Working Areas of Regulatory Toxicology

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Abstract

As in other technical fields, there is increasing diversification in the toxicological risk assessments undertaken by, or on behalf of regulatory agencies. This is reflected in the many ways in which regulatory toxicology (health and environmental risk assessment) work areas can be divided. These include by

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end use, by institution, by chemical properties, and by working methods. Although coordination is essential, different institutions sometimes make regulatory decisions independently of one another. Consistency of decision involves harmonizing; thus, cross-border cooperation of toxicologists and other regulatory affairs specialists is essential.

Institutions

Regulatory toxicologists do not operate in a vacuum. There is an objective and there are societal, legal, and philosophical contexts that underlie the scientific decision-making processes of regulatory toxicology. Setting these contexts involves other professionals and nonprofessional groups, such as citizen action committees, lobbying groups, trade associations, and legislators (politicians and lawyers). Understanding and explaining these contexts and how they operate is the role of psychologists and sociologists. Further information on this aspect of regulatory toxicology is beyond the scope of this chapter but can be found in, for example, Illing and Marrs (2009) and Illing (2009).

The expertise for undertaking regulatory risk assessments comes from toxicologists, epidemiologists and exposure specialists, and, in some cases, economists concerned with risk-benefit assessments. These may be found working in government authorities, industry, contract research organizations, and academia (Fig. 1). Each of these institutions has extended international communications networks (both to regional, e.g., European, and international [UN and OECD] bodies). Despite some competition, there is also a constructive cooperation between the institutions.

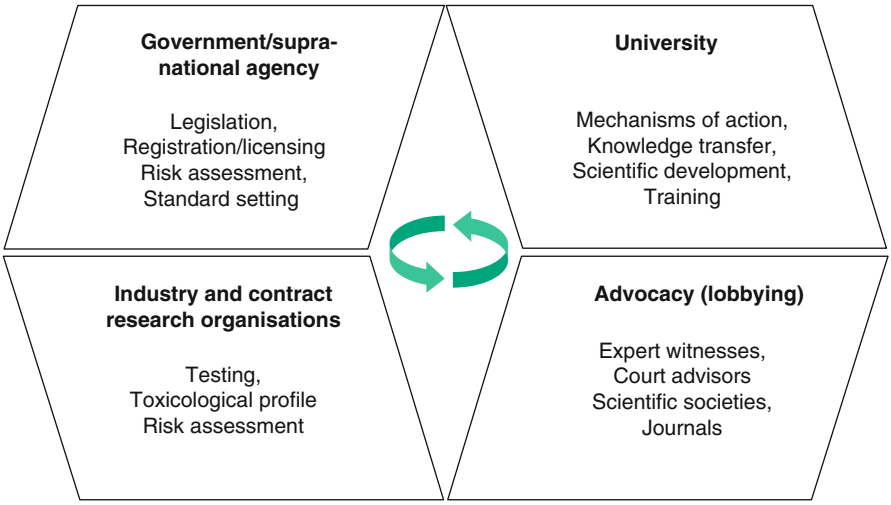

Fig. 1 Institutions

Authorities

Toxicologists, (including clinical toxicologists) and other related specialists such as epidemiologists, occupational hygienists, exposure specialists and policy makers in government (and supranational, including EU) agencies advise the authorities on various levels such as local administrations, ministries, and the government. Toxicologists are involved in the generation and monitoring of test method standards, audit procedures, and standards, registrations, and licensing procedures. Since they have to consider long-term unwanted aspects on the population and environment, they largely work on the basis of conservative risk assessments and, when dealing with environmental issues, the "precautionary principle." They use their toxicological and ecotoxicological expertise to estimate specific risks (in a risk assessment) and, when the risk is not sufficiently low to constitute an acceptable risk, they may then join with others in undertaking a risk-benefit analysis in order to determine a "tolerable risk" based on trading the usefulness of a substance with the necessity of protection.

