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Review article

Uncertainties in human health risk assessment of environmental contaminants: A review and perspective

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ABSTRACT

Addressing uncertainties in human health risk assessment is a critical issue when evaluating the effects of contaminants on public health. A range of uncertainties exist through the source-to-outcome continuum, including exposure assessment, hazard and risk characterisation. While various strategies have been applied to characterising uncertainty, classical approaches largely rely on how to maximise the available resources. Expert judgement, defaults and tools for characterising quantitative uncertainty attempt to fill the gap between data and regulation requirements. The experiences of researching 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) illustrated uncertainty sources and how to maximise available information to determine uncertainties, and thereby provide an 'adequate' protection to contaminant exposure. As regulatory requirements and recurring issues increase, the assessment of complex scenarios involving a large number of chemicals requires more sophisticated tools. Recent advances in exposure and toxicology science provide a large data set for environmental contaminants and public health. In particular, biomonitoring information, *in vitro* data streams and computational toxicology are the crucial factors in the NexGen risk assessment, as well as uncertainties minimisation. Although in this review we cannot yet predict how the exposure science and modern toxicology will develop in the long-term, current techniques from emerging science can be integrated to improve decision-making.

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1. Introduction

Understanding the effects of environmental contaminants on public health requires expert knowledge of the continuum from contaminant source to public health outcomes (U.S. NRC, 2009). The source-to-outcome continuum can be described as a conceptual framework for human health risk assessment (HHRA) which assimilates knowledge and techniques from chemistry, physiology, biology, mathematics, physics, medicine and other relevant disciplines. Current developments in HHRA provide important information on how to approach the release, dynamics, fate and behaviour of contaminants. However, the current paucity of knowledge concerning contaminant behaviour will inevitably result in uncertainties. Many factors including parameters, models and insufficient data, influence the frequency and degree of uncertainties (International Programme on Chemical Safety, 2005a; International Programme on Chemical Safety, 2014). The uncertainty not only points to the range and possibility of risk results to assessors, decision-makers and the public but also highlights the implications and limitations of assessment conclusions in HHRA (ENHEALTH, 2012; European Chemicals Agency, 2013; U.S. NRC, 2013).

Efforts to determine and quantify the risks posed by environmental contaminants to human health have also systemically addressed their uncertainties. In 1983, the U.S. National Research Council (NRC) published a landmark report titled 'Risk Assessment in the Federal Government: Managing the Process' (Red Book), in which the NRC not only constructed the fundamental framework for HHRA, but also documented critical uncertainties (U.S. NRC, 1983). In particular NRC recommended that those uncertainties related to the statistical, biological issues and choices of assessment and exposed population should be summarised in each step of the risk assessment process (U.S. NRC, 1983). Subsequently, the 'Guidelines for Carcinogen Risk Assessment' described the sources of uncertainties, including dose extrapolation, data and model assumption and identification for carcinogens (U.S. EPA, 1986). During the 1980s the U.S. Environmental Protection Agency (U.S. EPA) released at least five additional guidance documents to discuss how to address and determine uncertainties in HHRA for carcinogens, chemical mixtures and developmental toxicants (Williams and Paustenbach, 2002). Later, the National Academy of Sciences (NAS) emphasised uncertainty as one of several critical factors, and highlighted this issue in a series of reports published in the 1990s (U.S. NRC, 1994; U.S. NRC, 1996).

