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Forum paper

Regulatory toxicology: objectives and tasks defined by the working group of the German society of experimental and clinical pharmacology and toxicology

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Abstract

Regulatory Toxicology encompasses the collection, processing and evaluation of epidemiological as well as experimental toxicology data to permit toxicologically based decisions directed towards the protection of health against harmful effects of chemical substances. Furthermore, Regulatory Toxicology supports the development of standard protocols and new testing methods in order to continuously improve the scientific basis for decision-making processes. The objective of the Working Group 'Regulatory Toxicology' within the Section of Toxicology of the 'German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT)', is the transparent discussion and further development of the scientific principles of Regulatory Toxicology. Present methodologies for risk assessment should be evaluated with the objective of finding harmonised standards. This objective is being achieved through informal meetings, symposia and written communications on both a national and as far as feasible international level. Principal target audiences are, in particular, members of the scientific community who work in government agencies, universities, and industry, as well as contract organisations and consulting institutions. Being experts in this field, they are expected to carry forward the outcomes of harmonisation processes related to testing methods and risk assessment. © 2002 Published by Elsevier Science Ireland Ltd.

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1. Current situation of regulatory toxicology

Regulatory Toxicology deals with concepts for risk assessment and management of substances with potentially toxic properties. An integral part of this field is the evaluation of risks with the

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objective of setting standards that would protect the public against potential risks of substances such as chemicals, biocides, food additives, cosmetics, pharmaceuticals, medicinal and genetically manufactured products. For this purpose, regulatory agencies generally use toxicological datasets predominantly arising from Industry, as well as experimental findings relevant for the evaluation of modes of action, that are often derived from scientific publications of university institutes. Agencies also define conditions for the conduct of toxicological studies.

Toxicological evaluations are often prepared by interdisciplinary groups of toxicological experts. Measures resulting therefrom comprise classification, labelling, regulations for use, restrictions as well as bans. The transformation of scientific evaluations into regulatory decisions such as recommendations, directives, regulations or laws may also involve non-scientific criteria. These may include considerations on legal feasibility, evaluation of technical solutions and costs, risk balancing, compatibility with existing laws and public perception. Transparency and acceptability may be hampered by the fact that national decisions, EU-regulations and existing international agreements are not always harmonised. However, efforts are being undertaken by the European Commission in the form of a EU-Technical Guidance Document (published October, 2000), as well as by the German Federal Institute for Radiation Protection, to establish harmonised risk-assessment procedures.

Many toxicologists introduce their scientific expertise into regulatory committees to ensure the protection of the public against harmful effects of toxic substances. Until recently, there was no specialised platform in Germany to discuss and develop new toxicological approaches, decision criteria and future concepts. In view of ongoing complex scientific developments, an interdisciplinary discussion among toxicologists of various sectors is ultimately required. For this very reason, the Section of Toxicology of the DGPT has founded a Working Group on Regulatory Toxicology with the aim of developing a unified concept in this complex field.

1.1. Working areas in regulatory toxicology

Working areas in Regulatory Toxicology can be grouped according to the institutions involved, the areas regulated or the methodologies applied. This results in a wide range of tasks for regulatory toxicologists.

1.1.1. Institutions

A clear sharing of tasks is evident for toxicologists working in different types of institutions. Characteristic profiles can be summarised as follows.

1.1.1.1. Regulatory agencies. Toxicologists in regulatory agencies give advice to Ministries and Governments at various levels. In particular, they are involved in the derivation and surveillance of standards. Using their toxicological expertise, they describe health risks, and define the margins of public health protection. They adapt their evaluations to the methodological progress in the field of Toxicology. This progress may be based upon the findings of their own research or by work subcontracted to Contract Research Organisations. The regulation of specific areas and public relations work is being undertaken by specialised authorities that work relatively independently of each other.