While it may be developed by individual scientists and regulatory specialists, acceptance of the relevant conceptual underpinning for this work is usually very slow and obtained via authoritative national and international bodies. Test methods and audit systems ("Good Laboratory/Clinical/Manufacturing Practice guidelines") are also developed through authoritative international bodies. Of particular importance are the OECD (Organisation for Economic Cooperation and Development), the ICH (International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use), the EU Scientific Committees, and academic bodies such as the US National Academy of Sciences, the UK Royal Society, and the DFG (Deutsche Forschungsgemeinschaft). The regulation of different sectors may be a) by sector defined by end use: pharmaceuticals, veterinary medicines, medical devices, food (including additives and contaminants), animal feed, plant protection products, and biocides; b) by environmental compartment: water quality; indoor, outdoor, or workplace air quality; soil contamination; or c) reserve schemes for chemicals or radiation. These sectors can involve different agencies and the agencies may be largely independent of each other (Fig. 2). Here, more networking is required to allow for better harmonization.

Industry

Toxicologists and regulatory affairs specialists in industry have the responsibility to ensure that products placed on the market have a satisfactory risk/benefit ratio. This is of particular interest for quality conscious companies. Toxicologists in industry may commission contract research organizations (CROs) to undertake standard tests to protocols described by the authorities, or they may undertake testing "in house." Studies for regulatory purposes rely largely on internationally standardized protocols for determining the toxic potential of individual substances. These studies usually seek to identify pathological and clinical-chemical endpoints and a dose–response in

Authority	*Toxicological Responsibility*
US EPA/EU National Authorities (Environment Agencies)	toxicology of drinking water
EMEA (EU) /FDA (US)	pharmaceutical toxicology
Individual national or sub-national investigators (e.g. Police)	forensic toxicology
US Defense and Homeland Security/ EU National Defence and Interior Departments	toxicology of agents associated with warfare/terrorism
US OHSA/EU National bodies	workplace toxicology
US FDA and Dept Agric/ EU EFSA	food toxicology

Fig. 2 Examples of toxicology-associated agencies and fields

animals. Investigative studies using structure-activity relationships and/or in vitro methods may be conducted in order to better understand the potential toxicity. These results form the basis for the initial hazard assessment for a newly developed chemical. Exposure assessment is also conducted to see if there is a sufficient margin of exposure for the intended use. If specific risks have to be further clarified, additional experimental work related to, for example, toxicokinetics and mechanisms of action may be performed. Such nonstandard tests often require very specific methodologies and may be performed in cooperation with partners from universities or from contract research institutions. Where possible, the standardized regulatory testing is subjected to an audit process, Good Laboratory Practice, supervised by the relevant national authorities. The tests are conducted to standardized protocols, and the results evaluated using standard procedures. This is the main information source for the authorities, who make a regulatory decision about the registration and categorization of the compound.

Once a substance has been placed on the market, either for a specific use or more generally, there is a need for monitoring for unidentified toxic effects ("unknown unknowns"). For drugs this is called "pharmacovigilance." Through this process it is possible to check if the risk management procedures (either for the specific chemical or use or more generally) are adequate or, if not, to reassess and reevaluate the risks.

Universities and Other Basic Research Institutions

Toxicologists at universities and basic research mainly aim at understanding toxicological mechanisms at the cellular level. They often use investigation techniques which are not subject to standardization but provide new methodological approaches and scientific knowledge. In this context, they develop novel methods that are suited to better predict toxic effects. Epidemiologists and experts in exposure modelling and measurement also contribute to the sciences underpinning risk analysis. All of these specialists must encourage cooperation with neighboring scientific disciplines and networking with regional and national partners. They often act as experts in regulatory committees. Finally, they play a central role in the education of young academics.

When there is a need for risk-benefit analysis, there is a need to environmental economists. Integrating their role with that of the other participants in the risk (or risk-benefit) evaluation is still at an early stage, and there is therefore much scope for academic research in this field.

Of increasing importance is the need for an understanding of the psychological and sociological aspects of the process of risk analysis (risk assessment and risk management) and of how the public perceives risks. It is essential that the public (as a whole) has confidence in the regulators and a key need is an understanding of how public and regulatory understanding can be merged. Psychologists and sociologists working on aspects of risk perception offer insights into this process, and their contribution should not be disregarded.

