The Regulatory Process in Toxicology

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Abstract

The regulation to avoid or reduce potential health and *environmental risks* due to chemicals or physical factors in Germany, the European Union, and worldwide carries extremely heterogeneous features. Fundamental differences are encountered not only with regard to institutional responsibilities but also – and in particular – to nomenclature(s); definition of aims of protection; types of organization; scientific basis and extent of justification, implementation, and controls; as well as the legal status. The situation is even more complicated by interfering mandates. The system suffers from a crisis of credibility. However, recent efforts toward harmonization gain pace.

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Keywords

Banning · Commission of experts · Nomenclatures for limit values · Participation · Proctecive procedures · Restriction · Scientific evaluation · Threshold Limit Values · Transparency

Possibilities of Regulation

On principle, there are four organizational types of regulation: *banning of production, sale, and uses of toxic materials*; *restrictions on use*; *mandatory use of protective procedures to avoid/reduce hazardous exposure(s)*; and the introduction of *health-based environmental threshold limit values*. Banning of production is only realized for materials with very high hazard potential. As voluntary *withdrawals from the market* by producers, bans regarding production or import (e.g., 2-naphthylamine, PCBs, pentachlorophenol) may be reduced in their effectiveness by imports due to globalization and removal of trade barriers. Bans are also excluded in case of materials which cannot be waived due to technical reasons, are formed by transformation processes in the environment, or have natural sources (such as heavy metals). In these situations, more and more preference has been given to the development and introduction of *alternative compounds* which are designed to avoid undesirable properties such as high stability in the environment. While intelligently designed alternatives may have significant advantages such as reduced potential for specific toxicities, complete toxicological data and experience from practical use of such alternatives are often not available; thus, other potential risks may be present. Another domain is *restrictions in practical applications* – a field of activities more for administrators than for toxicologists. *Protective measures* in loco (exposure prevention by personal protective equipment or using closed processes) are mostly dealt with by specialists in occupational toxicology. The most important protective instrument is the establishment and application of *threshold limit values (TLVs).* They constitute the most frequently used method of health-based protection. Therefore, the following description will focus on such limit values.

Threshold Limit Values (TLV)

Threshold limit values (and environmental standards) are maximum permissible concentrations of chemicals (and physical stressors such as electromagnetic radiation) in specified environmental compartments, in specific tissues of organisms, or in excretion products. They are presented in the form of definitive figures, expressed as mass/volume, mass/mass, volume/volume, or doses in the form of mass/time. In case of *physical stressors* (radiation, noise, heat, pressure), physical quantities are valid accordingly. Such *official limit values* are established in laws, enactments, or regulations. They are either to be adhered to or function as recommendations. *Nonofficial limit values* are established by private institutions in the form of recommendations,

which may or may not be taken over in legal technical rules (e.g., *MAK values*) (DFG = German Research Association, VDI = Professional Organization of Engineers, DIN = Administration for Technical Norms).

Stock-Taking

According to a systematic analysis performed by the Expert Council for Environmental Questions in Germany, there are more than 150 types of limit values in Germany alone. Chronologically, these were first developed for pharmaceuticals. The first dose limit for a pharmaceutical was introduced by the official German Pharmacopoeia (second edition in 1882) in the form of a maximum single or daily dose. The first limit values for workplace exposures to chemicals were introduced in 1886 (K.B. Lehmann). The numbers of limit values for chemicals in occupational or environmental settings were steadily increasing since 1960 with an exponential tendency, often enforced by increasing public pressure. More recently, ca. 20% of the derived limits each account for victuals and soil, ca. 10% each for air and water, and less than 10% each for chemicals, noise, and radioactivity. Human health is the predominant aim for the protective measures and presents 93%, followed by general protection of environment (19%), plants (16%), and animals (14%) (in part repetitive counting). Regarding the legal status, 50% each are introduced as official and nonofficial standards. At least 30 different nomenclatures are in use (see Table 1).

