Toxicological Risk Assessment

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Abstract

Risk analysis encompasses the scientific review and evaluation of all relevant scientific data on the toxicity of, and the exposure to, a certain compound or mixture. To enable a systematic analysis of the different types of information needed, various risk analysis paradigms have been developed. Among these, the scheme developed in 1983 by the US National Academy of Sciences (NAS) has been the most widely utilized. Risk analysis provides the scientific basis for regulatory actions within the context of risk management.

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Adverse-Outcome-Pathways (AOP) · Hazard · Risk · Risk analysis · Risk assessment · Weigh-of-evidence (WoE)

Introduction

The term "risk analysis" is not used in a uniform manner. In some instances, the term is considered to have the same meaning as "risk assessment," while some institutions, as is the case with the Codex Alimentarius Commission, employ the term to describe the broader concept of risk regulations, encompassing risk assessment, management, and communication. For others, risk analysis is seen as the mathematical analysis and quantification of risks. Given these differences in using the term risk analysis, a clear, uniform definition cannot be given. For the purposes of this chapter, risk analysis will be described as the broader process encompassing the scientific assessment, management, and communication of risks.

Why Risk Analysis?

The toxicity of a given substance can be defined as its ability to harm living organisms. This is an inherent characteristic of any compound and will only be expressed as a function of the dose as described already by Paracelsus. Thus, any compound can be toxic if a certain threshold of exposure is surpassed. This is the reason why a distinction between "toxic" and "nontoxic" or "harmful" and "safe" substances makes no sense. In fact, the toxicity of a given substance cannot be defined without reference to the administered/absorbed amount (dose); the route through which the exposure and distribution of the substance take place (e.g., by inhalation, ingestion, dermal absorption); the level, frequency, and duration of exposure; the type and grade of the damage caused; and the lag time required to illicit the toxic effect.

It is only once the potential to cause harm and the probability of a damage are known that options to reduce/eliminate potential harm can be assessed and regulatory action be taken (risk management). Such measures need to consider other factors besides the scientific evaluation of risks, for example, socioeconomic impacts and the risk-benefit relation. The aim of risk management is to avoid risk or, if this is not possible, to reduce it as far as achievable. The basis for meaningful risk management decisions remains, however, a thorough characterization and evaluation of scientific data on toxicity and exposure: risk assessment.

Steps in Risk Regulation

In the scheme of the German Risk Commission (Deutsche Risikokommission), risk regulation encompasses the whole societal process of dealing with risks. Ideally, the process should cover three areas of risk analysis: risk assessment, risk evaluation, and risk management.

Risk Assessment

Risk assessment is the process of identifying and quantifying the potential harm due to a certain exposure to a substance (risk). Normally, it targets individuals, but there are several instances in which population risk is assessed. To accomplish this task, knowledge about toxicity and exposure, but also information on the dose-response (or exposure-effect) relation, and target populations including vulnerable groups is required (see below).

Risk Evaluation

Risk evaluation bridges risk assessment and risk management. It encompasses a value judgment of the risk posed by the substance under consideration. Questions addressed here include whether or not the risk is higher than seen with other comparable compounds, what the risk-benefit ratio is, and if there are any protective measures that can be taken to reduce the risk. In addition, social, cultural, and political factors may also be considered. The outcome of this process is a recommendation for risk management.

Risk Management

Risk management is the decision process during which the results of the risk assessment are used to develop and analyze options for avoiding or minimizing risks of exposure to a given substance, taking into consideration political, social, cultural, economic, and technical aspects. The aim of this process is to define the best possible and feasible action(s). Risk assessment and management are distinct, though closely related, interactive processes: while risk assessment is a scientific, technical discipline, risk management is a sociopolitical decision-making process. Newer models of risk analysis have endeavored to develop a closer interlink between the two processes (see below).

The Process of Risk Assessment

Scientific information needed to conduct risk assessment includes qualitative and quantitative data on the toxicity of the agent in question, on the dose-response relation, as well as on the exposure (WHO 1999; Younes et al. 1999).