Contract Research Organizations

CROs are often specialists in specific tests or evaluations, in which they are highly experienced. In these niches, they are likely to be more efficient and more economical than other institutions.

Advocacy (Lobbying)

Advocacy groups (such as Greenpeace, Friends of the Earth, anti-vivisectionists, trade associations) are essentially aimed at trying to persuade regulators, either directly or through persuading public opinion, that their views concerning issues should be preferred in place of those accepted by or about to be accepted by the regulator.

Expert Witness/Court and Public Enquiry Advisor Work

Generally this work is carried out by the individual rather than by a type of institution. The focus of this type of specialist is in defined problem fields, such as advising in litigation or in criminal prosecutions concerning causes of damage or in Public Enquiries into incidents/accidents. The expert witness prepares expert statements containing toxicity profiles set against information on specific incidents (and the requirements of the legislation) in order to indicate to the parties and, if it comes to Court, the Court the relevant facts and their implications. The Public enquiry expert advisor advises the presiding officer (usually a Judge) on the scientific facts and their implications for the enquiry.

Scientific Societies and Journals

The toxicological scientific societies are self-administered organizations of toxicologists from the different working areas. They have the main aim to promote

the toxicological sciences. Scientific questions concerning how toxic agents work are traditionally the main focus of these societies.

Risk is a statistical concept that relies on toxicological data to define the hazard on one hand and statistics (probability) to define the likelihood of the event occurring or of the exposure resulting in harm. Traditionally, scientists in universities and university-associated research units are research-oriented and not much interested in the principles and issues associated with the risk evaluation part of the regulatory process. These issues involve nonscientific aspects of risk (such as attitudes to risk and risk perception) and nonscientific aspects may prevail.

As a political process is involved, there is room for contributions from the social sciences (sociological and psychological aspects of risk, notably the influence of risk perception on risk evaluation). The ability to obtain a compromise may have a greater role in toxic risk regulation than scientific exactness. Hence the ability to influence regulatory decisions is becoming increasingly important as an activity in which chemical and toxicological societies participate. It also provides a platform for the participation of science in international regulatory spheres and sometimes opens the door to highly interesting new ideas for research.

So it is not surprising that many scientific societies are increasingly engaging in issues of regulatory toxicology at the national and international level. They provide a forum in which basic scientists, risk analysts, and toxicologists can freely exchange ideas, without the restrictions, which they might have within their institution.

As a consequence of the recognition of this wider role for experts in regulatory toxicology, risk assessment and risk evaluation are increasingly important parts of the training of toxicologists. This is being encouraged by the scientific societies. In parallel, articles on topics involving regulatory toxicology are increasingly found in the scientific journals. This trend has been early recognized and promoted by the "International Society of Regulatory Toxicology and Pharmacology" and its journal and the foundation and development of journals in the field of risk analysis that accept articles on toxicological aspects of risk analysis.

Chemical Properties

The chemist is usually most interested in the chemical properties of a substance and will therefore find it logical to classify toxic substances according to their chemical properties. Thus, one can distinguish between the regulation of inorganic chemicals (e.g., metal toxicology), organic chemicals (many industrial chemicals), and natural products (e.g., toxins, genetically engineered products – these are a subgroup of organic molecules, usually of high complexity). A more far-reaching differentiation can be based on functional groups (nitrosamine regulation) or the chemical backbone (dioxin regulation). Finally, it may be crucial for the toxicological assessment whether one deals with a pure substance or a mixture (combination effects such as inhibition or synergism) and whether these are dissolved or in particulate form (e.g., dust).

The effect researcher, who may typically be a biologist or physician, is more interested in biological and medical effects. He/she accordingly arranges groups of substances with the same effect, such as allergens, irritants, initiators, promoters, endocrine disruptors, cytochrome inductors, and neurotoxic or hepatotoxic substances.

The attention of toxicologists in the event of toxicological emergencies is focused on the harmful effects and the causing substances (e.g., dioxins after the accident at Seveso). The legal regulation then follows mainly the pattern of the regulated areas.