1.1.1.2. Industry. Industry toxicologists conduct studies using largely standardised methods for testing the toxic potential of individual substances. Dose–response relationships on pathological and clinical-chemical findings in animal tests and in vitro studies form the bases for evaluating the risk of newly developed compounds. Toxicokinetics and the mechanisms of action are being studied if special hazards need to be better understood. Standardised and well-accepted documentation and evaluation of the results serve as a basis for decisions made by regulatory agencies.

1.1.1.3. Universities and institutions for basic research. Toxicologists at universities or basic research institutions use experimental approaches which do not necessarily follow standardised protocols. The methods used are designed to investi-

gate mechanisms of action thereby improving the basis for risk assessments. In addition, they develop new methodologies that allow a better prediction of toxic actions. They also cooperate with related scientific disciplines as well as with national and international partners. Finally, they are playing a central role in the training of young toxicologists and are active experts in various regulatory committees. One should keep in mind that university representatives are also members of scientific committees and are taking part in essential decisions.

1.1.1.4. Contract research organisations and consulting institutions. Contract Research Organisations and Consulting Institutions work on various fields: advising in cases of incurred damage, development of concepts, data searches, elaboration of toxicological profiles of individual substances, information processing for regulatory agencies, and establishing expert reports. Contract Research Organisations are generally equipped with laboratory facilities. They conduct, on one hand, subcontracted toxicological tests for industry according to standardised methods, and, on the other hand, special studies in the field of applied research to improve the scientific basis of toxic effects.

1.2. Regulated areas

Toxicology is a science that aims at recognising, preventing and dealing with the damage of health due to exposure to chemical substances. In this context, depending upon the regulated area, various protective measures are defined and different criteria are applied. With substances that have a highly beneficial potential (e.g. drugs), a health-damaging potential can be tolerated to a certain extent, which would not have been accepted in other cases (risk–benefit equation).

1.3. Regulated groups of substances

These may include pharmaceuticals, industrial chemicals, cosmetics, pesticides, food additives, drinking water constituents, natural toxins, industrial and environmental chemicals, and others.

1.4. Fields of regulations

These may cover food, drinking water, consumer products, cosmetics, toys, the working place, environmental media (ambient air, indoor air, water, soil), feed, genetically modified products, etc.

1.5. Methods of work

Using toxicological data, and considering the safety requirements of the regulated field, regulatory toxicologists estimate under which conditions, and up to what level, the public—including populations at special risk—can be exposed to a particular substance without risk of any health damage. This requires specific knowledge and experience in the interpretation of toxicological findings, as well as profound knowledge of regulatory standards, the legal frameworks and the procedures for implementation. The following methods are characteristic elements in regulatory toxicology:

- conducting animal and in vitro experiments to examine acute and chronic toxicity, skin irritation, eye irritation, sensitisation, mutagenicity and carcinogenicity, as well as studies on fertility and teratogenicity. These studies apply standard protocols (experimental toxicology)
- evaluating human data
- examining and evaluating physical–chemical properties of chemical substances and their behaviour in human and animal bodies (toxicokinetics)
- developing methodologies to examine, in particular, modes and mechanisms of action (toxicodynamics)
- conducting specific evaluations using mathematical and statistical models
- examining available data with regard to their comprehensiveness, quality and value (data assessment)
- determining the type, extent and duration of human exposure
- applying adjustment and uncertainty factors to extrapolate appropriate data to the human situation (data evaluation)

- assessing and quantifying risk, its consequences and uncertainties in the estimates
- providing proposals for risk management (e.g. restrictions for use or exposure; classification and labelling) with adequate reasoning
- making recommendations for the generation, application and monitoring of rules, directives and laws.

2. Current questions in regulatory toxicology

2.1. Risk assessment

With respect to exploring mechanisms of action, toxicology has to be considered a precise science. In the field of Regulatory Toxicology risk assessments as such are conducted by using hypotheses, e.g. with regard to mathematical modelling, exposure levels and adversity of effects. Often, there is no adequate consensus on such approaches at the international or, in some instances, even at the national level. One of the aims of the Scientific Community should be to discuss harmonisation of standards and to find a common consensus.