The process of collecting or extracting relevant data to be used for the risk assessment includes various steps which are tightly related to the problem formulation (the scientific question to be answered), the conceptual framework, and the definition of the evidence needs. The aforementioned considerations should always be clearly addressed in advance before the actual risk assessment begins. When the collection of the data has been completed, the risk assessment can be conducted.

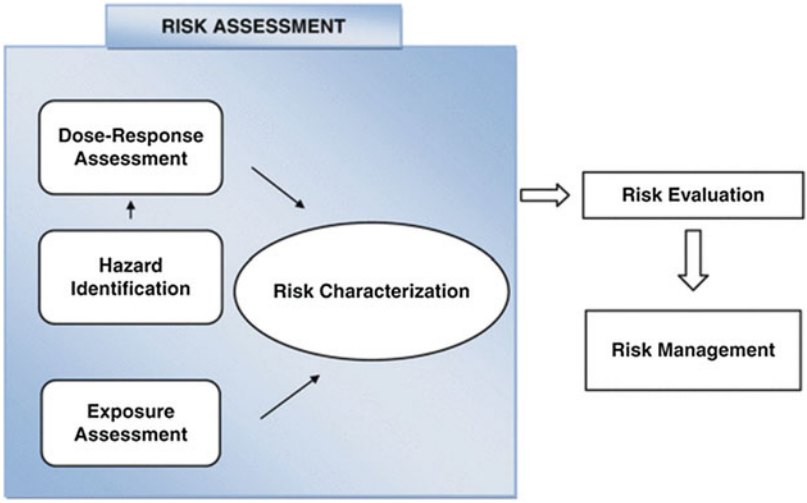

Fig. 1 Schematic presentation of the risk analysis process: Following risk assessment, with its four components, risk evaluation is conducted to allow for consideration of additional factors, such as socio-economic impacts, before risk management decisions are taken

Various paradigms have been developed to facilitate a systematic analysis of such complex data and, consequently, to allow for the development of a comprehensive estimation of potential risks. The most commonly used scheme worldwide is the one developed by the US National academy of Sciences (NAS) in 1983 (NRC 1983, 2009). It is currently in use by many regulatory agencies, though some variations of it are also applied, and more modern approaches have expanded on it to provide a better link between the processes of risk assessment, management, and communication. The NAS model divides the process of risk assessment into 4 distinct steps (Fig. 1).

Hazard Assessment

In order to better understand the important step of hazard assessment, it will be subcategorized below in two steps which altogether consist the process of assessing the hazardous properties of an agent.

Hazard Identification: Assessing the Potential to Cause Harm

It is worth noting that the terms "hazard" and "risk" are often used synonymously. This is incorrect. The term "hazard" describes the "potential to harm," that is, the principal ability of a given substance to exert a toxic effect (which, logically, will

only occur at a certain exposure level). Hazard is therefore an inherent characteristic of the agent in question. "Risk," by way of contrast, describes the probability that a harmful effect will, in fact, occur. Risk is the actual or potential danger posed by an existing or an expected exposure.

Hazard identification is the step during which all relevant data are analyzed that provide information to assess the inherent potential of an agent to exert harmful effects.

When the scientific question is relatively simple and can be addressed directly then a straightforward assessment can be conducted to reach an outcome following the steps described in this chapter.

In many assessments, however, questions may need to be subdivided to yield more directly answerable questions, and a weight of evidence assessment needs to be conducted.

The weight of evidence is comprised by three basic steps (see Fig. 2):

1. Assembling the evidence into lines of evidence of similar type which involves searching for and selecting evidence that is relevant for answering the question at hand, and deciding whether and how to group it into lines of evidence
2. Weighing the evidence which involves detailed evaluation and weighing of the evidence

