

SCIENCE FOR A SAFE CHEMICAL ENVIRONMENT is an interim report from the [NewS](#) research programme (A new strategy for risk assessment and management of chemicals), financed by [Mistra](#). Below is an excerpt from the abovementioned book. The excerpt consists of the preface (including an overview of the book content), and chapter one, containing a discussion on validation of test systems.

A copy of the book can be ordered by sending a request by email to [Christina Rudén](#).

SCIENCE FOR A SAFE CHEMICAL ENVIRONMENT

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Preface

Traditionally, scientific involvement in the regulation of chemicals has focused on the interpretation of toxicological and ecotoxicological data and the derivation of dose-response relationships. Sophisticated dose-response models have been constructed for different endpoints and toxicological mechanisms. This is an important and fascinating development, but there is a hitch in its application.

The hitch is that there are only a couple of hundred substances for which enough toxicological data are available for meaningful application of such sophisticated tools of risk assessment. It has been estimated that between 30 000 and 70 000 chemical substances are commercially available on the Euro-pean market. For most of these, little or no toxicological or eco-toxicological data are available to the scientific community. With no data, no science-based risk assessment is possible. From the regulator's perspective, the crucial problem in chemicals regulation is how to deal with this massive lack of

information. Clearly, we cannot fill this enormous knowledge gap in one piece.

Therefore, a strategy is needed to cope with the lack of data. More testing is needed, but which tests and which substances should be given the highest priority? Can we make meaningful preliminary assessments on simple initial tests or perhaps even on the chemical properties of a compound? Can safety margins compensate for lack of data? How should an efficient test system be constructed, and how can a science-based test strategy combine efficiency with a precautionary approach?

These are the issues at focus in the NewS research programme (A New Strategy for Risk Assessment and Management of Chemicals). In NewS, toxicologists, ecotoxicologists, chemists, decision theorists, statisticians, and political scientists combine their forces to attack the problems connected with the many untested chemicals, rather than with the few reasonably well-tested substances. Our aim is to develop new methods and strategies for testing that can be used by regulators and the industry.

In 1999, when the NewS programme started, this perspective on chemical risk assessment was rather unusual. That has changed during the first six years of the programme. The European Union is now finalizing a new legislative system for chemicals control, the REACH system, that aims at substantially increasing the knowledge base for chemicals risk management. When the NewS programme started, there was no legal framework in which our proposals could be realized. Now REACH provides such a framework.

Our previous yearbook, *BETTER CHEMICALS CONTROL WITHIN REACH*, focused on how results from NewS can be implemented in the new European legislation. In the present book, some of the researchers of the programme give their views of how scientific research can contribute to improved risk assessment and risk management of chemicals.

In chapter 1 some general principles for the use of scientific data and science-based testing strategies for regulatory purposes are outlined (Rudén and Hansson).

In chapter 2 the selection of endpoints and organisms to be used in environmental risk assessment to meet the objectives of REACH is discussed. The vital importance of continuing to develop test methods and testing strategies that include scientifically well-based combinations of test methods, species, and endpoints is emphasized. In this chapter ten fundamental aspects to take into account in order to improve environmental risk assessment are pointed out (Breitholtz, Rudén and Bengtsson).

In chapter 3 a tiered test system for assessing adrenocortical toxicity is proposed. The authors argue that many compounds may need to be tested with respect to adrenocortical toxicity bearing in mind the great number of metabolizing enzymes that are active in this organ (Asp, Hermansson, and Brandt).

Fish tests are an important component of screening and testing strategies for endocrine disruption due to the ecological relevance of these species, as well as the similarities between fish and other mammals. In chapter 4 a tiered test strategy for predicting the ecological risk of endocrine disrupting compounds to fish populations is presented (Norrgrén and Förlin).

In chapter 5, the evaluation of adverse developmental effects in mammals is discussed, and the importance to consider the interspecies differences with respect to the dose, the time of administration of the chemical, and the need to adjust the dosing regimen to relevant biological parameters, such as sensitive life-stages (in this case the defined period of the brain growth spurt) is highlighted (Eriksson and Viberg).