Regulated Areas and Legislature

It is not unusual that different levels of protection are defined for different purposes. The two principal criteria are the "broadly acceptable" criterion and the "intolerable" criterion. There may be a range of circumstances between these two criteria where a risk-benefit analysis indicates that a risk is "tolerable." Thus, for a pharmaceutical with a high positive effect (e.g., a "lifesaving" drug), it may be acceptable to take into account a certain level of unwanted effects that would be unacceptable for a treatment for a minor effect such as headache. This means that a risk-benefit analysis is applied. In the case of regulation of persistent environmental pollutants (e.g., dioxins) in the human body, one has to accept that it will take years before reduction measures, such as minimization of exposure, achieve visible success. These are circumstances where it might be appropriate to apply the "precautionary principle" and minimize exposure.

Regulations Concerning Marketing

When marketing a chemical there is a clearly identifiable supplier. Regulations are made according to the use to which the substance is put, with a reserve scheme for those chemicals and uses not subject to more specific legislation. Regulated uses include pharmaceuticals, cosmetics, biocides, flame retardants, food additives, industrial chemicals, radiochemicals, solvents, or chemical weapons. Regulations concerned with ambient media are more difficult to enforce as there may be no clearly identifiable source and/or they have no identifiable supplier. They are regulated by medium (air, water, soil) where it occurs.

Ambient Media

Among the regulated media are water, soil, ambient air, indoor air, workplace, food, consumer products, and human body fluids. The example of "water" can demonstrate, in how many subareas regulations of chemicals are effective: drinking water, mineral water, bottled water, water for baby food, water for injection, pool water, river water, bathing water, wastewater, surface water, groundwater, etc. A clear demarcation between regulated uses and regulated media is not always possible.

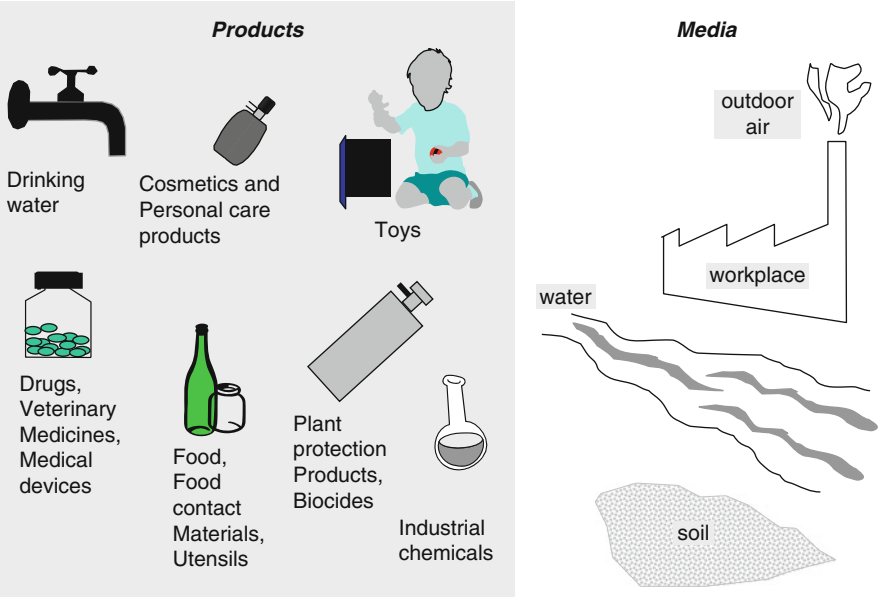

Fig. 3 Regulated products and media (examples)

Understanding Regulations

Often, there are detailed technical specifications, guidelines, and limit values associated with legislation and administrative measures associated with the control of toxic chemicals (Fig. 3). The relevant laws and regulations usually describe the levels of protection required and provide guidance on the technical rules and procedures that were applied in order to generate a guideline or a limit value. Knowledge about the background of the respective regulations and about the state of discussion among experts in the relevant area is a prerequisite for appropriate work by the regulatory toxicologists. Regulations are often updated in order to take into account new developments and insights to protect the population and environment. Much of this work is becoming international in nature. For an individual toxicologist, it is no longer possible to keep an overview of the entire width of all areas either nationally or internationally. Therefore, a division of labour is essential. But it is just as important to have an exchange between the fields and to encourage harmonization, provided that it does not impose a "drag" on the implementation of new procedures.

