

News

A new strategy for risk
assessment and management
of chemicals

Programme plan for phase 2 (2003-2006)
[Revised 2004-11-30]

Summary

This programme proposes a new strategy for coping with potential unwanted adverse effects to human health and to the environment from exposure to chemical substances. The new strategy is based on the combination of three elements: (1) The systematic use of a chain-of-events model in order to obtain as early signals as possible from potential health and environment problems. (2) An integrated model of risk assessment and risk management, based on frequent feedback and exchange of information between risk managers and scientists. (3) The use of decision-theoretical methods to optimize the total process of risk assessment and risk management in a way that accords with the precautionary principle, in particular through the application of the default approach that has been developed in the programme.

The combined force of these three elements provides a structure for more efficient risk assessment and risk management. The projects included in the programme have been selected and designed to develop the scientific basis of this structure, and together the projects provide the broad competence necessary for the programme synthesis. An overview of the programme structure is found in Figure 1.

This application refers to the second phase of the programme (years 5-8). The basic programme aims remain the same as in phase 1. Our focus is still on persistent organic pollutants, with a particular emphasis on reproductive and developmental effects and with the Baltic Sea region as our common study region. In phase 2 we make use of experiences from the first phase to adjust the programme to satisfy its aims more efficiently. The following changes have been made in the programme.

- We focus more on two essential parts of the chemicals control system, namely (1) the system for classification and labelling of chemicals and (2) programmes for testing of previously untested chemicals.
- We put still more emphasis on the precautionary principle as a guiding principle for decision-making. The approach to the precautionary principle that was developed during phase 1, i.e. the notion of precautionary defaults, is now used as a unifying principle for data interpretation in the programme.
- We put more emphasis on the definition and measurement of persistency and on the use of QSAR and related methods to judge chemical and ecotoxicological properties of substances.
- We now focus more on the development of standardized tests that can be used to improve the regulatory system.
- We have added a social science project that studies the decision process in the European Union with respect to chemicals policies in order to increase the understanding of how decisions are made in this area, who the participating actors are, and how influence in the decision-process is achieved.
- Due to REACH and other recent initiatives, action on the borderline between science and policy has become a much more acute issue than previously. A detailed study will be conducted in order to clarify the distinction between science and policy in regulatory toxicology and ecotoxicology.
- A new steering group will be appointed in order to speed up coordination and synthesis. The steering group will consist of the programme director and a few project leaders.
- Communication activities will increase. We have agreements on contact and cooperation with several problem owners, namely the National Chemicals

Inspectorate (Kemikalieinspektionen), The Swedish Environmental Protection Agency (Naturvårdsverket), The European Commission (both DG Environment and DG Enterprise), The Swedish Plastics and Chemical Federation (Plast- och Kemiföretagen), and the Swedish Society for Nature Conservation (Svenska Naturskyddsföreningen). In addition, there are numerous other contacts between individual researchers in the programme and decision-makers.

- We intensify the synthesis work, with a focus on regulatory toxicology. All synthesis activities will be collaborative.
- We will regularly perform risk assessment of the model substances. The purpose of this is to show how the methods that have been developed within NewS can be put to practical use in risk assessment.

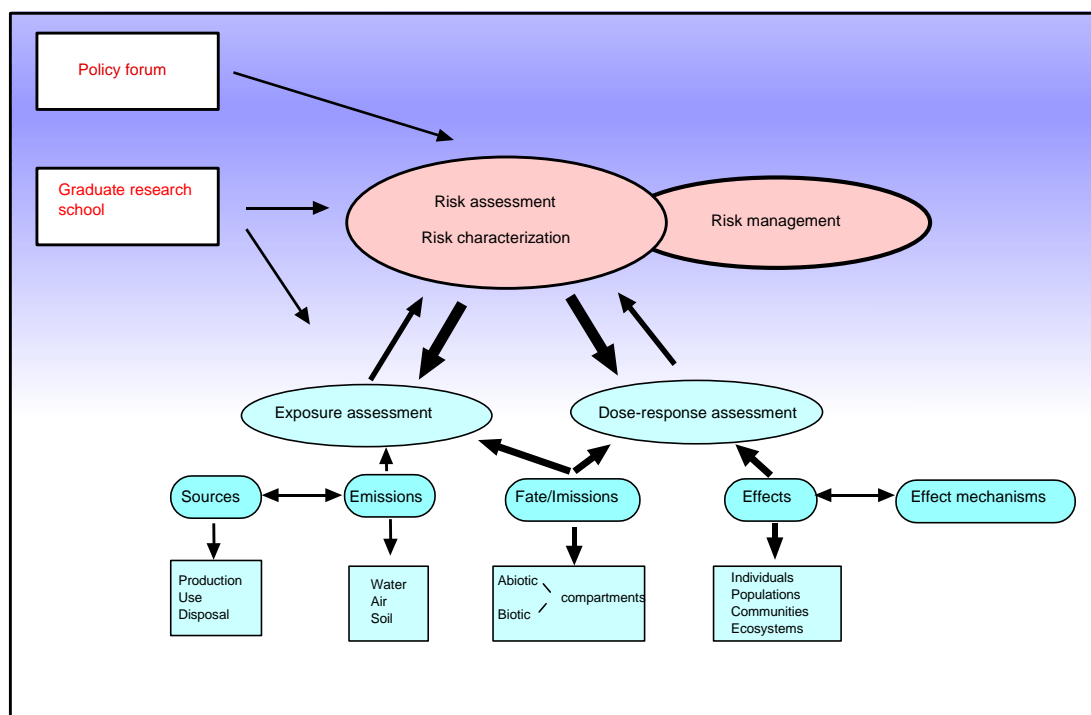
The programme now consists of three project groups, in the areas synthesis and communication, toxicology and ecotoxicology, and exposure.

In order to increase the pace and take advantage of the experience and knowledge accumulated in the individual projects, there will be an increased hiring of post-docs within the programme.

The programme will continue to be a basis for the Policy Forum, a Sweden-based international forum for qualified dialogues between scientists, regulators, industry, and other stakeholders on strategic issues in chemicals policy. The graduate research school that provides education for our graduate students and for qualified professionals both in government agencies and in industry will also continue in phase 2.

The programme has run for its first period. This programme plan refers to its second phase, years 2003-2006.

FIGURE 1. An overview of the programme structure



Why do we need a new strategy?

20 000 to 70 000 chemicals are currently in use on the European market. In addition to this, an unknown number of contaminants and by-products are already in the technosphere and the ecosphere. Only a minor part of all these have been properly risk assessed. In these assessments, only a few substances have been investigated with respect to interactive effects. In addition, a multitude of substances with unknown properties have already been deposited, as waste or otherwise, in urban areas.

Arguably the most serious problem is the slow pace at which risk assessments of chemicals are performed. The existing chemicals programme of OECD and the existing substances programme of the EU are among the best illustrations of this. It is understandable, given the size and nature of the task to assess the toxicity of this huge amount of chemicals, that progress is slow. It has been observed that it will take 100 years to complete the list of the first 2000 high volume chemicals, provided 20 of them are assessed annually (van Leeuwen *et al.* 1996 cf. European Environmental Agency 1998).

It is easy to get the impression that risk assessment has lagged behind. At any rate, major problems in risk assessment remain to be solved.¹ It is necessary both to develop new scientific practices and to improve the way science is used in risk assessment and as a basis for risk management. A new strategy is needed for the risk management of chemical substances. This strategy must include more efficient ways to use incomplete information, and more efficient priority-setting methods for obtaining new information.

Developments during the first phase of the NewS programme have confirmed that the need for a new strategy is perceived by both authorities and industry:

A. WSSD

At the highest political level, the World Summit on Sustainable development in Johannesburg, September 2002, made specific recommendations for chemical safety in its Plan of Implementation, to:

- Renew the commitment, as advanced in Agenda 21, to sound management of chemicals throughout their life cycle and of hazardous wastes for sustainable development and for the protection of human health and the environment, inter alia, aiming to achieve by 2020 that chemicals are used and produced in ways that lead to the minimization of significant adverse effects on human health and the environment, using transparent science-based risk assessment procedures and science-based risk management procedures, taking into account the precautionary approach, as set out in principle 15 of the Rio Declaration.
- Further develop a strategic approach to international chemicals management based on the Bahia Declaration and Priorities for Action beyond 2000 of the Intergovernmental Forum on Chemical Safety (IFCS) by 2005.
- implement the new globally harmonized system for the classification and labelling of chemicals as soon as possible with a view to having the system fully operational by 2008 (www.unece.org).

¹ The phrase “risk management” is sometimes used to cover the whole process including both assessment and regulation, and sometimes to cover only the regulatory part of the process. “Risk management” is used in the name of this programme to indicate that all activities in the programme aim at improving the scientific basis of risk management.

- Encouraging the collection and use of additional scientific data and development of coherent and integrated information on chemicals, such as through national pollutant release and transfer registers.
- Promote reduction of the risks posed by heavy metals that are harmful to human health and the environment.
- [With respect to research and development in general:] Improve policy and decision-making at all levels through, inter alia, improved collaboration between natural and social scientists, and between scientists and policy makers.
- Make greater use of integrated scientific assessments, risk assessments and interdisciplinary and intersectoral approaches
- Continue to support and collaborate with international scientific assessments supporting decision-making
- Establish partnerships between scientific, public and private institutions, and by integrating scientists' advice into decision-making bodies in order to ensure a greater role for science, technology development and engineering sectors
- Promote and improve science-based decision-making and reaffirm the precautionary approach as set out in principle 15 of the Rio Declaration on Environment and Development, which states: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation
- Improve their use of science and technology for environmental monitoring, assessment models, accurate databases and integrated information systems;

B. USA

An ambitious initiative to increase toxicological testing has been taken in the USA through an agreement between the U.S. Environmental Protection Agency (U.S.EPA), the Chemical Manufacturer's Association (CMA), and the Environmental Defense Fund (EDF), i.e. the Chemical Right-to-Know Initiative (ChemRTK). By this agreement some 470 companies have voluntarily committed to provide basic toxicological testing for 2155 high production volume chemicals (www.epa.gov/chemrtk/).

C. EU

A new chemicals policy was proposed in a White Paper by the European Commission in the spring of 2001. It was essentially accepted later in the same year by both the European Council and the European Parliament. The new strategy will lead to a single system – REACH – in which both existing and new substances will be subject to the same procedures (European Commission 2001). The REACH system will be composed of three elements: **R**egistration, **E**valuation and **A**uthorisation of **C**hemicals. One of the major purposes of this proposal is to increase the responsibilities for industry to perform tests of previously untested substances.

Registration of basic information will, according to the Commission's proposal be required for the about 30 000 chemical substances that are marketed in the European Union in volumes exceeding 1 tonne (European Commission 2001). This information is to be submitted by the industry and registered in a central database.

Evaluation of the registered information will be required for the about 5000 substances exceeding a production volume of 100 tonnes per year. A preliminary risk assessment of these substances should be made by industry, and further evaluation may be made by the authorities and will include priority setting for further testing.