Chapter 6 focuses on the importance of performing systematic evaluations of the actual performance of risk assessment and management. It also provides an overview of methodologies that can be used for this purpose (Rudén and Hansson).

Chapter 7 constitutes a first attempt to describe the possibility of bias in experimental toxicology in a systematic way. This includes the identification of areas of toxicological testing and research that may be at risk of bias. Some suggestions are provided on what measures might be taken in order to diminish that risk (Wandall).

In the last chapter (8) the role of expertise in chemicals control is discussed. In the European Community there is a strong conviction that the independent scientific community should play a more vigorous role in policy-making. But do we really want to give more powers to experts beyond the control of elected assemblies, or do we want experts producing 'truths' that are only acceptable if they pass the test of current public opinion and the views of stakeholders involved? It is argued that the contentious issues regarding the health, safety and welfare of European citizens and the environment need to be informed by science, but settled by decision-makers who must face the scrutiny of the people (Persson).

One important conclusion that can be drawn from these presentations is that the development of simplified tests to be used on a large number of chemicals requires even more in-depth knowledge about toxicological and ecotoxicological mechanisms than what was required for the assessments of fewer substances that could be more extensively tested.

The innovative potential of academic research is indispensable for the development of more efficient and more proactive test systems. Equally indispensable is a dialogue between academics, regulators, industry, interest groups, and the public. We hope for responses and suggestion that can be used in the last two years of this eight-year research programme.

Stockholm March 7, 2005

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1. Science-based test systems

Christina Rudén and Sven Ove Hansson

In regulatory applications, toxicological tests are combined into test systems. A test system contains several tests, and it also contains rules for when and in what order the different tests should be applied. Most test systems are tiered, which means that initial tests are used to determine the need for further testing, often in several stages. Different substances will take different paths in the test system, depending on the outcomes obtained in the tests to which they are successively subjected. Examples of such test systems are the regulatory testing requirements for pharmaceuticals, that are divided into several consecutive steps, and the rather extensive test batteries required for pre-marketing risk assessment of pesticides.

In the existing EU legislation a fairly extensive test battery is required for notification of “new” substances. Each year about 250-300 chemicals are tested and notified according to this legislation, and so far they represent a relatively small group of about 3000 chemicals (see: ecb.jrc.it). On the other hand, there are effectively no testing requirements for the about 100 000 compounds currently regulated as “existing” substances.

In REACH, new and existing industrial chemicals (i.e. the about 30 000 substances produced in over 1 tonne per year per manufacturer) will be regulated in a single system. The implementation of REACH will thereby eliminate the previous large differences in test requirements between “new” and “existing” substances. The demands in this new system thus differ significantly compared to those currently in force, since it needs to handle testing requirements for a sizeable number of previously largely untested substances. In order to fulfil the major objectives of REACH, a scientifically justified *and* resource efficient process for testing (and risk assessment) thus needs to be developed. This includes the availability of reliable and scientifically relevant test methods, as well as the combination of such tests into science-based test systems.

Validation of test systems

The tests included in current regulatory test systems are all carefully constructed according to scientific principles. However, for a *test system* to be science-based, it is not sufficient that each individual test is scientifically justified. In addition, the test system as a whole, i.e. the combination of tests and the rules for how tests follow each other, have to be based on scientific principles. This is a weak point in current regulations. Whereas scientific principles have been used to construct individual tests, the systemic level is largely based on more intuitive judgments.

The traditional approach to (single) test validation aims at ensuring the reliability and the reproducibility of the results, i.e. that the test measures what it is suppose to measure, and that its results are reproducible over time and between laboratories. This information is however not enough for designing science-based test systems for regulatory purposes. To develop such a system, the single tests certainly need to be reliable and reproducible, but they also need to be validated with respect to their predictive capacity in relation to the effect or risk that they are intended to predict, and ultimately to human or ecosystem risk. However, in most cases it is not possible to determine the relevance of a single test or a test system in relation to effects in humans or entire ecosystems. Instead a reference test, such as a well established long-term *in vivo* test, often has to be used as the gold standard (Hartung *et al* 2004). Validation can also be made against a well-established combination of tests. The selection of tests, or combinations of tests, to be used as references in the validation of test systems should be made on the basis of in-depth toxicological and ecotoxicological knowledge, including findings about mechanisms of toxicity, and the predictive capacity of any test or test system should be validated according to the best available interpretation of such a (combination of) well-established test(s). It should be noted that such a validation should be made for the purposes of risk management. This means that for many purposes fairly rough predictions of the magnitude of risk are sufficient. Furthermore, the usefulness of a new test method or test system must also be assessed in terms of how resource demanding it is. In other words, there may be a trade-off between cost and predictive capacity; in some cases, it might be advantageous to have a system with slightly less predictive capacity if