The authorization for the organization of work to be performed to justify a derived value varies widely, from multidisciplinary recruited commissions or committees, down to the desk of a single clerk of an agency. This confusing complexity is, in its major proportion, due to the historical development: different academic disciplines picked up, mostly incidentally, a problem and made use of their

Table 1 Designations of threshold values as used in 154 German systems of regulation of hazardous materials (according to SRU = Council of Experts of Environmental questions, 1996)

Environmental values	Unhesitating values
Tolerance values	Maximum values
Maximum tolerance values	Precarium values
Scrutiny values	Background values
Encumbrance values	Input values
Hazard suspicion values	Target values
Interference values	Acceptance values
Intervention values	Adjusting values
Action values	Coordination values
Occasion values	Damaging values
Restoration values	Threshold values
Alarm values	Preliminary values
Release values	Hesitation values
Release threshold	Environmental standards
Orientation values	Toxicity values
Scruple values	

categories of reasoning and evaluation, thus paving the way for a great variety of experience and competence. Since approximately two decades, increasing criticism of status and further development is arising, mainly driven by the interest of industry and jurisdiction to achieve reliability for planning and legal status. The lack of clear-cut targeting and rules of procedure induced activities to improve harmonization, standardization, and simplification. As a result, useful and intentionally calibrated criteria have been elaborated (SRU = Council of Environmental Questions 1996); a new commission for risk evaluation has been charged with establishing and handling uniform rules.

Profiles of Demand

Regulatory processes are understood as political decisions – ideally in the form of consensus – based on scientific assessment of potential risks, under adequate participation of societal groups. The substantial elements of demand are:

1. *Participation of the public* before and in the course of procedures
2. *Complete transparency of all steps of procedure*, e.g., publish intentions and timing
3. An essential element of transparency is to be seen in the obligation of a detailed *justification* of
4. *All scientific evaluations and proposals for regulations and decisions* in the form of detailed documents which should be available to everybody
5. Concerned *societal groups should be involved* in the discussions for the preparations of decisions
6. Accomplished decisions, particularly regarding the level of a standard, need to be enforced by validated analytical methodology to warrant *compliance*

A new element has been introduced later: obligation of *continuous reevaluation in predetermined intervals*, taking into consideration new scientific data and eventually changes in sociopolitical principles.

Procedural Steps

The profiles of demand require the integrated cooperation of expertise of different scientific domains, making the process of regulation a multidisciplinary task. The evaluations to be performed require working elements of different groups of experts. This necessitates a *sequential procedure* of defined steps, which allows for recourses from one step to each other. A model of sequential steps is presented in Fig. 1.

The process starts with the determination of *objects of protection* (targets) (human beings, plants, soil, etc.) and with *aims of protection* (e.g., complete elimination or gradual reduction of risk). Right and duty of making proposals is not restricted to governmental institutions but open to everybody. The decision about the aim(s) of