2.1.1. Stages in risk assessment (the risk assessment paradigm)

The National Research Council (National Academy of Sciences) in the USA has divided risk assessment into the following separate steps which also refers to current EU-regulations: The description of toxic properties of a substance (hazard identification), the evaluation of effects as a function of dose (dose–response assessment and hazard characterisation), the estimation of levels of substances that interact with the target (exposure assessment), and the overall description of the risk (risk characterisation). The mechanism of action may provide crucial information for risk evaluation as well as to the degree of uncertainty factors to be applied. In the case of common environmental exposures, the exposure assessment process is accompanied by a number of uncertainties since multiple sources of various influence are very often involved. Especially in the field of environmental and consumer protection there is an ultimate need for improving realistic exposure assessment approaches and for the validation of exposure scenarios. For example, it would be useful to study the contribution of probabilistic exposure models to a practicable quantification of risk.

2.1.2. Uncertainty factors

Estimating the risk for humans on the basis of results of animal experiments depends on various types of extrapolations: (a) from high experimental doses to low doses; (b) from animal to human; (c) from an 'average human' to the individual; and (d) from short term to long term exposure duration. The better the mechanism of action is elucidated the more precisely uncertainty factors can be defined. Some institutions differentiate between uncertainty factors that cannot be derived by experimentation, which is the case for data gaps or especially serious effects such as cancer, and extrapolation factors that are quantitatively supported from empirical data.

2.1.3. Risk/safety assessment

There is a need to discuss the difference between safety assessment and risk assessment. Safety assessment aims at precaution. The goal is to establish exposure standard and limit values. Starting from a NOAEL/LOAEL (no/lowest observed adverse effect level) or from a benchmark dose (lower 95th confidence limit of an extrapolated risk value, corresponding to a definite acceptable risk, generally 5% incidence), and considering variability and all uncertainties, a guidance value for exposure considered not to be associated with health risks is being established. Risk assessment, in contrast, is generally performed in context with higher exposures. To do so, the exposure level is compared with the dose–response curve, and the actual risk level (incidence of adverse effect) is determined.

2.1.4. The concepts of limit values and margin of safety

Two concepts of risk assessment are currently being discussed alternatively in Regulatory Toxicology, i.e. the 'classical' limit/guidance value concept and the concept of Margin of Safety (MOS).

In the case of the limit/guidance value concept, the experimentally derived NO(A)EL or LO(A)EL is divided by safety/uncertainty factors. In this manner, health-based acceptable/tolerable levels (ADIs/TDIs) for humans are calculated. The MOS concept, in contrast, is not based on the mere determination of probable non-toxic and hence tolerable quantities but is rather based on the estimation and evaluation of the margin between the experimental dose still showing toxic effects and the assumed or measured concentration in the environment which humans are exposed to. This difference is defined as the MOS. In both cases, the evaluation requires toxicological expertise and considers factors such as the severity of a potential damage, the slope of the dose–response curve, the degree of inter- and intraspecies variability in the kinetics and dynamics of the substance concerned, as well as special groups at risk. The outcome of a MOS evaluation is either that there is no reason for concern, or that there is. In the latter case, the conclusion is either to submit additional studies to clarify the open questions, or that there is need to reduce exposure.

2.1.5. The threshold concept for carcinogens

The validity of the current concept for evaluating the irreversible toxic effects of mutagenicity and carcinogenicity is being questioned. This concept assumes that any dose, even if it is very low, might exert health effects in the case of genotoxic carcinogens. In contrast for non-genotoxic carcinogens ('epigenetic carcinogens') the determination of a threshold exerting no adverse effect is applicable and well accepted.