Authorisation will be necessary for substances “with certain hazardous properties that give rise to very high concern” (European Commission 2001). The criteria for selection of substances to be subject to authorisation procedures remain to be established. Examples of candidate substance groups are substances classified as carcinogenic, mutagenic or toxic to reproduction in categories 1 or 2, POPs (persistent organic pollutants), endocrine disrupting chemicals, PBT substances (persistent, bioaccumulating and toxic), and VPVB substances (very persistent and very bioaccumulating).

For high-volume substances, comparatively extensive testing will be required, but for substances produced in lower volumes (1-10 tonne) only very basic (*in vitro*) testing will be mandatory, according to the current proposal. It is notable that only *in vitro* data alone is not sufficient for classification of single substances. Hence, according to this proposal the testing requirements for (previously untested) existing chemicals will increase, while the requirements for new chemicals will decrease.

The REACH proposal is still under discussion and the new regulations required for its implementation have not yet been agreed upon.

D. OECD

Efforts by several countries and organisations to generate and make available hazard data have focussed on a basic set of hazard information known as the Screening Information Data Set (SIDS) developed by the OECD, promoting significant co-ordination, see <http://ww1.oecd.org/ehs/hpv.htm>.

E. IFCS

The Intergovernmental Forum on Chemical Safety has given priority to a project addressing international views on the need for generating and making available hazard data for chemicals. Sweden is lead sponsor for this work which will be discussed at the meeting of the Forum in November 2003.

It must be emphasized that although important progress has been made in these international fora during the first period of the NewS programme, this is still progress in planning rather than in execution. Major obstacles remain to be overcome in order to substantially improve the situation with respect to data access for chemical substances. It should also be noted that for most substances, the data collected will be limited, and uncertainties will remain even after data have been obtained. There is an urgent need for rational decision-criteria, based on science and decision theory, for the prioritization and interpretation processes pertaining to data on existing chemicals.

With the REACH proposal it is now clear that two parts of the risk assessment and management process will be particularly essential for the outcome of the overall process: (1) prioritization strategies for data collection through which gaps of knowledge are filled, and (2) the classification of substances, which constitutes the background for further risk assessments and is directly coupled to risk management through downstream regulations. We will therefore focus, in the second phase of the programme, on research that is relevant to these two parts of the process.

Priority setting

Previous activities in chemicals policies have often been characterized by a lack of adequate priority-setting. Policy-makers and risk managers should attend to potential problems in a reasonable order of priority, giving precedence to the most serious problems and the problems most accessible to abatement. This is essential both in terms of the protection of health and the environment and in terms of cost-effectiveness. Unfortunately, priority-setting in regulatory toxicology – and in environmental policies in

general – often seems to go in the wrong directions. One important force that often acts contrary to efficient priority-setting is what Judge Beyer called “tunnel vision”, the tendency to focus on well-known problems at the expense of others that may be more serious (Breyer 1993). This may lead to the costly elimination of the last few per cent of a problem, although measures directed at other more serious problems would have been more efficient. There has been a strong tendency for demands of stricter control and more safety to take the form of requirements for more extensive testing of each substance, and for improved and more sophisticated methods of risk assessment. Such endeavours may become counterproductive if they lead to the concentration of limited resources to a small fraction of the potentially problematic substances. It is one of the major purposes of NewS to achieve better prioritization processes through which such counterproductive effects can be avoided.

Data interpretation and decision-making under uncertainty

The collection of new data on individual substances will decrease uncertainty so that decisions can be made on safer grounds. However, even for substances that have been extensively investigated, important uncertainties remain, as can be seen from the controversies of data interpretation that have taken place for many such substances. The nature of such controversies was studied in detail in the trichloroethylene case study in which 29 carcinogen risk assessments made by different expert groups of the industrial solvent trichloroethylene were compared (Rudén 2002). Trichloroethylene was chosen for this case study since there are unusually many risk assessments made of this substance and since the scientific database is relatively rich in data.² The analysis of the trichloroethylene case indicates that the differences in conclusions cannot exclusively be explained by an evolving database (data availability). The data sets utilized by the trichloroethylene risk assessors are surprisingly diverse and incomplete, and biased data selection may have influenced some of the risk assessors' conclusions. The TCE risk assessors often interpret and evaluate scientific data in different ways. These differences are considered to be within the scope of the scientifically acceptable (Rudén 2001a, Rudén 2001b, Rudén 2002b).

In the second part of the trichloroethylene case study the European Union regulatory process for classification and labeling served as study object of the risk assessment process in a setting where all risk assessors had access to exactly the same data. This part of the study indicates that there is a scope of possible interpretations of the primary data in relation to the classification criteria and thus that there may be more than one possible alternative for the classification of an individual substance. The main controversies in this process were found to concern issues that include policy consideration and thus are not readily resolved by further research. It was concluded that the uncertainty inherent in scientific data opens up a scope of possible interpretations and conclusions and that differences in the assessment and handling of this scientific

² The trichloroethylene database contains a total of twelve long-term carcinogenicity experiments, six experiments in mice, five in rats and one in hamsters. Long-term bioassays have been performed by all the relevant exposure routes (oral, inhalation and dermal). Furthermore, at least eight epidemiological studies of reasonable to high quality are available. This is a huge amount of data compared to what is available for the average existing substance and compared to what is currently required for the notification of new substances, as well as the test requirements proposed in REACH.

uncertainty has the potential to influence the overall assessment of risk (Rudén 2002c; Rudén 2003).

The studied assessments of trichloroethylene also show that even if an enormous amount of resources are spent on testing and assessment of an individual substance (orders of magnitude more than what is required according to existing and proposed regulations), significant uncertainty about its potential to cause harm may still remain.

Hence, chemical risk management is inescapably a case of decision-making under uncertainty. With the increased number of decisions on individual substances that is foreseen in the REACH proposal, improved criteria and procedures for decision-making under uncertainty are urgently needed in order to avoid time-consuming conflicts on data interpretation. Such criteria should be based on scientifically sound applications of the precautionary principle.

We need, therefore, to develop tools both for priority-setting (for data collection) and for decision-making under uncertainty (primarily for decisions in the classification system). This involves the development both of new science and of new ways to use science for decision-making purposes. In the second phase of the NewS programme this contribution will be completed and made more practically applicable. We enter the second phase at a point in time when the need for simple methods of risk assessment that comply with the precautionary principle is greater than ever.

Visions and goals

VISIONS

- * *The risks that chemical compounds interfere with human health or give rise to environmental impact are assessed with mechanism-related procedures that are simple, fast, sensitive, and reliable.*
- * *New and more reliable methods for the provisional assessment of chemicals are available.*
- * *The information required for the assessment of environmental impacts is systematically derived from the event chain “from the cradle to the grave” of substances. It takes the unique Scandinavian environmental conditions into account.*
- * *Risk management is based on efficient priority-setting methods, and complies with the precautionary principle.*

PROGRAMME GOALS

A new model for risk assessment, extending into and simplifying risk management, that makes more efficient use of scientific information and therefore is better equipped to prevent damage to human health and to the environment is available in a preliminary version.

In the model...

... the use of testing and assessment resources is optimized by new decision-making tools.

... methods for estimating exposures to chemicals of man and ecosystems are simplified.

... test methods focused on endpoints in developmental and reproductive toxicity are available.

The model...

... provides input to EU risk assessment procedures, especially regarding effects of unique Scandinavian environmental conditions.

... creates a link between regulatory agencies and the research community focused on risk assessment procedures by (1) initiating an informal network, and (2) establishing a Policy Forum.

A graduate research school focused on risk assessment is in operation.

From phase 1 to phase 2 of NewS

The first phase of NewS gave rise to important and well-published scientific results. Some examples of these results are the development of better and simpler tests for reproductive and developmental toxicity in crustaceans (*Nitocra*) and fish, more sensitive test for mammalian neurotoxicity (the neonatal mouse model), and improved quantification of mother's milk transferred contaminants. One of the tests is already used in regulatory toxicology (the neonatal mouse model) and another one is being processed to become an OECD guideline (the *Nitocra* full life-cycle test).

Several policy proposals also came out of phase 1. Among these can be noted that ways to operationalize the precautionary principle through the notion of precautionary defaults have been proposed. This proposal was discussed at the Policy Forum, and is presented in a manuscript to which all the projects have contributed. Furthermore, a modification of the classification and labelling system that can provide increased incentives for testing and data collection was proposed.

In all 98 international scientific publications (published, in press, accepted or in manuscript), 46 posters and 34 presentations have been produced. For a more complete description of the achievements of phase 1 we refer to the report "NewS for evaluation", and to the NewS homepage (newstrategy.ecotox.lu.se).

Members of the NewS research team had major roles in the the Swedish Committee on New Guidelines on Chemicals Policy (SOU 2000:53), that proposed new, precaution-based regulations for persistent and bioaccumulating substances. These proposals have begun to be discussed both among regulators and researchers. The Committee also mentioned NewS as an example of research activities that can give "further important basic knowledge and understanding of great importance for Sweden's standpoint on environmental issues". Furthermore, during phase 1, important policy proposals – in particularly the White Paper on chemicals policy and REACH – have gone in the direction of NewS ideas, so that we now act in an environment that is much more prepared for our ideas than when the programme started.

Based on experiences from phase 1 and on proposals from the project leaders, the NewS Board developed a programme plan for phase 2 that was submitted to Mistra and to a scientific review process. The board considers the comments of the reviewers to be constructive and useful in the further development of the programme plan.

The report of the scientific review panel and the preliminary decision of the Mistra board that contained a specified budget for phase 2, have been the starting point for finalising the present programme plan that is submitted for final review and decision.

A significant amount of effort and resources has been spent in phase 1 on integrating the projects with the overall aims of the programme. This work has been successful, and in order to make the best possible use of it, a high degree of continuity with phase 1 will be retained in phase 2. Most of the projects proposed for phase 2 constitute a modified continuation of projects from phase 1. However, not all phase 1 projects will have a continuation in phase 2; instead, new projects are proposed that support the programme goals.

The changes of the programme, as compared to phase 1, can be summarized as follows:

- We put still more emphasis on the precautionary principle as a guiding principle for decision-making, The approach to the precautionary principle that was

developed during phase 1, i.e. the notion of precautionary defaults, is now used as a unifying principle for data interpretation in the programme.

- We focus more on two essential parts of the chemicals control system, namely (1) the system for classification and labelling of chemicals and (2) programmes for testing of previously untested chemicals.
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- We intensify the synthesis work, with a focus on regulatory toxicology. All synthesis activities will be collaborative.
- We will regularly perform risk assessment of the model substances. The purpose of this is to show how the methods that have been developed within NewS can be put to practical use in risk assessment.

The comments of the scientific review panel, and our responses to them, are summarized in an appendix to this programme plan.

Risk Assessment and Risk Management: State of the Art and the NewS approach

The standard approach to risk assessment and risk management

Current ideas on the assessment and management of risks have developed out of attempts to systematize the work carried out by regulatory toxicologists at national authorities such as EPA in the USA and corresponding European agencies. These ideas are summarized in Figure 2, that belongs to the influential 1983 report by the American National Academy of Sciences National Research Council (NRC 1983), that “has formed the bases of the EU's new and existing chemicals legislation” (European Environmental Agency 1998).