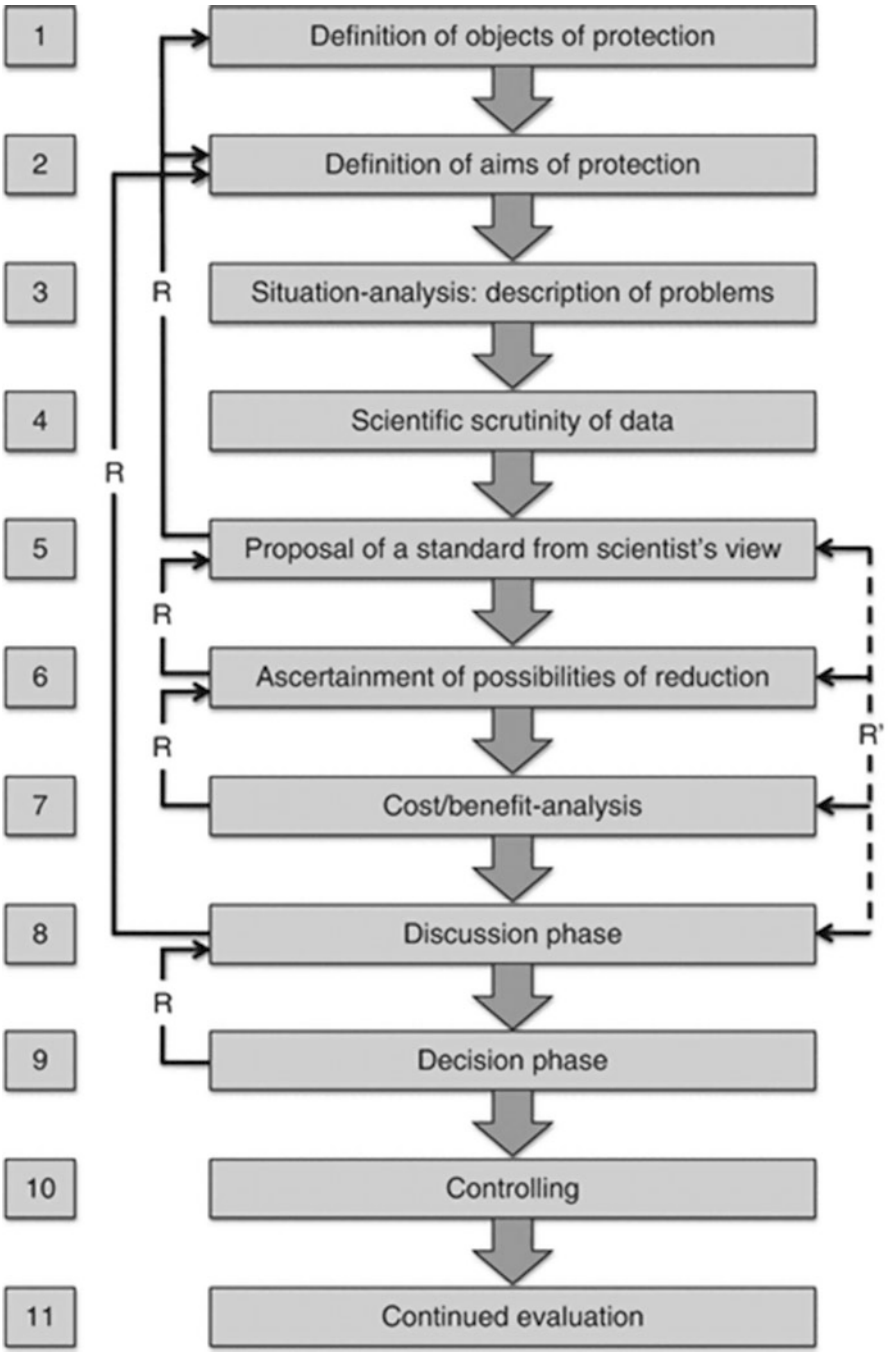

Fig. 1 Scheme of sequential progress in the form of an ideal model of steps in the regulatory process (R, R′ = checkback; SRU 1996)

protection is bound to the duty of detailed justification. This is followed by a *scientific analysis*, including a risk evaluation mostly based on published data on toxicological information or results of targeted toxicity test. Normally, a *proposal for a standard* is elaborated by the group of scientists who evaluated the data as a result of the critical evaluation of all data for which a detailed justification is mandatory, including the identification of gaps of knowledge. This step is followed by the ascertainment of *possible technical reduction of risk(s)* (often called "status of technology"), as well as the elaboration of a *benefit/risk analysis* and a *cost analysis*, both steps involving experts in engineering and economy. Again, these proposals have to be justified in detail.

After these basic steps have been accomplished, a *discussion phase* tries to set a starting point for a solution, may be in the form of several alternatives. Participants are societal groups (producers, users, employers); for checkback questions, scientists who participated in the foregoing steps should be available. The guidance of the discussions should be handled by those responsible for the (final) decision-making (governmental and/or nongovernmental). They should prepare, in the following *decision phase*, the finalized version of the standard proposal, including the detailed justification, and put through the final decision. The same group of participating experts shall also prepare the operational steps of *control of compliance* to the standard and for a *continued reevaluation* in predetermined intervals, taking into account new developments in data production and interpretation. For this purpose, a new standard necessitates the provision of suitable analytical methodology according to internationally accepted rules.