The more knowledge that accumulates about relevant mechanisms triggering mutagenic and carcinogenic effects in a dose dependent manner, the more it becomes evident that, for some substances, a biologically justified threshold may be defined even in the case of genotoxic carcinogens.

2.2. Harmonisation

Different approaches for risk assessment are being applied in different regulatory bodies leading to partly divergent results. Therefore, efforts are currently being undertaken to harmonise standards for evaluation. One major aim is that schemes for the evaluation of health effects are clearly explained and that their application is being understood throughout the whole process, preferably at the international level.

2.2.1. Formal procedures for standard-setting

In terms of setting standards, it is important to distinguish between risk assessment (science-based toxicological evaluation) and risk management (conversion taking into account legal criteria, utility considerations and cost–benefit analysis). The German Council of Experts for Environmental Issues made some detailed proposals in its environmental expert report in 1996 to enhance transparency in setting environmental standards that could provide guidance. The key point is a multiple step schematic approach that involves all potentially affected groups of society. The steps consist of the definition of objects to be protected, the aims of protection, data collection for a situation analysis, scientifically based standard proposals, determination of technically feasible risk reductions, cost–benefit analysis, discussion phase, decision-making phase, controls and implementation. Many steps thereof are subject to a feedback mechanism.

2.3. Access to information

In view of the availability of many national and international data bases, efforts are being undertaken to further improve data search possibilities through promotion of unified structures, improvement of human toxicology data, and quality assurance. In addition, regulatory agencies and, in part, universities expect industry to

- provide access or publish data of toxicological testing (cf. 'Freedom of Information Act' in the US)
- increasingly offer the possibility for training of external colleagues
- disclose methods for the industry-internal derivation of toxicological endpoints.

Industry expects standard-setting institutions to promote:

- the application of harmonised classification procedures
- the adherence to quality criteria for experiments (e.g. GLP conformity) and publications to avoid misinformation.

2.4. Validation of test methods

New experimental test methods are increasingly needed and are becoming available within the course of efforts to reduce, refine and replace animal experiments by in vitro methods, and through biological–analytical developments especially in the fields of molecular and cell biology. Novel in vivo and in vitro methods are partly being used without adequate validation. The results are, therefore, often difficult to interpret in an unequivocal manner. It is important for new experimental methods to be validated before being internationally accepted for regulatory purposes.

3. Tasks and objectives of the working group

The tasks of the Working Group are resulting from actual issues described above and from submitted proposals of members of the group.

3.1. Creation of a discussion forum across sectors

The Working Group aims at creating a forum to discuss toxicological and regulatory questions among DGPT members from regulatory agencies, academia, industry and consulting institutions. This allows an understanding of each other's point of view outside of the regulatory decision-making process, and subsequently, the development of a common approach to increase efficiency. Such contacts have also the potential to promote professional convergence at the national and international level.

3.2. Promotion of interdisciplinary cooperation and contacts

Regulatory Toxicology is not an independent scientific discipline, but rather a conceptual framework to organise relevant information from various disciplines. Besides experimental Toxicology, other disciplines such as Pathology, Epidemiology, Analytical Chemistry and Biomathematics ('modelling') play an important role. Concerning risk communication, the important questions are the acceptability of risk and, consequently, risk acceptance by the public. In all these areas, there is a need to promote interdisciplinary collaboration. Since regulatory processes are often taking place at an international level, the Working Group should promote the strengthening of international contacts and the exchange of information between countries.

3.3. Early and adequate consideration of new methods

3.3.1. Timely discussion of new methods

New methods that would potentially be of benefit for toxicology can only be adequately discussed and developed in a dynamic environment. Herein lies a major task for the Working Group.