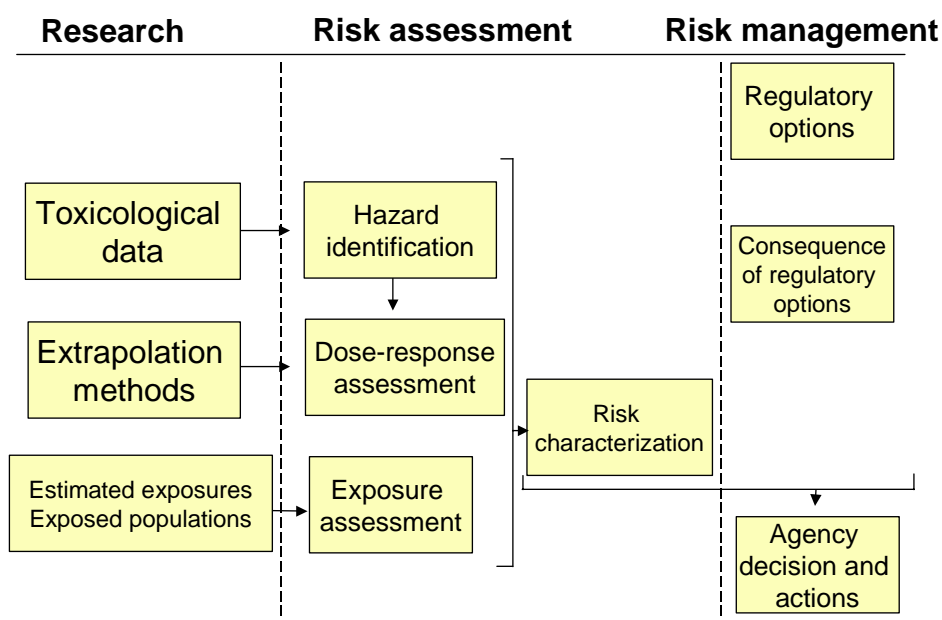


FIGURE 2. Outline of the risk assessment process extending into regulatory risk management, according to the National Research Council 1983.

A characteristic feature of this approach, and of all influential recommendations for risk decision procedures that we are aware of, is their emphasis on the division of these procedures into two distinct parts to be performed consecutively.

The first of these, commonly called risk assessment, is a scientific undertaking. It consists of collecting and assessing the relevant information about sources, transport, exposure, uptake, toxicokinetics, toxic effects etc., and on this base characterizing the types of toxic effects, their magnitudes and the endangered subpopulations or environments. The second procedure is called risk management. Contrary to risk assessment, this is not a scientific undertaking. Its starting-point is the outcome of risk assessment, which it combines with economical and technological information pertaining to various ways of reducing or eliminating the risk in question, and also with political and

social information. Based on this, a decision is made on what measures – if any – should be taken to reduce the risk; if this decision is taken to implement protective legislation it is called a regulatory decision.

This consecutive model has served the important purpose of systematizing a previously much too unsystematic undertaking. In particular, it has served to defend the integrity of science and to prevent improper practices such as letting estimates of risk depend on whether or not risk reduction is considered feasible. On the other hand, a rigid implementation of this model also has disadvantages that in our view make it necessary to reconsider the conventional approach and develop an alternative model for the science-based assessment and management of chemical hazards. In particular, it has led to inefficient use of resources. The model prescribes that one first obtain a standardized and reasonably complete set of data on a substance, and only after that decide on possible measures of risk abatement. This approach is inefficient when resources for testing are a limiting factor. Often, preliminary risk management decisions have to be made on the basis of incomplete, sometimes rudimentary, information. Scientific models of risk assessment are needed that can support such decisions. Largely, such models are lacking. Although tiered approaches have been introduced in several instances, this has only been done to an insufficient degree and mostly without a systematic analysis of the information needed for decision-making.

NewS in risk assessment and risk management: Precautionary defaults

We have started to develop a new, integrated model of the risk reduction procedure, to replace the old two-step model with its consecutive risk assessment and risk management phases.

Background. Precaution and the science/policy division

There is an emerging consensus that risk management should be based on the principle that it is better to err on the side of safety. In particular in Europe, but also in several international treaties, this has been called the precautionary principle. It is essential that changes made in risk assessment procedures to comply with the precautionary principle are compatible with scientific method and the scientific database. Risk assessment is a scientific process, and should so remain. What we need is risk assessment procedures that are (1) scientifically sound, (2) suited for precautionary risk management, and (3) simplified.

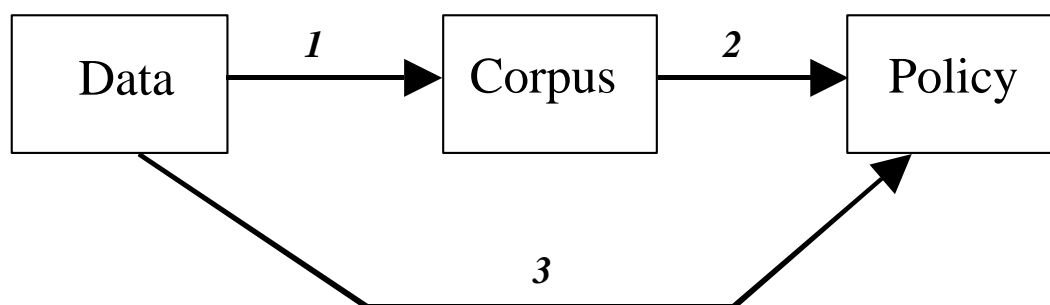


FIGURE 3. The use of science in risk management.

Figure 3 illustrates the use of science for policy purposes (Hansson 2002). Scientific knowledge is based on *data* that originate in laboratory experiments, field studies and other observations. Through a process of critical assessment, these data give rise to the scientific *corpus* (arrow 1). Roughly speaking, the corpus consists of those statements that could, at the time being, legitimately be made, without reservation, in a (sufficiently detailed) textbook. The obvious way to use scientific information for *policy* purpose is to use information from the corpus (arrow 2). For many purposes, this is the only sensible thing to do. However, in the context of protecting health and the environment exclusive reliance on the corpus may have unwanted consequences. Suppose that there are suspicions, based on relevant but insufficient scientific evidence, that a certain chemical substance is dangerous to human health. Since the evidence is not sufficient to warrant an addition to the scientific corpus, this information cannot influence policies via the “standard” way, arrows 1 and 2. However, the evidence may nevertheless be sufficient to warrant changes in the handling and use of that chemical. We want, in cases like this, to have a direct way from data to policies (arrow 3). It is essential, however, that this does not lead to arbitrary decisions with priorities determined by the whims of uninformed opinion. The direct road from data to policy needs to be based on science in essentially the same way as that from data to corpus, but with different requirements on the level of evidence.

In intra-scientific decision-making, e.g., when determining whether or not a scientific hypothesis should be accepted for the time being (included in the corpus), the onus of proof falls squarely to its adherents. Those who claim the existence of a previously unknown phenomenon – such as the existence of an as yet unidentified hormone – have the burden of proof. It is essential for the scientific process that this burden of proof not be reversed. If that happened, then scientific progress would be blocked by the pursuit of all sorts of blind alleys. We need to defend the integrity and the quality of the scientific corpus. This applies to the environmental sciences to no less degree than to other scientific disciplines.

As we see it, a rational decision-maker who applies the precautionary principle should use the same type of scientific evidence, and assign the same relative weights to different kinds of evidence, as a decision-maker who requires more complete scientific evidence before action is taken. The essential difference is in the level of evidence required for action. In order to enable risk managers to apply the precautionary principle, risk assessors should search for and report information about scientifically sound indications of risk or hazard, even if these indications do not amount to full scientific evidence. Such a practice should not be confused with lowering the standard of scientific evidence.

Precautionary defaults

One of the major results of the first phase of the programme is a model, the precautionary default approach, that is intended to be a major component in our model for making risk assessment more useful for risk managers.

The way that risk managers deal with scientific uncertainty and insufficient information can be expressed in terms of *defaults*. A regulatory default is an assumption that is prescribed to be used in the absence of adequate information. Clearly, all default assumptions must be liable to adjustment when more scientific information is obtained.

For intra-scientific purposes, if we are not reasonably certain of, for instance, the fate of a substance in the environment or of its effects on fish, then we say that it has an unknown fate and that its effects on fish are unknown. For decision-making purposes, this is not sufficient. We have to treat the substance in one way or the other while waiting

for more evidence. Hence, for regulatory purposes, a substance with unknown toxicity will have to be treated for instance *as if* it were severely toxic, as if it were moderately toxic, as if it were non-toxic, etc. It is in practice unavoidable that a regulatory decision (or non-decision) on a substance with unknown properties will have the effect of treating it in the same way as if its properties were known to be in one way or the other. Rules for risk management decisions under lack of information can therefore be described as (*regulatory*) *defaults*. We will call a regulatory default *precautionary* if it complies with the precautionary principle. It is important to distinguish between regulatory defaults (whether precautionary or not) and judgments that particular substances actually have one or the other property.

The traditional approach has been to treat substances differently, depending upon which legislation they are covered by. When it comes to substances that are proposed for use as food additives or pesticides, substances with unknown properties are in general treated in the same way as highly toxic substances, i.e. they are prohibited for these purposes. (This is called the positive list approach; only the substances on the agency's list of approved substances may be used.) For general industrial substances, the opposite approach has been used, i.e. substances with unknown properties have been treated in the same way as non-toxic substances (the negative list approach). Both of these approaches can be described as the application of regulatory defaults. However, only the first of them can be described as a precautionary default.

In cancer risk assessment, a number of presumptions for biological interpretations have been established, that have the function of precautionary defaults (See IARC 2000 and U.S. EPA 1999). Probably the most well-known of these assumptions is that positive effects in animal cancer studies are taken to indicate that the substance under study can have a carcinogenic potential in humans (IARC 2000; U.S. EPA 1999). This has the effect of a (precautionary) default that treats animal carcinogens as human carcinogens, unless sufficient evidence to the contrary is available. (The same basic assumption is made with respect to other toxic effects, and it is not wrong to say that laboratory toxicology is based on the default assumption that effects in animals indicate a high probability of corresponding effects in humans.)

Since the purpose of using a regulatory default is to overcome data gaps and scientific uncertainty, new data and increasing knowledge have the potential to motivate departures from such defaults. One example of this is improved knowledge about carcinogenic mechanisms. In the EU regulation for the classification and labelling of chemical substances (Council Directive 67/548/EEC) it is stated that if the mechanism of experimental tumour formation is "clearly identified", with "good evidence" that this process cannot be extrapolated to man, then the substance should not be classified as carcinogenic (Council Directive 67/548/EEC, par 4.2.1.2.). This is in fact a rule that allows departures from the (precautionary) default to treat animal carcinogens as human carcinogens.