Alarm Systems

There are three types of risk: "known knowns" (identifiable and quantifiable risks), "known unknowns" (identifiable but unquantifiable risks), and "unknown unknowns" (risks that have not yet been identified). There are also accidents and failures to

adhere to risk reduction measures. Even a good regulation for the protection of workers, consumers, and the public and good management systems may not completely exclude the possibility of a toxicological accident or an unforeseen situation. This is, for example, the case, when an unforeseen rare immunological sensitivity is triggered by a compound in few individuals or when a substance is applied the wrong way. To detect such incidents, many countries have a monitoring requirement. For medicines, one such scheme is known as "pharmacovigilance," and physicians are expected to report suspicions of "side effects." The collected information is analyzed by toxicologists, who thus gain insight into the role of specific substances in incidents and can change the risk management measures (greater supervision, e.g., by restricting prescribers and outlets, improved regulation).

Working Methods

Based on toxicological data, the regulatory toxicologist considers the safety requirements for the particular use and then estimates under what conditions and to what extent the population, including pre-defined groups at extra risk, may be exposed to a substance, ideally without incurring any ill health. For this task, he/she requires special knowledge and experience in the interpretation of toxicological findings, the regulatory standards, the legal framework, and the implementation process. Specifically, in-depth knowledge of the common working methods, shown in the figure, is required (Fig. 4).

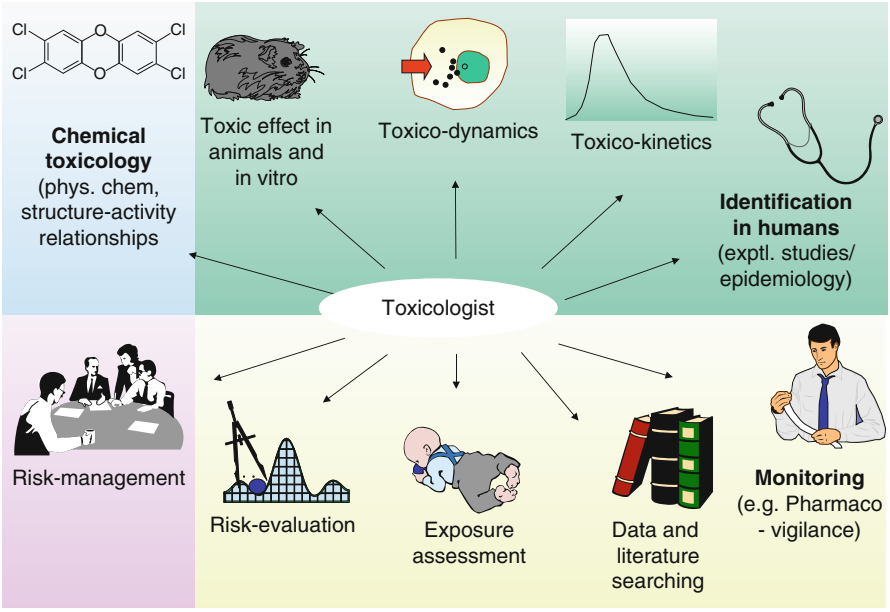

Fig. 4 Work areas in regulatory toxicology

In addition to that methodological experience, the regulatory toxicologist should have some technical creativity that helps to find acceptable solutions for unsolvable problems and should exhibit a high communicative competence. The latter is required, because the regulatory toxicologist must sometimes explain unpleasant findings or defend unpopular decisions in his institution or in public. In conflict situations, he must be able to defend the ethics of toxicology, explain safety standards, and discuss technical feasibility.

As in all professions, there is a hierarchy concerning the professional status of toxicologists. The experimental toxicologist can publish in esteemed journals and thus contribute to global knowledge and ensure its status among peers. The regulatory toxicologist will remain more anonymous, since his written work will normally be used by commissions, who will incorporate it in statements or in laws. This gives little scientific credit, but a great deal of satisfaction due to the practical importance of his/her work.

Recommended Reading

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