conflicts of interest.

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