It is important to distinguish between precautionary defaults and a traditional tiered approach. In a traditional tiered approach, as can be seen in figure 4, the lower tiers are used to determine what further testing to perform, and risk management measures are typically not taken unless adverse effects have been shown in the tests included in the highest tier. In a system based on precautionary defaults, positive findings in the lower tiers can lead to preliminary risk management decisions that may have to be reversed if and when more reliable information has been obtained from the higher tiers. This procedure is illustrated in figure 5. We call the former type of tiers WAS-tiers (Wait And See), and the latter type IS-tiers (Improve Stepwise) (Hansson and Rudén, manuscript in preparation).

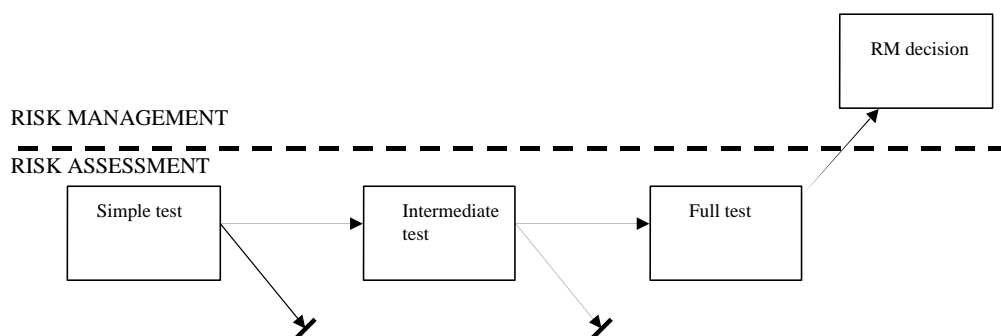


FIGURE 4. A traditional tiered approach (WAS-tiers)

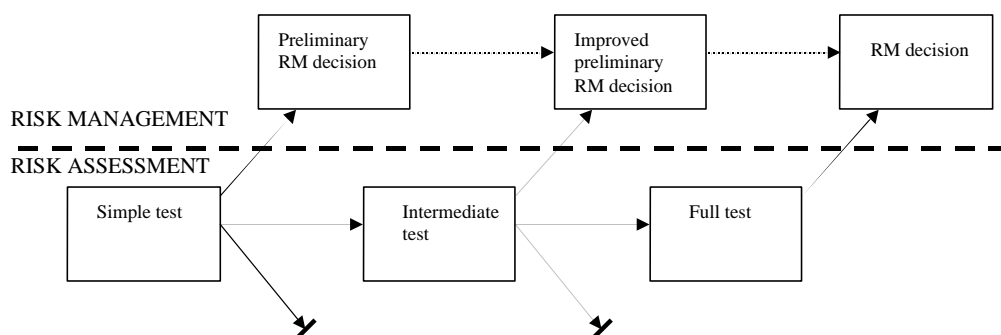


FIGURE 5. A system with precautionary defaults (IS-tiers).

The role of precautionary defaults in the event chain

A system of precautionary defaults requires the development of scientifically sound indicators that give us reason to suspect toxic or ecotoxic effects. In order for default rules to be operative there must be scientific indicators that correspond to the degrees of scientific evidence that risk managers have chosen for regulatory action. Since the development of such scientific indicators is a qualified scientific task, this approach requires extensive cooperation between risk assessors and risk managers. Since we are used to communicating well-established science rather than uncertain scientific indications, new forms of communication may also be needed.

In the search for indicators that can support a precautionary approach, emphasis should be put on the following criteria:

- reliability
- sensitivity
- early discovery
- availability at low cost
- animal welfare

In phase 1, we have focused on developing precautionary defaults that satisfy these criteria. This is work in progress but we have given a few examples of indicators that are

already available or can, with relatively little additional development, be used as the basis for precautionary defaults.

- The persistency and bioaccumulating properties of a substance can be used as preliminary indicators of its potential capacity to create environmental problems.
- Remote areas such as the Arctic and Antarctica can serve as indicator areas for global pollution. Unless proof to the contrary can be given, an anthropogenic chemical found in biota in these areas should be considered to be a persistent pollutant. Such findings imply long-range transport and regulatory actions should be considered.
- Data on the presence of pollutants in human milk can be used as indicators of exposure of sensitive humans, and could be the basis for regulatory action even in cases when full evidence of toxic effects is not available.
- Tests showing behavioural changes in animals after neonatal exposure appear to be useful and sensitive indicators of developmental toxicity.
- Effects on reproduction in simple tests, for instance in crustaceans, can be used as indicators of ecotoxicity.
- Characterizations of chemical reactivity and chemico-physical properties can potentially be used as indicators of properties related to the potential environmental fate of chemical substances

Empirical cohesion of the programme

All projects aim at making our overall model of risk assessment and management as operative as possible. In addition to this, they are linked together in three other ways.

1. All our toxicological and ecotoxicological projects are devoted to reproductive and developmental toxicity.
2. All ecotoxicological projects have the same study area, namely the Baltic Sea.
3. The projects focus on the same model substances.

Toxicological endpoints

In phase 1, the programme has focused on reproductive and developmental endpoints. The reason for this choice is that reproductive toxicity often appears at lower levels of exposure than most other toxic effects. The central role of reproduction in ecological systems contributes to make reproductive toxicology an important focus of concern.

In the field of developmental and reproductive toxicology it is essential to identify critical stages when chemical agents can be harmful. Results obtained in phase 1 confirm this approach. As an example of this, we have found indications of behavioural toxicity in mammals at surprisingly low exposures of the model substances at early stages of development (Eriksson *et al.* 2001). In studies on *Nitocra* we found larval development rate to be a more sensitive indicator of toxicity than population growth rate (Breitholz 2002).

The focus on reproductive and developmental toxicity and ecotoxicity will remain in the second phase of the programme.

Study region

The Baltic Sea has for ages been used by man both as a resource and as a dump for wastes. In connection with rapid growth of the heavy industry around the Sea, the latter use has increased considerably. Anthropogenic pollution is today considered to be a key factor responsible for disturbances in the reproduction of mammals, birds, and fish species in the Baltic Sea. For example, during the 1960s poor recruitment was common in ringed seal populations (Helle *et al.* 1976), and the white-tailed eagle suffered from decline in hatching success (Hellander *et al.* 1982). Since 1974, a disease has been observed in salmon populations resulting in increased yolk sac fry mortality (Bengtsson *et al.* 1994). Due to the accumulation of persistent lipophilic residues like DDT, PCBs, and dioxins in fish, Swedish authorities have issued diet recommendations (especially directed at pregnant women) in order to limit exposure to these substances.

The Baltic Sea thus represents a pool of anthropogenic pollution that is threatening both to its own ecosystem and to man. The situation calls for further studies to identify the risks, set priorities, and manage the risks accordingly. The NewS programme wishes to contribute to these efforts, and therefore the Baltic Sea has been chosen as the environment that is our primary object of study. Using a set of “representative” pollutants, predictions will be made of exposure concentrations for POPs in general, and disturbances primarily in reproduction will be looked for. The

results will be used in risk assessment procedures that eventually will be made use of in risk management of the Baltic Sea drainage basin.

Although the Baltic sea and its catchment area form our study region, neither the problems that we intend to study nor the new strategy that we want to develop are limited to this region. The long range transport of chemicals and the fact that the Baltic Sea, the North Sea, the Arctic, etc., are sinks for chemicals, show that this is a truly international problem. In particular, the protection of Europe from chemically induced damages is a joint responsibility for all European countries. The Policy Forum in October 2002, contributed to showing this by focusing on the issues that are common to protecting the Baltic Sea and the Mediterranean.

Model substances

In order to ensure coherence, ease of cooperation, and efficient use of resources, the projects participating in the first phase of this project used a common set of model substances, primarily brominated flame retardants and to a lesser extent musks. In the second phase of the programme, the use of model substances that are common to all projects in the programme will be continued.

Based on experience from the first phase we have decided that musk substances will not have a prominent role in the programme during phase 2. We intend to focus on brominated flame retardants, in particular: PBDE, HBCDD, and TBBPA, as was decided by the NewS Board during phase 1 (Board meeting minutes 1999-03-16). However, it may be advantageous to use other substances for particular purposes in individual projects. We also aim at generalizing, in the second phase, results obtained on model substances to other organic pollutants. Therefore, the previous model substances will to some extent be supplemented by other such substances in the second phase of the programme.

Brominated flame retardants: Brominated flame retardants are members of a large group of about 350 chemicals used to prevent fires. These may be brominated, chlorinated, containing phosphates, or a mixture thereof. About 20 of them are used frequently and in large quantities. The brominated flame retardants are not produced in Sweden but are imported in various goods. Just prior to the start of phase 1 of NewS, the Swedish National Chemicals Inspectorate took a closer look at seven of these substances, chosen due to their persistent character, bioavailability, and assumed toxic properties (Kemikalieinspektionen 1994; 1995; 1996). The study included polybrominated biphenyls (PBB) and polybrominated diphenyl ethers (PBDE) used in, for example, covers and cases of computers and household utilities, electrical switches, relays, fuses etc. In 2002 the Chemicals Inspectorate received an assignment from the Government to investigate the possibility to implement a Swedish national ban on brominated flame retardants.

The brominated flame retardants were first discovered in the US environment (DeCarlo 1979). In Sweden, their occurrence in fish nearby textile industries was reported in 1981 (Andersson and Blomkvist 1981). Further studies showed the presence of PBDEs in the fauna of the Baltic Sea, the North Sea, and the Arctic Ocean (Jansson *et al.* 1987; Jansson *et al.* 1993; Sellström *et al.* 1993; deWit 2000), indicating a large scale distribution. Accordingly, they were also detected in human adipose tissue (Cramer *et al.* 1990; Stanley *et al.* 1991). Their levels in breast milk in Sweden were increasing

for a long time (Norén *et al.* 2000), but from 1998 the level has been decreasing (Meironyté *et al.* 2001).

Some of the flame retardants are covalently bound to a polymer and are therefore less likely to leach out into the environment while others are mixed with or dissolved in the material and may migrate out of the products during their lifetime. However, since most of these products may end up in ordinary wastes, most flame retardants are likely to enter the environment. Some of the PBDEs show dioxinlike toxicity (Hanberg *et al.* 1991) and induce EROD activity in fish (Holm *et al.* 1993; Norrgren *et al.* 1993). Sellström *et al.* (1993) have summarized the occurrence and distribution of PBDEs in the Swedish environment.

It should again be emphasized that we use the brominated flame retardants as model substances. Our primary aim is not to investigate in detail the toxicity of certain specific substances but to develop a new strategy for risk assessment and risk management. However, in order to facilitate coordination and cooperation within our programme, it is extremely important that all participating groups work with the same model substances. The wide range of physico-chemical properties among the BFRs facilitate the generalization of our results to other substances that threaten human health and the environment.

Synthesis and communication

Synthesis

In the second phase of the programme, the emphasis on synthesis and communication will increase. In phase 2, the overall model for risk assessment that is the ultimate goal of the programme will be developed. This will be a cooperative effort involving all projects in the programme. Additional empirical results and scientific interpretations will be needed, as well as new and refined tools from decision theory and regulatory toxicology. Our aim is to show how available resources for testing, risk assessment and risk management can be put to more efficient use through the application of methods developed in this interdisciplinary programme synthesis.

