Checklist: Toxicological Risk Assessment in Practice

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Abstract

The checklist gives brief practical hints for all those who are occasionally or professionally involved in risk assessment, risk management, and risk regulation. Further details to each topic can be found in the relevant chapters of this book.

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Checklist and Comments

Checklist	Comments
Which are the steps of the risk regulation process?	
The IPCS document (IPCS, 1994) identifies these as: **Risk assessment** (in 4 steps): Hazard identification Hazard characterization (including dose–response relationship) Exposure assessment Risk characterization **Risk management** Risk evaluation Emission and exposure control Risk monitoring	Risk assessments are made on the basis of a scientific examination of toxicity and exposure, leading to a risk characterisation. The risk management process is aimed at developing an appropriate response to the hazard (regulatory, technical, legal). Risk (or risk-benefit) evaluation, the first step in risk management, establishes a qualitative or quantitative relationship between risks and benefits of exposure to an agent and the influence of possible control measures on that evaluation. It may be necessary to examine relative risk and benefit for different agents used for the same purpose.
What data on toxic properties are needed for risk assessment?	
Chemistry Basic physical and chemical properties. Structure-activity relationships (if available) for the test substance and related substances. **Identification of toxic effects** Animal testing results (acute, subacute, and chronic toxicity; carcinogenicity; and toxicity to reproduction). Evidence of irritation and sensitization. Genotoxicity. Results from in vitro tests. Biochemical mechanism of action. Experience in humans. **Toxicodynamics** Dose–response relationships (size of response). Rates of development and duration of effects. **Toxicokinetics** Absorption rates (oral, inhalation, dermal) Distribution, half-life Metabolites Routes and rates of elimination Experience with humans	By proper assessment of the physicochemical properties (“insoluble . . .”), it is often possible to get a first estimate of the risk level. Data quality (this includes whether appropriate protocols and audit procedures were employed) must be considered. For chemical assessment, Klimisch gradings are often used (see Klimisch et al. 1997) The overall picture will emerge only from the sum of all available information. If in doubt, additional information must be asked from poison control centers and manufacturers. Toxicokinetic data are often ignored in risk assessments – which is a fault.

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What information is provided by the dose–response relationship?	
Shows threshold above which effects can be observed (NOAEL/LOAEL/BMD). Large steepness of the dose–response relationship means reduced safety margin. Shape of the curve influences values obtained by extrapolation to low doses (e.g., unit risk).	Non-sigmoidal dose–response relationship increases the uncertainty in extrapolation to low concentrations. NOAEL values of different studies often differ as they are the dose below the dose at which effects were seen and therefore depend on the dose intervals between doses in the study. They also depend on what parameters were measured in the studies. If in doubt, it should be checked as to whether one of the studies is better suited for a particular risk assessment.
How is an exposure assessment made?	
External exposure Measurement or estimation of the extent of external exposure (in the intake, in the medium [air, water, food basket], or, using more complicated models, in the input to the medium [e.g., water] from the source [e.g., outlet sewer of chemical factory/sewage treatment works]). Observe all routes of exposure (oral, inhalation, dermal). Consider sensitive persons. **Internal exposure** Calculation of the assumed maximum uptake on the basis of (worst case) scenarios. Probabilistic assessment of the different routes of intake. Measurement of the internal concentration (human biomonitoring).	Exposure estimates can be extremely uncertain. Scenarios (models) should be clearly set out and estimates calculated according to standardized procedures. Estimates should not contain multiple "worst-case" assumptions (if the P value of 0.1 [i.e., 1 in 10 will show the effect] is applied three times, this gives a P value of 0.001 [1 in 1,000]). Monte Carlo analysis is essential in these circumstances. Human biomonitoring is a very good method for internal exposure assessment.
Which safety factors are often used?	
Usual safety factor for extrapolation for a threshold effect from a good animal data to a general human population = 100 (depends on circumstances). US-EPA and other regulatory agencies often use safety factors up to 10,000 (see e.g., IPCS 1994).	Depending on the size of the selected safety factors, risk assessments can vary enormously even when the experimental data base is identical. This can easily lead to dispute.
Why does epidemiology rarely find a threshold value?	
Large uncertainty in the estimation of exposure. Large uncertainty of the effects at low doses. High interindividual variability.	Lack of thresholds in epidemiological studies may be artificially caused by the multiplication of several uncertainty factors.
Who belong to the vulnerable groups?	
Pregnant women (organogenesis of the child), infants, and children (organ development, toxicokinetics). Elderly and sick people (low functional reserves, low repair capacity). Allergic people (hypersensitivity).	Often, sensitive groups are given special regulatory protection in various laws (occupational safety, baby food, allergens, etc.). This must be considered in the risk management process.

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What else must be considered in risk management?	
Protection philosophy of the respective areas. Guideline values and their rationale. Are they applicable? Verification of measurement results. Quality assurance of the process.	The safety philosophy may be for good hygiene practice, precautionary, or danger-oriented In order that a risk assessment finds acceptance, it is important to understand the origin of existing regulations as well as the present state of scientific interpretation of the toxicological data.
What does "traffic light principle" mean in regulation	
Green: no effect and no action required. **Yellow**: slightly below threshold level. Adequate action: monitoring. **Red**: above the threshold of action. Swift action to reduce exposure.	Multistage systems such as the traffic light system are more flexible. Where only a single limit value exists, a brief or minor overrun may cause action or legal consequences, even if the excess is toxicologically irrelevant.
When is a disease due to toxic substances?	
Causality can be assumed if exposure levels and exposure duration were sufficient and the response spectrum (the affected organ, expression) characteristic for a compound. The rarer the symptoms occur in daily life, the more secure a causal relationship can be assumed. The criteria to be considered are given in Hill (1965) and are applicable to all toxicological data, not only epidemiological data.	The causality principle is often presumed for toxic substances. But it is not easy to prove causality. With many drugs, possible unwanted effects are often overlooked. And the dramatic health effects of smoking and alcohol are often socially trivialized and ignored. Some dangerous substances produce very specific disease patterns (e.g., asbestos and mesothelioma).
In which way can the modes of thinking influence the risk awareness?	
Scientific way of thinking ("objective risk") Risk assessment Risk comparison Risk management (technical) **Emotional way of thinking by the general public (perceived risk)** Risk acceptance **Political way of thinking (perceived risk)** Risk exaggeration (phantom risk) Risk trivializing Conclusion: understanding the sociological and psychological aspects of risk perception and communication is critical to effective risk management.	Many social groups (toxicologists, engineers, politicians, stakeholders, arbitrator, government representatives, etc.) are potentially involved in risk communication and risk management. In this process, it often happens that different ways of thinking collide. This leads to inner discomfort and confrontation. Knowledge of the various ways of thinking of the general public, as described by psychologists and sociologists, can reduce conflict. A good moderator can help overcome these hurdles. Note: the eloquent charlatan and the lobbyist usually receive more credibility than the highly educated toxicologist and the regulator.

References

Hill AB (1965) The environment and disease: association or causation? Proc R Soc Med 58:295–300

IPCS (1994) Assessing human health risks of chemicals: derivation of guidance values for health based limits. Environmental health criteria 170. World Health Organisation, Geneva

Klimisch HJ, Andreae E, Tillman U (1997) A systematic approach for evaluating the quality of experimental and ecotoxicological data. Regul Toxicol Pharmacol 25:1–5