3.3.2. Validation of new test methods prior to their introduction

In light of the many existing in vitro methods it is important for toxicologists to maintain a view for the organism as a whole. It is inevitable, however, to establish more alternative methods to replace animal experiments. New tests must be sufficiently validated and accepted (e.g. in international ring studies) before they are introduced into regulatory processes. This would ensure that no differences in assessment exist between industry and regulatory agencies, or among regulatory agencies, respectively. New methods in molecular toxicology and the chip techniques are capable of identifying modifications of the genome, but they cannot differentiate between wanted (cytostatic drugs for instance), unwanted or unimportant effects. Developing methods should be discussed in this framework by the Working Group on Regulatory Toxicology. Overall, the development of adequate systems and strategies for the improvement of toxicity testing should be promoted.

3.3.3. Use of knowledge on the mechanism of action for risk assessment purposes

The more that is known about the toxic mechanism of action of a substance, the more precisely substance-mediated potential risks may be assessed. It is important, therefore, to promote both basic and applied research in this field. One aim should be to ensure that the results are equally judged and evaluated in different regulatory fields with regard to their utility and conclusions.

3.4. Development of scientific principles of risk assessment

3.4.1. New approaches for non-threshold effects and effects on fertility

In view of spontaneous DNA damage and the efficiency of cellular DNA repair mechanisms, the concept of 'non-threshold' needs to be re-evaluated. The risk assessment of non-threshold compounds (i.e. genotoxic carcinogens) requires new approaches. Similarly, a discussion on methodologies for risk assessment and limit value determination for effects on fertility and organ development on the basis of practical examples is needed.

3.4.2. Justification of uncertainty/safety factors

Safety/uncertainty factors for extrapolation of experimental results obtained in animals to humans are not always explained in a transparent manner. Therefore, they are often disputed. For this reason, the scientific basis for the derivation of numeric values of uncertainty factors needs to be improved. Probabilistic models should be further developed insofar as they are suitable for the derivation of a realistic overall factor from individual uncertainty factors. For this purpose, there is a need for a large amount of substance-related information.

3.5. Professional harmonisation of risk assessment among regulatory agencies

Many committees deal with the same substances from various viewpoints and with regard to different protection goals (workplace, consumer protection, indoor environment, human biomonitoring, etc.). As a result, environmental standards are derived largely in an uncoordinated manner. Harmonisation in this context aims at unifying and increasing the transparency in the methods forming the bases for an evaluation process. In this context, decisions concerning the following parameters play a role:

- adverse versus non-adverse effects (at times, an adverse effect can become beneficial depending on what one is trying to accomplish; and this is dependent on the endpoint chosen)
- threshold for genotoxic substances
- type of extrapolation (unit risk model, benchmark approach, etc.)
- numeric values for uncertainty/safety and extrapolation/adjustment factors
- probabilistic models versus worst case scenarios
- MOS approach versus the ADI concept.

The success of harmonisation can finally be judged by considering whether or not the risk assessment is based on a qualified data evaluation, and if similar assumptions were made for the same substances under comparable conditions throughout the whole evaluation procedure.

3.5.1. Improvement of access to available data

Toxicological databases play an important role as sources of information for risk assessment. Nowadays, a large number of extensive national and international databases are available. It is desirable to systematically unify and expand them according to quality criteria, particularly with a view towards a stronger consideration of observations in humans. Suggestions in this matter could come from the Working Group.

Although Industry is in possession of most toxicological data, they are, if at all, difficult to access. As a consequence, risk assessment by regulatory agencies is being seriously hampered. In addition, the difficulty in accessing existing data creates suspicion about what it may reveal. There is a need to establish conditions under which Industry can provide their data and evaluations openly without suffering any competitive disadvantages.

3.5.2. Harmonisation of toxicological terminology

Many terms have different meanings in different scientific disciplines. For example, the term 'limit value' is reserved for legally binding values by some experts, but is being more widely used by others, encompassing both guidance values and standards or even 'threshold limit'. There are also terms in English that do not have a unique German translation (e.g. risk assessment/safety assessment), as well as German and international abbreviations that can be interpreted in different ways. The German terminology needs to be unified and made compatible with the English terminology.