Regular risk assessments

By regularly performing risk assessments of the model substances, we intend to show how the methods that have been developed within NewS can be put to practical use in risk assessment. This work will be initiated in the very beginning of phase 2, and it will make NewS serve as a “microcosm” of the integrated management process where new methods and a limited amount of data are used in risk assessment and made serviceable to risk management. This type of effort will be recurring with about one year’s interval, each time with a new focus that will contribute to make these risk assessments scientifically interesting for problem-owners and the participating projects. The first task should be to perform a risk assessment in which we apply the idea of precautionary defaults to a number of BFRs that are under discussion in the European Union.

Reproductive and developmental toxicity

Reproductive and developmental toxicity is one of the major factors that should be taken into account in the regulation of chemicals. Unfortunately the regulatory framework is much less developed in this area than for instance in the regulation of carcinogens. There is an urgent need to develop better regulatory tools for testing and risk assessment in this area. Both the toxicological and ecotoxicological projects in NewS have important contributions to make in developing improved and simplified procedures for testing and risk assessment of reproductive toxicity. This will therefore be one of the focus areas in the programme synthesis. In this work we will collaborate with the REPROSAFE research programme funded by the Swedish Environmental Protection Agency (For further information, see their homepage: www-cru.slu.se/ReproSafe.htm). The collaboration with REPROSAFE will also include the arrangement of a joint seminar in this field. Our contact person in REPROSAFE is Ulf Magnusson (Programme Manager). Possibly, the second risk assessment activity in the programme can focus on the ideas for simplified reproductive risk assessment that will be proposed early in phase 2.

Simplified exposure analysis

We will also develop tools for simplified exposure analysis. Currently, exposure analysis is time consuming and is in practice only performed for relatively few substances. Simple indicators are sometimes used as a substitute for a more comprehensive exposure analysis. Examples of such indicators are total production volume and use in consumer products. Such simple indicators are used for many regulatory purposes but it is not

known how good these indicators actually are (Bennett *et al.* 2002). Results from phase 1 can be used in an analysis of this problem, and also in a discussion of whether indicators can be developed that are intermediate in terms of simplicity.

Indicators for priority setting

Physico-chemical properties and chemical structure can be used as simple indicators in priority setting. We will perform studies that aim at finding useful indicators of persistence and bioaccumulation for regulatory purposes. A project devoted to the use of chemical information for risk assessment purposes through QSAR and similar methods has also been added to the programme in phase 2. It is of course essential that the application and interpretation of QSAR and related methods be compatible with the precautionary principle. The precautionary default approach that was developed in the first phase of the programme provides a framework for developing a precautionary approach in this area. One possibility is to create QSARs which could guide the setting of "pessimistic" defaults. These assumptions can be used for regulatory purposes, but they can later be overruled by empirical data that justify less pessimistic assumptions. This, and possible alternative approaches will be worked out in practical detail.

Other issues

In phase 1 a typology of how uncertainty is communicated in risk assessments was developed. Further efforts will be made in this area and will lead to practical proposals for how uncertainty should be expressed in risk assessments.

Our studies of the system of classification and labelling will be continued, and so will the ongoing studies of test optimization. They will result in concrete recommendations for modifications of current priority-setting and test requirements.

In phase 2 all synthesis work will be collaborative and our emphasis on regulatory issues will increase. All projects will be put more in a regulatory perspective, and the precautionary default approach will be further developed, with an emphasis on concrete proposals for its application to toxicological, ecotoxicological, and chemical properties of substances. Joint articles, written in collaboration between several projects, will be the major way in which the programme synthesis is reported. The synthesis project will have a coordinating role in these activities.

Our experience from phase 1 confirms that it is essential for success that we are able to respond to developments in the rapidly changing field of chemicals regulation, and to adjust our planning in order to grasp opportunities that open up. Therefore, our planning must be flexible. The developments following from the White Paper of the European Commission will be a major concern, and so will the process of international harmonization of chemicals regulations.

Proposals for EU assessment improvements

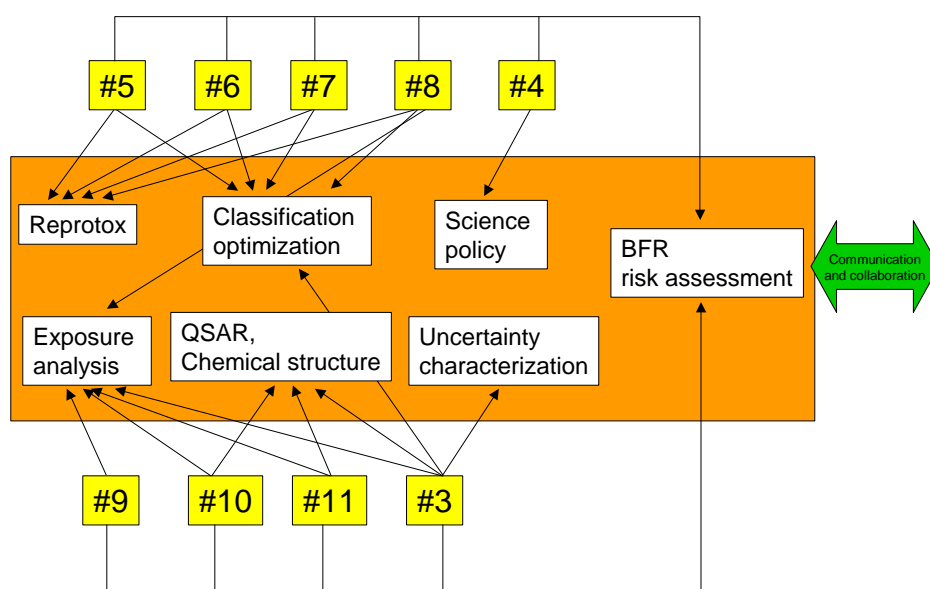
Continuously during phase 2, texts will be produced that summarize the major results of the NewS programme and will be made available to problem owners. This will include concrete proposals for important improvements of the European risk assessment procedures, for instance of the type that are typically laid down in technical guidance documents. We are going to show how the massively increasing load of risk assessment work can be handled in a simplified procedure that also complies with the precautionary principle. Concrete applications of the principle of precautionary defaults, that was outlined in phase 1 of the programme, will have a central role in this new model. Improved use of information about chemical structure and physico-chemical properties will be proposed, and improved practices will be proposed for the assessment of

reproductive and developmental toxicity. We will show how test strategies can be optimized, and propose a unified and principled method for reporting uncertainties in risk assessments. Through Policy Fora and intensive communication with stakeholders and decisionmakers the ground will be well prepared for the adoption of these new strategies in a situation when the need for it will be more urgent than ever due to the massive increase in risk assessment tasks in the European Union and elsewhere.

Communication and collaboration

To become successful, it is necessary to keep the focus on the common programme goal, through a close scientific cooperation between the different projects. Figure 6 illustrates how the different projects will collaborate to various parts of the programme synthesis. Further details about this are given in the project plan of the synthesis project.

FIGURE 6. Synthesis collaborations.



In addition, regular exchange of information with problem-owners, and authorities about the progress of the programme is vital.

In phase 1, the project leaders were included in a seminar group that met frequently. This tradition will continue. Discussion of programme matters, sharing information and identifying problems of general interest will dominate these meetings. As in phase 1, matters related to the graduate school will also be reviewed and commented upon.

A modelling group has been formed encompassing those projects that provide models for the material balance, persistence, and exposure to be used in the integrated risk assessment model. This group will continue its activities. The same applies to the cooperations already established by the projects that cover aquatic dose-response and mammalian dose-response. Coordination of research activities, practical matters and

reporting of results are on the agenda of these groups. In phase 2, these groups will move on from technical to more assessment – and policy – related issues.

A steering group will be appointed by the programme board, consisting of the programme director and a few (about three) project leaders. This group can meet more often than the whole group of project leaders and will therefore be helpful in speeding up cooperation and synthesis work. The operative management of the programme will remain with the programme director.

Contacts with problem-owners will be even more important in the second than in the first phase of the programme. We have a structure for such contacts from the first phase that will now have to be reinforced in phase 2.

Policy Forum

Policy Forum is an international forum created to serve as a platform for qualified discussions on the strategy for solving the health and environmental problems connected with chemical substances. In phase 1, two Policy Fora have been arranged. The Falkenberg meeting in April 2001 focused on the development of a precautionary approach to persistent and bioaccumulating substances. The meeting in Javea, Spain in October 2002 discussed joint issues in risk assessment of chemical pollutants in the Baltic Sea and the Mediterranean. Both meetings attracted 50-60 participants, including top-level risk managers and scientists from several countries and international organizations. The Policy Forum will continue in phase 2, as a series of major seminars and conferences on chemicals policies. Its invited speakers will be influential scientists and decision-makers both from the European Union and from other parts of the world. This type of activity sometimes comes close to the responsibilities of government authorities, and contacts are therefore necessary to clarify the division of responsibilities.

The Policy Forum will focus on the new European chemicals policy. The Forum will also commission investigative reports, mostly as part of the preparation of a seminar. These reports will in most cases be scientific analyses of important policy issues. Some reports may have the form of synthesis reports, that are based on the combined efforts of top level scientists and key actors on the international scene.

The activities of the Policy Forum cannot be planned many years beforehand. They must on each occasion center around issues that are on an appropriate pre-decision preparatory stage so that future policies can be influenced. Some possible subjects for policy conferences include:

- Assessing reproductive hazards – a joint effort for toxicologists, ecotoxicologists, and risk managers.
- Simplified risk assessments – can simplification and quality be combined.
- The division of responsibility in chemicals control: between industry, national authorities and international organizations.
- Risk communication on chemical hazards.

The original plan to have a special board for the Policy Forum turned out to be impracticable. In practice, the programme board has also made all the major decisions on the Policy Forum in phase 1. It should be left to the new programme board to decide on the organization of the Policy Forum.

During the first year of phase 2 (2003) a Swedish-American seminar will be arranged in cooperation with The Swedish Plastics and Chemical Federation and with King's college in London (professor Ragnar Löfstedt). The purpose of this seminar is to

clarify differences and search for common ground in the interpretation of precautionary approaches to chemical risk management.

Graduate research school

The graduate research school arranges courses, seminars and workshops that cover different steps in the event chain leading to the overall risk assessment and risk management continue accordingly in phase 2.

We believe that the graduate research school will continue to attract and benefit persons outside of the programme. We will make it possible for both government agencies and industry to use the graduate research school as a means to the continuous updating of the competence of their scientific staff.

In the first year of phase 2, we intend to arrange a short course that focuses on basic risk assessment methods, on the regulatory context, and on decision-making under uncertainty. The themes for the graduate school in the following three years will have to be determined later.

The Chemicals Inspectorate

We have discussed extensively with the Swedish National Chemicals Inspectorate (Kemikalieinspektionen, KemI) how we can best increase our cooperation in phase 2. In phase 1, we had an ambitious structure with contact persons at KemI for each project. However, contacts were in most cases not as intensive as we had hoped for. A clearer connection between NewS and more regular KemI activities seems to be needed in order to improve our cooperation.