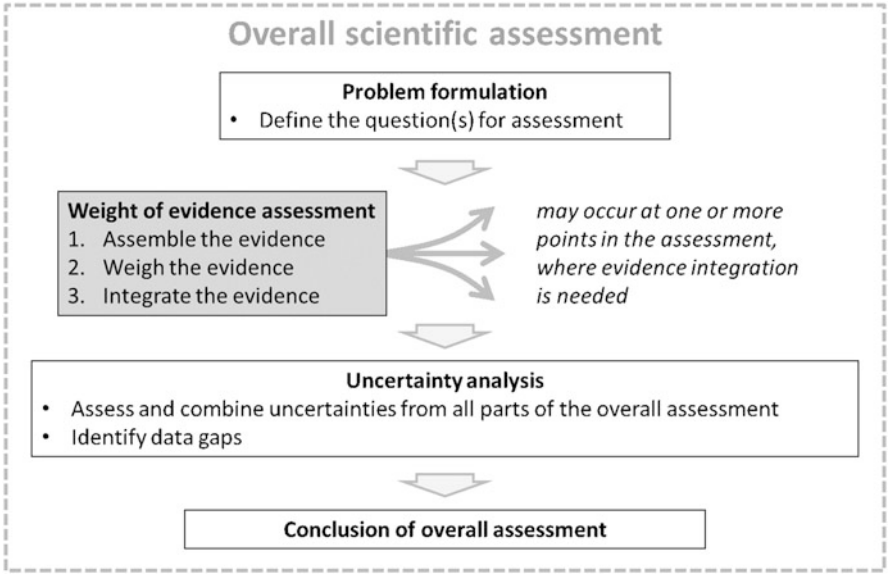

Fig. 2 Diagrammatic illustration of weight of evidence assessment as a 3-step process which may occur at one or more points in the course of a scientific assessment (EFSA 2017)

3. Integrating the evidence to arrive at conclusions, which involves weighing the relative support for possible answers to the question

It is important to note that reliability, relevance, and consistency of data are the three basic considerations for weighing evidence.

- Reliability is the extent to which the information is correct.
- Relevance is the contribution a piece or line of evidence would make to answer a specified question and how much could alter how decisions for a specific problem are taken, if the information comprising the evidence was fully reliable. This includes biological relevance.
- Consistency is the extent to which the contributions of different pieces or lines of evidence to answering the specified question are compatible.

Relevance and reliability may be considered in both the first and second steps since they are essential elements in order to identify the evidence to be used for the risk assessment but also when weighing the identified evidence.

Sources of data to be used for the hazard identification can be in vivo studies, in vitro studies, in silico (QSAR, read across, etc.), epidemiological studies, and control clinical studies on humans. A variety of studies are used to identify potential hazards of a chemical. More specifically, toxicokinetics considers how the body absorbs, distributes, metabolizes, and eliminates chemicals while toxicodynamics focus on the effects that chemicals have on the human body.

Especially, when assessing a chemical for potential adverse effects, analysis of a mode of action (MoA) and the development of an "adverse outcome pathway" (AOP) are currently used.

MoA is a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. A given agent may work by more than one MoA. For instance, when assessing a chemical for carcinogenic effects, the chemical might be involved in MoA both at different tumor sites as well as at the same site (Boobis et al. 2008).

The AOP approach provides a framework for organizing information at the chemical and biological level, allowing evidence from both in silico and in vitro studies to be rationally combined to fill gaps in knowledge concerning toxicological events. Fundamental to this new paradigm is a greater understanding of the mechanisms of toxicity and, in particular, where these mechanisms may be conserved across taxa, such as between model animals and related wild species. (Madden et al. 2014).

An AOP is defined as the information on the causal links between a molecular initiating event (MIE) which is the initial point of chemical-biological interaction within the organism that starts the pathway, intermediate definable key events (KEs) which make sense from a physiological and biochemical perspective and an adverse outcome (AO) of regulatory concern that is adverse at the individual level if discussing human health or population level if discussing environmental effects (see Fig. 3) (Ankley et al., 2010; Meek et al. 2014; OECD 2013).