3.5.3. Promotion of knowledge in risk perception and communication

Regulatory Toxicologists must often explain possible risks and dangers emerging from the use and application of chemicals to both the public and politicians. At this juncture, a toxicologist needs to be aware of risk perception (is the magnitude of risk correctly estimated?) and risk communication (e.g. how to successfully conduct a controversial discussion about risks?). The Working Group should promote the knowledge about communication techniques among interested toxicologists.

3.5.4. Participation in the elaboration of quality criteria for scientific studies and publications

The Commission for Self Control in Science of the German Research Foundation (DFG) recommends scientific professional societies to set standards for good scientific practice and publications in their respective areas of work. These should be made publicly known, and society members should commit themselves to these rules. Such quality criteria are of particular importance in Regulatory Toxicology. Most often single results that do not fulfil the usual quality criteria necessitate the conduction of large experimental studies, only to prove the invalidity of eventually marginal or irreproducible effects. This contradicts good scientific practice and the principles of animal welfare. At this point, the Working Group itself could propagate that Good Laboratory Praxis (GLP) and Quality Assurance are a basis for a transparent documentation of studies. The Working Group should serve as a good example in doing so.

3.5.5. Professional quality assurance in standardised methodologies

The scientific basis for regulations is different in various fields and in different countries. There is a need to improve the bases for unified approaches in the following areas:

- standardised labelling of products
- international harmonisation of evaluation/judgment criteria and testing methods
- regular adaptation to the technical progress.

3.6. Better representation of regulatory toxicology

3.6.1. Preparation of a monograph on regulatory toxicology

A need to improve the level of knowledge in Regulatory Toxicology is perceived. In this context, it would be desirable to be able to have access to a didactically sound German version of a monograph on 'Regulatory Toxicology'. So far, existing representation of this subject occurs only in a fragmentary manner in textbooks of toxicology as well as monographs in English and review articles. Interested specialists should be asked as to their willingness to contribute in the preparation of such a monograph.

3.6.2. Stronger presence in scientific journals

Most often results of work related to Regulatory Toxicology are either not published or published only as 'grey literature', accessible only to a few. To enhance transparency, and to better reach the public, those concerned should place more value on publishing in the peer reviewed scientific journals. This needs to be supported by the institutions, supported by the journals, and recognised by experts. The Working Group will address this issue.

3.6.3. Stronger participation in meetings

More presentations (posters, oral presentations) on Regulatory Toxicology, given especially by colleagues from regulatory agencies and industry, would make the methodology and the results of

this professional area more transparent within the DGPT.

3.6.4. Events for (continuing) education; work on public relations

Besides professional toxicologists, other professional groups such as physicians, judges, lawyers, journalists are concerned with questions relating to Regulatory Toxicology. Therefore, it would be strongly desirable to hold more informative meetings to convey the views of Regulatory Toxicology. Corresponding initiatives should be supported by the Working Group.

3.7. Ways of implementation

Of course, all envisaged tasks listed above cannot be achieved by the Working Group on Regulatory Toxicology on its own. Well-aimed activities triggered by the Working Group may serve, however, as the necessary driving force. To do so, it would be of ultimate importance for Toxicologists from Regulatory Agencies, Industry, University and Consulting Institutions to subordinate eventual partial interests to overall scientific and professional interests.

4. The development of this text

This contribution arose from intensive discussions within the study group 'Regulatory Toxicology', under inclusion of contributions and suggestions from toxicologists such as Dieter, Heidrun Greim, Gundert-Remy, Heinemeyer, Hillesheim, Hofmann, Konietzka, Koss, Kramer, Lilienblum, Lutz, Oesch, Ott, Otter, Ruthsatz, Schneider, Singer, Spielmann, Stalder, Werner, Wolf, Younes and many unnamed toxicologists. It was compiled and translated by the authors, who thank all the contributors.