In phase 2, a working group will be formed for cooperation between KemI and NewS. The deputy director general (Nils-Gunnar Lindquist) will be one of the participants from KemI's side, and the programme director one of the participants from NewS. The task of this group will be to continuously follow activities on both sides in order to find issues of common interest that can lead to cooperation and joint activities. Some specific areas of cooperation have already been identified:

- The group will identify situations where the competence and experience from NewS can and will be used as support for the risk assessment work performed at KemI
- The group will further the cooperation on exposure analysis, especially in relation to the technosphere, that will take place in project #9.
- The group will actively search for arrangements through which personnel at KemI spend part of their time ("kompetensutvecklingstid") in NewS projects, participating in their work and bringing regulatory experience to the projects.
- The group will facilitate and follow NewS contacts with the European Union and its expert committees, as well as other international organizations.

The Swedish Environmental Protection Agency

The Swedish Environmental Protection Agency will be offered to participate in the abovementioned working group with KemI, as a means to further developing the programme's cooperation with the Environmental Protection Agency.

Swedish Ministry of the Environment

We intend to keep the Swedish Ministry of the Environment informed of our main results. For these contacts we will seek the advice and the mediation of the Chemicals Inspectorate and the Environmental Protection Agency.

European Commission, DG Environment

In phase 1, NewS has had valuable contacts with various decision-making and administrative bodies in the European Union. Mistra helped us to arrange a seminar in the European Parliament in September 2001 on research results from the programme. The seminar was well-attended and gave rise to important contacts with several organizations, including DG Environment. NewS seems to be a useful source of information for DG Environment due to our focus on basic strategic issues in chemicals control.

Unfortunately, very few research programmes have such a focus. Two projects leaders from NewS have been invited to present results from NewS at meetings with the personnel of the Chemicals Unit of DG Environment who work with the implementation of REACH. We have an agreement that the NewS programme will continuously inform DG Environment of our results, in particular with respect to regulatory issues and to the programme synthesis. We have reasons to believe that these contacts will be very valuable for the programme as a whole. We will of course keep the Swedish National Chemicals Inspectorate informed of our contacts with DG Environment.

European Commission, DG Enterprise

We have an agreement with Wolfgang Hehn at DG Enterprise that we will keep them informed of our results, and on suitable occasions meet with them to discuss issues of common interests.

OECD

One of the members of the NewS Board will be a person who has a leading role in the OECD's chemicals programme and who will ensure a good communication between NewS and that programme.

Swedish Industry

The Swedish Plastics and Chemical Federation is the trade organisation of the Swedish chemicals industry. They have member companies in the basic chemicals, pharmaceutical, paint, petrochemical, and chemical engineering industries. Through their membership in the Confederation of Swedish Enterprise (Svenskt näringsliv) they cooperate with other major branches of industry in Sweden. They are also members of the co-operative organisation of the European chemical industry, CEFIC (European Chemical Industry Council). In phase 1 they provided our programme with very valuable contacts in CEFIC.

In phase 1, we had important inputs from industry through the vice chairperson of the programme board (Anita Ringström), who is also deputy director general of the The Swedish Plastics and Chemical Federation. NewS researchers have also been regular speakers at the yearly "Kemikaliedagarna", that are arranged by the The Swedish Plastics and Chemical Federation. In phase 2, it is important to broaden our cooperation and dialogue with industry. We need to discuss various aspects of the programme synthesis with representatives of Swedish industry, and to use the information and advice that they can offer in our efforts to develop risk assessment methodology that can be used in practice.

In our preparations for phase 2 we have discussed our future cooperation with industry with the Swedish Plastics and Chemical Federation (Anita Ringström and Michael Reineskog). We are pleased to report that they have agreed to be our reference point for contacts with industry.

The most useful and realistic form of cooperation between NewS and industry is to arrange a series of meetings for discussions of issues of common interest. The first two meetings that we plan are the following:

(1) The Swedish Plastics and Chemical Federation will help us with the necessary contacts so that we can invite companies that use flame retardants in their production to a round table meeting. At this round table, results on BFRs from the NewS programme will be presented, and an opportunity will be offered to discuss how this information can be used in a risk management process. The Chemicals Inspectorate will of course also be invited to participate in this round table.

(2) We plan for a special session on risk assessment under uncertainty as part of the yearly Kemikaliedagarna. The preliminary schedule is for this to take place in 2004. Kemikaliedagarna is probably the best forum for reaching the Swedish chemical industry. At this meeting, several of the NewS projects will present our results, and we will offer our ideas for the programme synthesis for a general discussion.

The Swedish Association of Environmental Managers (Näringslivets miljöchefer, NMC): During phase 1 the programme has had regular contacts with The Swedish Association of Environmental Managers (Näringslivets miljöchefer). These contacts have included presentations made by NewS researchers at NMCs meetings and the exchange of written information.

Programme deliverables

PROGRAMME DELIVERABLES

- (1) *A model for risk assessment extending into risk management. The new model is based on frequent feedback and exchange of signals between scientists, regulators and industry.*
- (2) *Decision-theoretic methods to optimize testing, priority-setting, and risk abatement.*
- (3) *A chain of events model in order to obtain as early signals as possible from potential health and environment problems.*

Programme deliverables

Includes also all deliverables from the synthesis and communication projects

Deliverables planned for 2003	Delivered 2003
A manuscript outlining simplified and tiered approaches to the assessment of reproductive and developmental toxicity.	A joint seminar with ReproSafe has been held. A report from the seminar is finalised, and a manuscript is in preparation
A manuscript that outlines the changes in the decision procedure for chemicals regulation that have been proposed in NewS.	Manuscript in preparation. The yearly report from 2003, to be distributed in early 2004, will take the form of a booklet in English, "Better risk management within REACH", that describes the NewS model in its present state of development and explains how it is relevant to REACH. It will be distributed through Europe to key regulators, stake-holders, and scientists.
A seminar with representatives of industry in which results on BFR substances are reported, and possible consequences for risk management are discussed.	We have made several attempts to engage industry in such an event. Renewed attempts will be made.
A database for data on the model substances produced within the programme. The relevant data will be submitted for publication in the IUCLID database. Additional data (from other sources) that are relevant to the programme will be added to this database and updated regularly. The database will be made available via the internet in accordance with the standards for scientific publication.	Work is in progress.
A risk assessment in which the notion of precautionary defaults is applied to BFRs of regulatory interest.	Manuscript available. Will be submitted in 2003.
Coarrangement of a Swedish-American seminar on precautionary approaches to chemical risk management.	Has been arranged in Industrihuset in Stockholm, in cooperation with Plast och Kemiföretagen and King's college, London.
A first report on the science-policy and fact-value distinctions in chemicals policy and how they affect the regulatory process.	Available as a manuscript. Wandall, B. "Values in Science and Risk Assessment" <u>Has been published in <i>Toxicology Letters</i>.</u>
A first report on the accuracy of the present classification system, based on a statistical study of misclassifications.	Manuscript has been published in Toxicology Letters.
A methodological report on how statistical correlations between toxicity test outcomes can be used to determine optimized testing strategies.	Manuscript is in preparation.
An manuscript on to what extent various types of toxicity data modify classifications made solely on the	Database has been updated and analyses are ongoing.

basis of acute toxicity, with conclusions for test strategies and the optimal construction of tiered test systems.	Project has been extended to cover also <i>in vitro</i> data.
A manuscript outlining simplified and precautionary approaches to the assessment of reproductive and developmental toxicity.	A joint seminar with ReproSafe has been held. A report from the seminar is finalised, and a manuscript is in preparation.
An article analyzing how uncertainties are reported in comprehensive risk assessment documents produced in the European Union.	One article is submitted and one manuscript is in preparation. <u>The first article has been published in <i>Regulatory Toxicology and Pharmacology</i>.</u>
A seminar with representatives of industry in which results on BFR substances are reported, and possible consequences for risk management are discussed.	We have made several attempts to engage industry in such an event. Renewed attempts will be made.
A database for the data produced within the programme on the model substances. Additional data (from other sources) that are relevant to the programme will be added to this database and it will be updated regularly. The database will be made available on the internet in accordance with the standards for scientific publication. This activity will be coordinated by the synthesis project.	In progress.
A risk assessment in which the notion of precautionary defaults is applied to BFRs of regulatory interest.	<u>Rudén, C., Breitholtz, M., Eriksson, J., Green, N. "Testing and risk assessment of persistent and bioaccumulating chemical substances - improvements within REACH." manuscript.</u>
An article that outlines the changes in the decision procedure for chemicals regulation that have been proposed in NewS.	Manuscript in preparation. The yearly report from 2003, to be distributed in early 2004, will take the form of a booklet in English, "Better risk management within REACH", that describes the NewS model in its present state of development and explains how it is relevant to REACH. It will be distributed through Europe to key regulators, stake-holders, and scientists.
<u>A joint seminar with ReproSafe discussing risk assessment and management of reproductive toxicity.</u>	Performed on October 8, 2003.
<u>A report from the NewS/ReproSafe seminar on risk assessment of reproductive toxicity.</u>	Has been sent out to all participants and will serve as the basis for further joint activities.
Arrange a major international conference within 1 – 2 years Arrange a seminar on NewS aspects in Brussels in connection with discussions of future chemicals policy.	A Swedish-American workshop on the precautionary principle was successfully completed in the form of a high-level conference in Stockholm. Arranged in cooperation with Plast och Kemiföretagen and King's College, London.
Annual popular report in Swedish.	Annual report distributed

Broschure in English.	Available.
Meetings with NewS projects leaders, at least twice a year.	Two meeting with NewS project leaders have been held.
Continuous up-date of NewS web-site.	The web-site has been continuously updated.
Attend meetings of importance for the developments of NewS.	The agency group has been extended with a representative from the Work Environment Authority. The group has identified contact persons at the authorities, added persons to the programme's e-mail list, developed ideas for Policy Fora, and given input to the programme's work with REACH.
To use the net-work of stakeholders to distribute brochures, 2. inform about NewS publications and activities 3. promote Policy Forum meetings.	A list of policymakers and scientists interested in policy issues is compiled. The list currently contains 87 key persons, and is continuously updated.
	An article showing major discrepancies in the current classification and labelling system has been sent out to our list of policymakers and scientists.
	The first risk assessment of BFRs was discussed in detail at the programme meeting on October 13-14.
	A contribution from the programme to the Commission's internet consultation on REACH has been submitted.
	<p>A seminar presenting the NewS programme to KemI's risk assessment group was held March 31.</p> <p>A seminar with focus on statistics has been held. It has led to a reorientation of the NewS' statistics project to deal more with REACH, and issues related to technical guidance documents.</p> <p>A seminar presenting NewS, open to all KemI employees was held in October.</p> <p>A meeting with the director general of KemI was held held in October.</p>