Essentially, the U.S. EPA reiterated that scientific uncertainties are unavoidable in the risk assessment process, and should be identified along with their influence on assessment. To enable management of risk from exposure to contaminants based on quantitative measures of uncertainty, U.S. EPA established a host of tools, databases and guidance protocols. For example, the benchmark dose (BMD) method, which was proposed in 1995, has been considered superior to traditional lowest-observed-adverse-effect level (LOAEL) and no-observed-adverse-effect level (NOAEL) in deriving benchmark dose values. More recently, 'Computational Toxicology Research Program (CompTox)' has been anticipated to develop a statistical toolbox assisting in reducing uncertainties (U.S. EPA, 2009). Notably, the CompTox program has developed and managed the Aggregated Computational Toxicological Resource (ACToR), a collection of databases. The ACToR aggregates data from over 500 public sources on more than 500,000 environmental chemicals, and data includes conventional toxicity, high throughput screening (HTS) and genomics tests, chemical and physical data, structural parameters, chemical identifiers and exposure database (Fowler, 2013). Meanwhile, International Programme on Chemical Safety (IPCS) has projected the harmonisation of approaches for assessing risk from exposure to chemicals: one achievement has been the application of chemical-species adjustments factors (CSAF) for interspecies differences (International Programme on Chemical Safety, 2005a; International Programme on Chemical Safety, 2005b; International Programme on Chemical Safety, 2014). In the 2014 report, 'enough knowledge' is the key criteria to judge whether the assessment is an adequate measure (International Programme on Chemical Safety, 2014). Such efforts facilitated the recognition of uncertainties in HHRAs and assisted in making decisions, and the effective utilisation of available resources potentially guarantee the appropriate 'enough' and 'coverage' we can obtain. However, due to the need to regulate many chemicals (U.S. EPA, 2014b; U.S. NRC, 2009), bridging the gap between regulation requirements and uncertainty characterisation remains a challenge.

In 2008, the next generation (NexGen) project was proposed by U.S. EPA to address advances in exposure science and toxicity testing to create an economic, rapid and more robust system for chemical risk assessment (Cote et al., 2012; Krewski et al., 2014; U.S. EPA, 2014a). *In vitro* and *in vivo* assays, molecular modelling, emerging data from genomics and proteomics all offer the possibility to understand the adverse outcome pathway (AOP), whilst novel biomarker and *in silico* simulation offers the avenue to trace chemical behaviour efficiently (Krewski et al., 2014; U.S. EPA, 2014a; U.S. EPA, 2014b). Toward a 'fit for purpose' assessments (U.S. EPA, 2014a), the aims of these new technologies not only to minimise uncertainties. Meanwhile, new technologies offer the opportunity to get to the point of making a risk decision much more efficient by rapidly characterising uncertainties. In this review, we offer a broad yet comprehensive discussion of uncertainties and solutions in the context of HHRA practice. The objectives of this review are three-fold: i) describe the uncertainties existing in HHRA processes; ii) identify methods to uncertainty characterisation; and iii) address the opportunities, challenges and approaches from emerging science that can assist in characterising and reducing uncertainties. The overview on uncertainties presented here will provide a scientific basis that contributes to a cleaner and safer environment in the future.

2. Uncertainties in HHRA

Human response to contaminant exposure depends on the toxicity of a substance and the extent of exposure. Since HHRA can usually be divided into four components, the uncertainties are also illustrated for each component as shown in Table 1.

2.1. Uncertainties in exposure assessment

Exposure assessment traces events from source to final biomonitoring, which attempts to estimate the duration, frequency, and magnitude of the exposure to a designated target group. It is anticipated that such an assessment will determine the source of toxicants, their transportation through environmental media, and their external exposure and biomonitoring under various exposure scenarios (ENHEALTH, 2012). Definitions and applications of source, external exposure and biomonitoring have been described in detail elsewhere (Zeise et al., 2013). The uncertainties in this component have been classified into scenario, model and parameter uncertainties by IPCS (International Programme on Chemical Safety, 2005b). Scenario uncertainties refer to specifying the exposure information that is consistent with the province and objective of exposure assessment, including the agent, exposed populations, spatial and temporal information, microenvironments, population activities, pathways, durations, frequencies *etc.* (International Programme on Chemical Safety, 2005b). Such elements for the scenario uncertainties are probably related to descriptive errors, aggregation errors, judgement errors and incomplete analysis (U.S. EPA, 1992).

Referring to another issue, exposure assessment techniques are usually based on an estimation of total contaminant concentration and bioavailability both of which involve uncertainties associated with methods, models and parameters. Model uncertainties stem from model structure, detail, validation, extrapolation, resolution, boundary, scenario reasonableness, etc (Jardine et al., 2003; Williams and Paustenbach, 2002). Williams et al. have summarised commonly used models currently supported and used by the U.S. EPA to assess exposures to human (Williams, 2010), and most models rely on a common