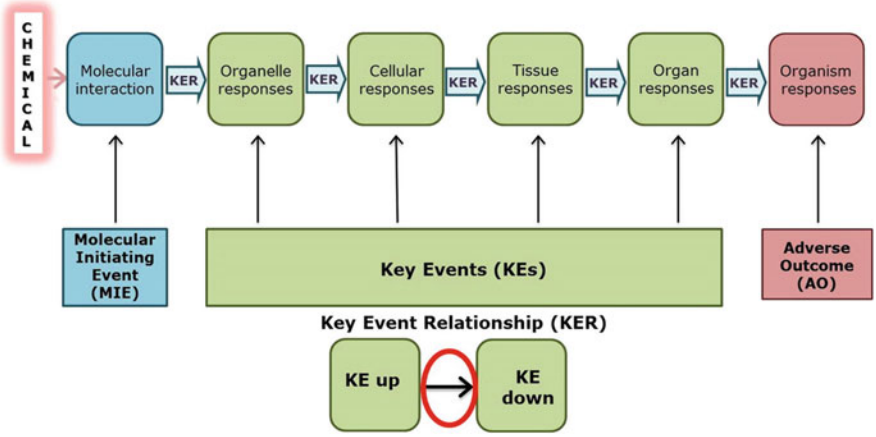

Fig. 3 An AOP consists of key events (KEs) and key events relationships (KERs) at different levels of biological organization starting from an initial interaction of a chemical with the biological system (molecular initiating event; MIE) through a sequence of KEs (cellular, tissue, organ, and organism) leading to an adverse outcome (AO) of regulatory relevance that represents overt adversity at either organism or population level. At sufficient concentrations and durations of exposure, KE up will trigger KE down, overcoming cell defense mechanisms and adaptation processes. (Anna Bal-Price et al. 2017)

Dose-Response Assessment: The Relation Between Exposure and Effect

The objective of hazard characterization is to document the dose-response relationship. Usually, as the dose increases, the measured response also increases. At low doses there may be no response. The adverse effect that occurs at the lowest dose is selected as the critical effect for risk assessment which serves for the derivation of a health-based guidance values. Different definitions can be found in bibliography (e.g., Acute Reference Dose (ARfD), Lowest or No-Observed–Adverse-Effect-Level (LOAEL/ NOAEL) or ideally BMD limit (BMDL))), but they all serve the same scope, which is to identify a reference point which will be consequently used for the derivation of a health based guidance value such as Margin Of Exposure (MOE) or Tolerable Daily or Weekly Intake (ADI/TDI). When this exercise is done, and the risk characterization is quantified, the risk assessor can conclude about the risk.

In the course of this step, a quantitative estimation of toxic effects, be it the severity of an observed outcome, such as the level of liver damage as evidenced by an increase in blood levels of liver-specific enzymes, or the frequency of occurrence of a yes-or-no outcome, such as cancer or even death, at different exposure levels is conducted. This allows for a characterization of potential toxic outcomes as a function of exposure or dose.

Table 1 shows the different reference points, health based guidance values, and ways to characterize the risk as they are used in risk assessment.

Table 1 Reference points and health based guidance values

Reference points (RPs)	Health based guidance value (HBGV)	Risk characterization
Benchmark response (BMR)	Acceptable daily intake (ADI)	Margin of exposure (MOE)
Lowest benchmark dose (BMDL)	Tolerable daily intake (TDI)	Risk characterization ratio (RC)
Benchmark dose (BMD)	Acute reference dose (ARfD)	Hazard quotient (HQ)
No observed (adverse) effect level (NO(A)EL)	Reference dose (RfD)	Margin of safety (MOS)
Lowest observed (adverse) effect level (LO(A)EL)	Derived-no-effect-level (DNEL)	Population at risk
No observed (adverse) effect concentration (NO(A)EC)	Derived-minimal-effect-kevel (DMEL)	
Lowest observed (adverse) effect concentration (LO(A)EC)	Population adjusted dose (PAD)	

Exposure Assessment

Exposure assessment encompasses the qualitative and/or quantitative determination of the level and frequency of exposure, potentially the lag time between subsequent exposures, the exposure media (air, drinking water, soil, recreational water, food), as well as the exposure route(s) (inhalation, ingestion, dermal absorption).

Uncertainty Analysis

A separate step is still needed to take account any uncertainties arising at all stages of the risk assessment. They should be addressed and described together with any data gaps. A separate step of uncertainty analysis is needed to take account of any uncertainties affecting the overall assessment. These are further categorized according to the source of uncertainty.