<p>Seminar: QSAR in theory and practice.</p> <p>Seminar: Background and theories behind the precautionary principle and the regulatory aspects.</p> <p>Course: Scientific philosophy</p>	<p>Due to the low number of graduate students in phase 2 of the programme, there is no basis for a graduate research school of the same type as in phase 1. Instead we (1) arrange other conferences that contribute to updating our competence, such as a joint conference with ReproSafe on risk assessment and regulation of reproductive and developmental effects (Uppsala Oct. 8) and (2) offer industry to contribute to REACH-related courses.</p>
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Deliverables planned for 2004	Delivered 2004
A Policy Forum conference on science-based precaution, probably in Brussels.	Due to advice from environmental organizations, the meeting is instead planned to take place in early 2005. It will focus on the management of toxicological uncertainty and on the use of chemical properties in a simplified risk assessment process.
A Policy Forum conference on proxies and precaution, probably in Great Britain.	A presentation was made by the programme manager at a meeting in Cambridge University on Sept 23, 2004, with representatives from academia and industry, It will be followed up with meetings on the UK and the USA in 2005.
A seminar on risk assessment under uncertainty at the yearly meeting (Kemikali dagarna) of the Swedish Plastics and Chemical Federation. (Depends, of course, on Plast- och Kemiföretagen, who arrange these conferences.)	We hope for an invitation in the year to come.
Input to the Commission's interimistic working groups on REACH, including the Technical Guidance Document, with focus on test methods and strategies, classification and labelling, and fast assessment methods such as QSAR and category approaches, after consultation with the agency group.	Continuous discussions with KemI. Input to the process goes through KemI.
A manuscript on adequacy conditions for characterizing uncertainty in risk assessments.	Available as manuscript.
A manuscript on bias in toxicology and risk assessment, and how it can be coped with.	Has been published in <i>Toxicology Letters</i> Wandall, B: Values in science and risk assessment, in <i>Toxicology Letters</i> , vol. 152 (2004) pp. 265–272.
A seminar with ReproSafe and relevant agency representatives on risk assessment and management of reproductive and developmental toxicity.	Cooperation with ReproSafe is ongoing. This seminar is however still in planning.

A joint NewS/ReproSafe manuscript on risk assessment of reproductive and developmental toxicity.	In planning.
A manuscript outlining simplified and precautionary approaches to the assessment of reproductive and developmental toxicity for BFRs.	Work is ongoing.
The article that outlines the changes in the decision procedure for chemicals regulation that have been proposed in NewS will be finalised.	Rudén, C. and Hansson, S.O. "Improving REACH" submitted for publication in a special issue on the use of science for policymaking in <i>Regulatory Toxicology and Pharmacology</i> .
An article proposing test and assessment strategies for low volume chemicals.	Hansson, S.O. and Rudén, C. 2004 "A Science-Based Strategy for Chemicals Control", <i>Industry and Environment</i> vol. 27(2-3):12-18.
A book or a series of articles outlining the major outcomes of NewS, with a particular emphasis on policy options.	The book "BETTER CHEMICAL CONTROL WITHIN REACH" has been distributed to relevant actors (600 copies) world wide. This has turned out to be an efficient mode of communication judging by the responses we have received from regulators, scientists and NGOs. Both the SNF and the Kemikaliesekretariatet have used the book and helped us distributing it.
At least one article outlining how exposure analysis can be simplified for the purpose of risk assessments.	Björkdahl, C. "Simplified assessment of exposure of chemicals with the help of 'intake fraction'" Master thesis 2004 Wajzman, D. "Bedömning och hantering av miljörisker med läkemedel. Försiktighetprincipen och fördelning av risk och nytta" Master Thesis 2004. Wajzman, D. and Rudén, C "Identification and evaluation of computer models for predicting environmental concentrations of pharmaceuticals and veterinary products in the Nordic environment" Submitted manuscript
<u>Participation in a two-day conference on REACH organised by the Institute for International Research AB.</u>	Has been realized. Rudén key note speaker and chair. NewS-model discussed with representatives from industry.
<u>A proposal for a session on REACH and risk assessment at the 2005 international EUROTOX conference will be submitted to the risk assessment speciality group (RASS) of EUROTOX.</u>	The submitted draft proposal has been accepted by the EUROTOX planning committee
The joint article from phase 1, on precautionary defaults, will be sent out to our list of policymakers and scientists, with an accompanying letter informing them of NewS.	Has been done.

A book on precaution in chemical risk management, in cooperation with King's college in London, with a focus on European – American dialogue.	Has not yet been realized due to difficulties in collecting contributions.
The agency group will actively search for arrangements through which personnel at KemI spend part of their time ("kompetensutvecklingstid") in NewS projects, participating in their work and bringing regulatory experience to the projects.	The offer has been given, but has not been realized.
Communications with key persons in relevant international organisations.	Continuous contacts with EEB, the Commission and national NGOs.
Seminar in Brussels with the key officials at DG Environment.	Offer still stands but has not been possible to fit in to their planning.
Meeting with DG Enterprise.	Offer still stands but has not been possible to fit in to their planning.
Contacts with CEFIC, to present our results and plans and in particular to discuss future cooperation in research on persistency characterization.	A meeting with CEFIC, Plast och Kemiföretagen and NewS representatives was held 2004-02-13.
A round table with industry in which results on BFRs from the NewS programme will be presented.	The offer has been made, and is still standing. It has however not yet been possible to get key industries sufficiently interested.
The list of addresses to key persons will continuously be updated and used for sending out policy-related material from NewS.	Has been done and is ongoing.
	<u>Rudén participating in REACH conference arranged by the Danish Society for Nature Conservation in Copenhagen 18/10-2004</u>
	<u>The NewS-model was presented at Miljödepartementet (Hansson, Melin, Rudén) 3/11-2004.</u>
	<u>Rudén presented the NewS-model at FOM (Forum för organiska miljögifter) 26/10-2004</u>
	<u>The NewS-model was presented at a meeting arranged in cooperation with Svensk förening för toxikologi (Rudén and Hansson) 25/5-2004.</u>
	<u>The NewS-model and communication strategies were discussed at a meeting with Naturskyddsföreningen (Hansson, Melin, Rudén) oct 2004.</u>

Deliverables planned for 2005	Delivered 2005
Two policy forum conferences on themes to be decided by the new NewS board.	2004
An article proposing test and assessment strategies for low volume chemicals.	2004
At least one article outlining how exposure analysis can be simplified for the purpose of risk assessments.	2004
An article proposing unified and principled ways of reporting uncertainties in risk assessments.	2004
Risk assessments of BFRs, continuously updated.	
An article analyzing how uncertainties are reported in comprehensive risk assessment documents produced in the European Union.	2004
At least one article outlining how chemical structure and physico-chemical properties can be used as simple indicators in priority setting, with a particular emphasis on the application of the precautionary principle.	
A special session on REACH and risk assessment at the 2005 international EUROTOX conference.	
A yearbook in English with a wide presentation of the programme will be published and distributed.	
Preparations for the 2005 yearbook that will focus on the use of chemistry in a simplified risk assessment process.	
Seminars on the NewS model for improving the REACH proposal. The seminars will be held in Brussels and probably in selected new member countries.	
Presentations of the NewS model are planned at meetings with key regulators and scientists in the United States.	
Presentations of the NewS model are planned at meetings with key regulators and scientists in the United Kingdom (2005 or 2006).	
Preparation and announcements for a large conference in late 2006.	
A seminar on risk assessment under uncertainty at the yearly meeting (Kemikaliedagarna) of the The Swedish Plastics and Chemicals Federation. Probably in 2005.	

A series of reports on the science-policy issue in chemicals regulation, with proposals for how the regulatory process can be improved to avoid confusions or stalemates related to the science-policy distinction.	
At least one manuscript investigating potential correlations between results different toxicity tests analysed in the light of the classification and labeling system	
At least one manuscript investigating potential correlations between C, M and R classifications and chemical properties.	
One manuscript defining methodology for evaluating risk assessment and management.	
At least one article outlining how chemical structure and physico-chemical properties can be used as simple indicators in priority setting, with a particular emphasis on the application of the precautionary principle.	
Meetings with NewS projects leaders, at least twice a year.	
Continuous up-date of NewS web-site.	
A series of popular materials that present the major results from NewS.	
<u>A literature search on breast milk transfer, chemicals detected in other human tissues, and on data on toxicokinetics related to milk transfer.</u>	
<u>A first analysis and report from the literature study on breast milk transfer.</u>	

Planned for 2006	Delivered 2006
A seminar on risk assessment under uncertainty at the yearly meeting (Kemikaliedagarna) of the Association of Swedish Chemical Industries. Probably in 2004.	
At least one article outlining how chemical structure and physico-chemical properties can be used as simple indicators in priority setting, with a particular emphasis on the application of the precautionary principle.	
Risk assessments of BFRs, continuously updated.	
A series of reports on the science-policy issue in chemicals regulation, with proposals for how the regulatory process can be improved to avoid confusions or stalemates related to the science-policy	

distinction.	
<u>At least one article outlining how QSARs can be used as simple indicators in priority setting, with a particular emphasis on the application of the precautionary principle.</u>	
<u>At least one manuscript investigating potential correlations between toxicity and physico-chemical properties.</u>	
Publication of the final yearbook, presenting the NewS-model.	
International conference.	

Overview of the programme

It is essential for the new strategy that decisions on chemical substances be based on information about both their toxicological and ecotoxicological properties. It is also a central feature of this strategy that chemical information will be used, both to supplement toxicological/ecotoxicological information and for preliminary assessments when toxicological/ecotoxicological information is lacking. Therefore, the NewS programme contained in its first phase, in addition to synthesis-oriented projects, projects devoted to toxicology and ecotoxicology, and to exposure. In the second phase, this structure will be maintained, and also announced more clearly through the division of the projects into three groups: Synthesis and communication, Toxicology and ecotoxicology, and Exposure.

Synthesis and communication

In its first phase, NewS contained two research projects with synthetic/comprehensive tasks: the Synthesis project (#11) and the Biometrics project (#15), that was a late addition in the programme. In addition, there were three communication projects: the Policy Forum, the Graduate Research School, and Communication and collaboration.

In phase 2, each of these projects will continue. Furthermore, a social science project on the EU decision process is added to the programme. In addition, the contributions from the other projects to synthesis and communication will increase, so that the whole programme shifts its focus in that direction. Below, an overview of the phase 2 programme is presented.

Project #1: Programme synthesis. The synthesis project will cooperate with all other projects in the programme in developing the overall method for risk assessment and risk management that is the ultimate goal of the programme. In phase 2 the emphasis on regulatory toxicology will increase. All synthesis work will be collaborative and the synthesis project will have a major role in coordinating the production of programme deliverables, including texts written in cooperation with several other projects.

Experience from phase 1 confirms that it is essential for success to be able to respond to developments in the rapidly changing field of chemicals regulation. Therefore, the planning must be flexible. The developments following from the White Paper of the European Commission will be a major concern, and so will the process of international harmonization of chemicals regulations.

The major activities of the synthesis project coincide with the planning for synthesis that was outlined in the above chapter on Synthesis and communication and are further detailed in the project plan: regular risk assessments of the model substances, a database for data on the model substances, studies of the classification system, optimization of test strategies, the use of chemical information (including QSAR) for risk assessment purposes, simplified exposure analysis, improved methods for the assessment of reproductive and developmental toxicity, uncertainty characterization, and clarification of the science/policy borderline in risk assessment and risk management.