Historic Developments

The classical form of organization of the process of regulation is the *commission of experts.* This has a long tradition in Germany, particularly by the DFG (German Research Association) who, according to their statutes, provides recommendations for health-related issues. Since 1952, DFG has established so-called Senate Commissions in different domains of regulations (occupational toxicants preparing MAK values = maximum tolerable concentrations, plant-protecting chemicals, foodstuffs, cancer research, etc.). The MAK Commission has held a pilot function for many other commissions. For ambient air pollution regulations, numerous commissions have been established and are still active in the VDI (Union of German Engineers). In addition, governmental agencies – from federal down to community level – have established their own committees for giving advice in environmental problems or setting standards of their own. Some are working permanently, some ad hoc only; the latter ones suffer, in some cases, from a lack of consistency and continuity.

Membership in these commissions of scientists in general, and of toxicologists in particular, should be based on independency in their professional activities and reasoning. There is a legal basis for proving the evidence of independency in the form of official rules of administration: new members of a commission have to declare by signature that they do not hold contracts with industry, share holding

included. In this context, there remains an open issue of membership of professionals in industry: on the one hand, they may contribute a high amount of special knowledge and competence, and they may contribute to the process by submitting valuable data (sometimes unpublished) and by specific experience. One way out of this conflicting situation may be seen in having them participate by seat but not by vote. But this certainly is not satisfactory to everybody. The agencies should create clear regulations referring to this sensitive point, now and forever.

Finally, there remains one important question to be solved: Who should participate in which sector of the regulatory process and who should take which part of responsibility? Two models are in operation: (1) Unitarian, every member of the commission participates in all steps of the procedure, participates in voting, and thus carries full responsibility. (2) Separatistic, the activities in the scientific analysis, discussion, and decision are strictly separated from each other, which means everybody participates just in that sector where he/she is professionally competent and thus takes responsibility just in that part. The separation shall avoid influences upon the scientific evaluation and decision by members of interested societal groups. Further development indicates preference of the separatistic model. However, the lawmakers in Germany have not yet taken decision toward a clear and comprehensive regulation of this issue.

Types of Organization

Similar processes as those described above for Germany have been developed on the level of the European Union and internationally. However, within the different legislative contexts, the involvement of scientific expert committees varies between the sole responsibility of the advisory group regarding limit values developed to an advisory role after the value has been defined by a regulatory authority.

For example, panels of the *European Food Safety Authority* (*EFSA*) and Scientific Committees of the European Commission with specific legislative mandates develop tolerable limits for food additives, food contact materials, food contaminants, or cosmetic ingredients based on scientific principles for health risk assessment and carry the sole responsibility for the process. In contrast, in the Registration, Evaluation, Authorization of Chemicals (REACH) process, the manufacturer or importer of a chemical (registrant) is responsible for performing risk assessment and for developing tolerable exposure following specific and detailed guidance outlined in REACH regulations. The Agency (ECHA – European Chemicals Agency) interacts with the registrant and can require specific information to address issues identified in the derived exposures and potential uncertainties in the evaluation. However, due to resource constraints, it is expected that only a limited number of the submitted registration dossiers will be evaluated in great detail.

In addition, a significant role of scientists employed by regulatory agencies (governments) in risk assessment is also frequently observed. In many cases, scientific advisory boards have the role to provide comments to the developed documents regarding risk assessment. For example, in the United States, many

regulatory decision documents regarding chemical safety are drafted by regulatory agencies, and conclusions are presented to a scientific advisory board and the general public requesting comments on the conclusions.

Cross-References

- ▶ Hygienic Versus Toxicological Approaches in Regulation
- ▶ Limit Value Setting in Different Regulatory Areas of Toxicology
- ▶ National and International Collaboration in Regulatory Toxicology
- ▶ Prohibition and Restrictions in Regulatory Toxicology

References

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Recommended Reading

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