many more substances can undergo testing in that system, and in other cases the situation may be the opposite.

One of the major goals of the NewS programme is to develop test systems that are science-based also on the systemic level. Two major approaches can be used to achieve this. In our view the best result can be achieved by combining them.

The first approach is to use mechanistic knowledge in a systematic way. The selection of a reference test, as explained above, always has to be based on such deliberations. Furthermore, the use of a screening test as a selection mechanism for a more extensive test should be supported by a credible mechanistic explanation of why substances that yield a positive outcome in the extensive test should do so in the screening test as well, and vice versa.

The second approach is to perform decision-theoretical analyses based on information from what we propose to call *correlation (eco)toxicology*. In order to know how tests can be combined in a cost effective way to predict human or ecosystem risk, we need to know how results from simple methods correlate with results from more extensive testing. This requires studies of the correlation between different test outcomes and (when available) between test outcomes and results from epidemiology and field studies as predictors of adverse effects in humans and ecosystems respectively. Some data are available on correlations between different types of toxicity and test methods (for examples and references see *Chapter 2*). However, little effort seems to have been made to develop the study of toxicological correlations as a general area of knowledge. Therefore, this is still largely an unexplored field lacking a comprehensive approach. The development of correlation (eco)toxicology is in our view necessary for the optimization of test strategies.

Tiered approaches to risk management

As mentioned above, the traditional approach to risk assessment in cases of incomplete data is a *tiered approach* in which comparatively simple and inexpensive investigations are performed on all substances. The outcomes of these tests are used to select substances for further, more extensive testing. In some cases, there may be a whole series of tests that satisfy the requirements to different degrees, and then a

system with more than two tiers can be optimal. *Figure 1.1* illustrates a three-tiered system.

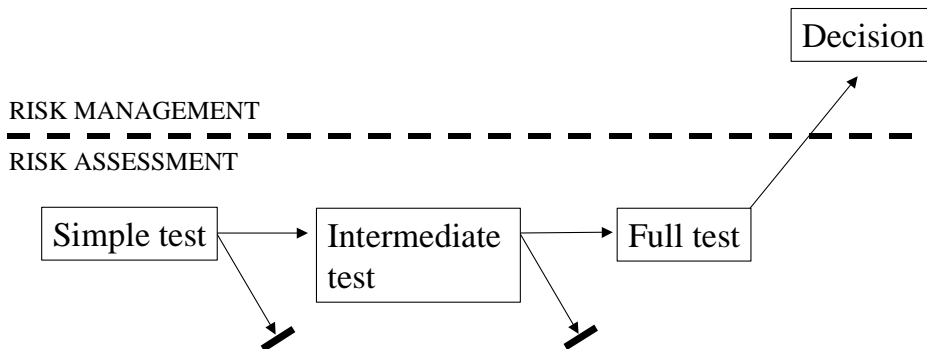


Figure 1.1 *The traditional tiered approach.*

In a tiered approach to chemicals control, initial simple testing is used to select substances for further testing. In a system based on a precautionary approach, initial simple testing is also used to select for preliminary risk management measures. We propose to use the same initial simple testing both as a means to select substances for further testing and as a means to select substances for preliminary risk management measures. The new combined tiered approach is illustrated in *Figure 1.2*.