A. Uncertainties associated with assessment inputs which include:
    1) Ambiguity
    2) Accuracy and precision of the measures
    3) Sampling uncertainty
    4) Missing data within studies
    5) Missing studies
    6) Assumptions about inputs
    7) Statistical estimates
    8) Extrapolation uncertainty (i.e., limitations in external validity)
    9) Other uncertainties

B. Uncertainties associated with assessment methodology which include:
   1) Ambiguity
   2) Excluded factors
   3) Distributional assumptions
   4) Use of fixed values
   5) Relationship between parts of the assessment
   6) Evidence for the structure of the assessment
   7) Uncertainties relating to the process for dealing with evidence from the literature
   8) Expert judgment
   9) Calibration or validation with independent data
   10) Dependency between sources of uncertainty
   11) Other uncertainties

Risk Characterization: The Synthesis of Risk Information

The last step in risk assessment is risk characterization (see also ► Chap. 56, "Risk Characterization in Regulatory Toxicology"), which is a synthesis of all evaluated data and information. Strengths and weaknesses of the database must be clearly identified, methods, and criteria of all evaluations described, and the results of the evaluation of all data outlined. The outcome of risk characterization is the basis for developing strategies to avoid or, if this is not possible, to minimize the risk (risk management). Vulnerable groups, which are at particular risk due to higher exposure levels and/or an enhanced susceptibility, must be characterized in order for risk management decisions and actions to take their particular situation(s) into consideration.

The scheme described is a conceptual framework which should help in organizing all scientific data in a manner that allows a sequential, logical analysis. Other models/schemes have been developed, but the NAS paradigm is the most widely used till now. Individual steps of the process are more exhaustively described in other parts of this book.

Recent advances have been made to better link risk assessment with risk management. The US National Research Council recommended in 2009 that risk analysis should be divided in three phases. The first phase should cover problem formulation and scoping in order to better identify data needs and target risk assessment. The second phase should encompass the planning (stage 1) and conduct (stage 2) of risk assessment, pretty much following the NAS paradigm, but with an additional stage 3 to confirm the utility of the assessment. In this latter stage, questions to address include if the assessment had the attributes called for in the planning, if the assessment provides sufficient information to discriminate among risk management options, and if the assessment has been sufficiently peer-reviewed. Only then phase 3, risk management, actions can be evaluated and decided upon.

The Need for Harmonization

Despite the fact that the scientific data used for risk assessment purposes by different institutions are mostly identical for the same compound, they are often analyzed and treated differently and may result in different outcomes. For example, carcinogenic risk is characterized in the USA through a calculation of an exposure corresponding to a theoretical tumor incidence. In this context, dose extrapolation is conducted via different methods to very low levels, often below analytical detection limits. In this manner, exposures leading to a tumor incidence of, for example, 1 in 100,000 or 1 in 1,000,000 are calculated. Such methodologies are seldom used in Europe. Still, it is possible to compare the results of risk assessments conducted in different ways and to use performed data analysis to a certain degree, as long as the methodology, including all assumptions and uncertainties, is clearly outlined. It should be noted that there are recommendations to unify risk assessments for carcinogens and non-carcinogens, for example, in the 2009 report of the NRC.

At the international level, efforts are underway to harmonize, though not to standardize, risk assessment methods. In this context, the aim is to promote the understanding of different approaches to risk assessment, so that the results of such assessments conducted by a different institution can be understood by other institutions and eventually adapted to their specific needs. Thus, risk assessments can be utilized universally.

Risk assessment and the subsequent risk evaluation are the basis for regulatory decisions to manage risks. Regulatory measures are obviously different in different areas of regulation: In the case of pharmaceuticals, for example, the risk related to treatment must be put in relation to its therapeutic value. In the case of chemicals, it is important to estimate the potential direct exposure of workers in all areas (production, use, storage, and transport) and consumers, as well as the indirect exposure through various environmental media in order to reach regulatory decisions that would, indeed, eliminate or reduce to a minimum the exposure of the respective groups of the population.

Cross-References

- ▶ Risk Characterization in Regulatory Toxicology
- ▶ Risk Comparison in Toxicology
- ▶ Risk Evaluation in Regulatory Toxicology

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