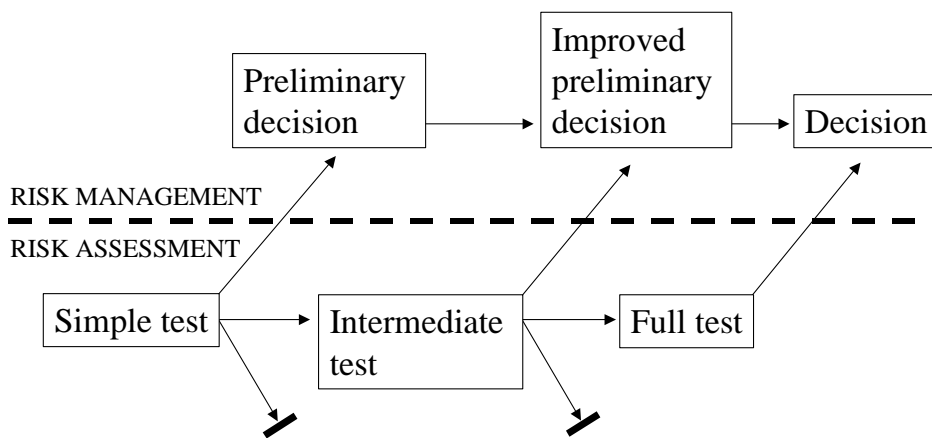


Figure 1.2 *A new combined approach to tiered systems.*

According to the approach shown in *Figure 1.2*, a risk management decision is taken on each tier of the system, so that risk management is improved stepwise. The risk management measures implied in such an approach should be preliminary and proportionate to the potential hazard and to the uncertainty in the scientific data-base.

There are several ways in which such a combined system for risk assessment and management can be developed. One interesting option is to make the risk management measures at the lower tiers sufficiently stringent so that further testing at higher levels can be optional. For a practical example of this approach, suppose that testing at the lowest tier gives an indication that the substance may be hazardous to the marine environment. The manufacturer will then be given two options, either to refrain from further testing and take the measures adequate for such a hazard, or to perform further testing which may (or may not) lead to acquittal of the substance in this respect. The decision tree in *Figure 1.3* illustrates this situation. One advantage with such a system is that economically unmotivated testing is avoided. The manufacturer has the option of *either* accepting the possibly overcautious measures that the precautionary default gives rise to, *or* accepting the costs for finding out whether or not there is a scientific basis for reducing or reversing these measures.

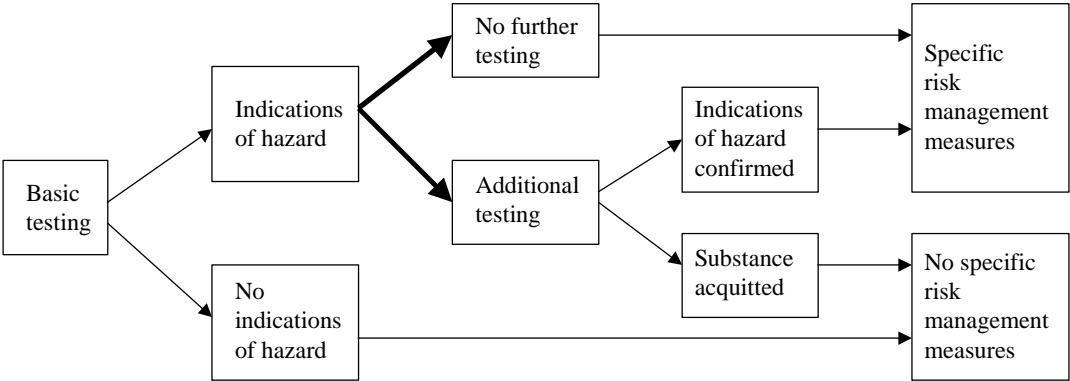


Figure 1.3 A decision tree for risk management in a tiered system with precautionary defaults. The thick arrows indicate the point at which the manufacturer decides whether or not to perform additional testing.

To develop and implement a system that is resource efficient and able to handle a large number of substances, and at the same time produces reasonably robust, and scientifically justified risk assessments that comply with a precautionary approach, is a challenging undertaking. In our view, to achieve such far reaching objectives, it is fundamental that scientists, regulators, and interest groups work in close collaboration.

Reference

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