Project #2: Communication and collaboration. This project consists of three subprojects; Policy Forum, Communication and collaboration, and the Graduate research school.

Project #2.1. The Policy Forum. This is an international forum for qualified discussions on the strategy for solving the health and environmental problems connected

with chemical substances. The plans for the Policy Forum in phase 2 were laid down in the above section on Communication.

Project #2.2: Communication. The activities of this project were described above in the sections on Communication and collaboration.

Project #2.3: The Graduate Research School. Seminars and workshops for graduate students involved in the programme were of major importance in phase 1, and will remain so in phase 2. We believe that these courses will continue to attract and benefit persons outside of the programme, such as the scientific staff of both government agencies and industry. In the first year of phase 2, we intend to arrange a short course that focuses on basic risk assessment methods, on the regulatory context, and on decision-making under uncertainty. The themes for the graduate school in the following three years will have to be determined later.

Project #3: Biometrics. This project aims at ensuring a high quality in the use of statistical methods, including experimental designs, and biometrical models in the programme as a whole, in particular with respect to the combination of results from the different projects in the programme synthesis. Since the statistical and mathematical tasks that need to be performed in the NewS project are rather diversified, a wide range of statistical and mathematical approaches and models will be used. The application of decision-theoretical methodology to toxicological and ecotoxicological data, and in particular the construction of optimised test strategies, are parts of the programme synthesis that require considerable statistical input.

Project #4: The EU decision process for chemicals regulation. Surprisingly little is known about the actual workings of the decision process on chemicals in the European Union and how influence is gained in this process. In particular, the distribution of tasks and influence between experts and policy-makers, between Commission and non-commission participants, between authorities and industry, and between different countries, are of vital importance for the final outcome. This study will provide a factual background for discussions on possible future reforms of the decision processes within EU. It will also analyse these issues in the context of the general discussion on decision processes in the European Union, which is essential both for the understanding and as a basis for discussions on possible reform. The major activities within the project are (1) empirical description of the decision-making process, including a network analysis, (2) case studies of individual decisions, and (3) normative analysis.

Toxicology and ecotoxicology

In phase 1, promising results have been obtained in developing relevant ecotoxicological tests, for example the production of a draft OECD guideline for full life-cycle tests with marine copepods, and methods to identify reproduction disturbances and biomarkers responses in fish. The guideline will simplify an international acceptance to use the method on a regular basis for environmental risk assessment. Our work with the OECD guideline will be followed through. Continued ecotoxicological work in phase 2 will focus on new and further development of simplified ecotoxicological methods that can replace or supplement present standard tests on invertebrates and fish, in particular simpler and/or more sensitive tests of reproductive effects.

In phase 1, the programme contained three experimental projects devoted to human/mammalian toxicology. Continued work in phase 2 will focus on the further development of simpler and/or more sensitive test that can replace or supplement the standard tests presently in use. It is a major challenge to develop improved test methods and procedures to determine effects and exposure-response relationships during critical

developmental stages (critical windows). An integrated approach is therefore proposed, that includes studies of neurobehavioural disturbances, improved methods to measure exposure via mother's milk, transplacental transport and local, and tissue-specific metabolic processes mediating toxicity in the developing organism.

Project #5: Development of invertebrate tests. It was discovered in phase 1 that the effects on the *Nitocra* population level are not necessarily as sensitive as effects on the individual level. Therefore, possible genetic changes in the surviving population will be followed up, in order to investigate if genetic biomarkers can be developed and used in new, sensitive and low cost test systems. The mysid shrimp *Neomysis integer* (body size about 20 mm) will be used to develop a new crustacean system in which tissue sampling for physiological and hormone level measurements is practicable. Furthermore, a similar concept as that developed in phase 1 will be applied to produce a cost effective reproduction test system with a new crustacean (e.g. *Canthocamptus* sp.) that represents the typical Scandinavian oligotrophic/weakly buffered fresh-waters that are threatened by low pH and by long distance air pollution by POPs and other toxic substances. The test will be designed as a chronic full life-cycle test (2 generations) including sexual reproduction and larval development and will, if successful, be developed into a standardized test guideline (e.g. SIS, ISO, OECD etc.).

Project #6: Development of fish tests. Additional low-dose and long-term exposure experiments with the model compounds will be performed with a focus on reproductive success. Several interesting results from phase 1 will be followed up. Hence, it was found in phase 1 that musk ketone and tonalide affect early life stages of zebra fish at environmentally relevant water concentrations while exposure to brominated flame retardants and their metabolites result in different responses indicating different modes of action and variation in toxicity. The underlying mechanisms for these disturbances will be investigated, in order to find out how they can be used for the development of new test systems. Another interesting result is that the flame retardant HBCDD inhibits CYP1A and seems to induce peroxisome proliferation. Since peroxisome proliferators have been studied only sparingly in fish, further studies are required to clarify the significance of these findings. Therefore, pregnant guppy and eelpout will be exposed to HBCDD to determine maternal transfer and effects (including biomarker responses) in the offspring. Furthermore, characteristic gene expressions caused by exposure to selected model compounds (including HBCDD) in fish will be investigated with techniques for expression profiles of mRNAs and proteins. This approach will improve our battery of fish reproductive tests and increase our understanding of biological responses to new and potential environmental contaminants.

Project #7.1 Mechanisms behind functional anomalies of the CNS. It was shown in phase 1 that exposure to the model substances during a defined critical stage of neonatal brain can induce functional anomalies of the CNS development in the mouse. The "neonatal animal model", that was developed in phase 1 of NewS, was adopted by the Swedish National Chemicals Inspectorate. For phase 2, a further development of this animal model is planned to find mechanisms involved in the development of functional anomalies of CNS, including gene expression, functional proteins, neuroreceptors and apoptosis in combination with spontaneous behavioural tests and toxicokinetic studies. Interaction between the model substances, and other environmental toxicants will be studied. The intention is to develop and systematize this methodology so that it can be used for standardized testing of new and existing chemicals.

Project #7.2 Endocrine organ culture test. A novel tissue culture procedure will be used to determine the ability of brominated and chlorinated pollutants to elicit endocrine disruption and cell-specific toxicity in fetal and maternal adrenal and gonadal tissue in

rodents and wild animals (if possible also in human tissue). A purpose of this comparative approach will be to enable modelling of effects in highly exposed and sensitive species/populations. This novel tissue-slice culture procedure is a promising tool that can strengthen risk assessment of cell-specific toxicants affecting e.g. the developing endocrine system.

Project #8: Breast milk contaminants. The method for milk collection developed in phase 1 will be improved and finally drafted as a test guideline. In order to fine-tune the methodology, the effect of reducing the litters on milk excretion will be investigated, and so will the effects of anaesthesia and repeated milking. In addition, the bioavailability of different BDE congeners will be compared after simulated digestion and uptake in Caco-2 cells. The purpose of these adjustments of the method is to make it more generally useful and more suitable for inclusion in guidelines for approved testing methods. The refined method will be used to compare milk excretion of different brominated diphenyl ethers and to study effects in the mammary gland on milk synthesis. Mechanistic studies will be performed in order to understand the transport mechanisms for chemicals across the mammary gland. Effects of BDE-99 in the suckling offspring, such as EROD activities in the liver and thyroxine levels in serum, will be studied. This project was concluded in 2004.

Exposure

The exposure assessment strategy section is devised of four subprojects that combine to provide information for the assessment of chemicals within the programme synthesis. Information will be provided at different levels of complexity to reflect use within different tiers of the overall NewS assessment. Recurring risk assessments within the Synthesis project will provide feedback for what is most crucially required from the Exposure projects and will provide an additional check for the progress of these subprojects. Project #9 provides mass balances and general methodology for exposure analysis. Project #10 is devoted to the definition and determination of persistency for regulatory purposes. Project #11 develops QSARs as regulatory tools, and also develops a model for biomagnification using these tools. Project #12 supports the other projects in the programme with chemical analysis and synthesis.

Conceptually, the projects in the exposure assessment strategy group will use as a starting-point the vPvB system of screening, adopted by the Swedish Government, in which compounds that are both very persistent and very bioaccumulative are highlighted for risk management action and investigation in subsequent tiers of risk assessment. This two-dimensional structure will be extended to include other indicators pertinent to exposure evaluation, such as production volume and/or volatility. The resulting graphical volume would contain those chemicals for which action should be considered, or that require further assessment within a more complex tier when additional, specific data are obtained. If data for any of the indicators were lacking for a chemical, the precautionary default value would inevitably place it within the 'concern volume'. The desire to minimize the frequency of recourse to default values requires that the indicators (at least for a first tier of assessment) need to be simple to define.

A principal goal of the Exposure Assessment project, therefore, is to establish simplified indicators of this property. For these simplified indicators of exposure to be valid it is necessary that they be based on greater scientific understanding, as opposed to merely practical considerations. Each subproject is constructed around the need to understand the scientific principles and details that underpin the separate issues that make up exposure.

Project #9: Completing the conceptual model of sources and materials flow. In order to get a better grip of the mass balances of the model compounds major routes of abiotic transport will be identified and classified in range and importance. Thus, sources will be identified and quantified within the study area as well as amounts transferred via environmental processes and imported via industrial products and consumer goods. A strong emphasis will be laid on the technosphere. In cooperation with several other projects a conceptual model will be constructed to predict flows of the model substances in commercial products from the technosphere into the Baltic Sea. The project will also contribute to the synthesis activity on simplified exposure analysis, that will largely be built on this model. This project will be a cooperative endeavour with the National Chemicals Inspectorate.

Project #10: Defining persistency for improving regulatory practices. At the end of phase 1, a subproject was initiated to look into ways to define persistency. This work is now up-graded to a separate project and is based on the hypothesis that persistency of a chemical can partly be described by the sum of the inherent reactivities, determined as reaction constants of a substance under defined conditions for photochemical transformations, radical reactions, substitution and/or elimination reactions (hydrolytic conditions), oxidation and reductions, all known to occur in the environment, either as part of biotic or abiotic processes. Reactivities for a broad set of BFR compounds will be summarized in the form of 'reactivity constants' (k_i) for each of the five mechanistic genres. Quantitative structure-reactivity relationship (QSRR) models will then be constructed based on the k_i values and physicochemical parameters for the training set of BFR compounds. Comparison with experimental k_i values will be used to evaluate the validity of the model

Project #11: QSAR as a regulatory tool. This project will present QSARs for predictive purposes as well as a tool for interpreting existing data. QSARs will be developed for persistency and bioaccumulation potential. Special attention will be given the possibility to obtain robust QSARs with high general applicability. This means that the models will be developed but also tested by an external set of chemicals. The QSARs will include physico-chemical properties of the target compounds as determined both experimentally and through quantum chemical semi-empirical calculations. Multivariate methods, such as principal component analysis and partial least squares, will be applied to correlate the chemical characteristics of the compounds with measures of persistency and bioaccumulation potential.

In phase 1, data were collected for the development of a biomagnification model to predict the exposure of Baltic Sea food webs. In phase 2, this work will be incorporated in the present project and the emphasis will now be in analysis of the collected data. The transport of the selected compounds in the food chain and between different compartments in the animals will be modelled by Quantitative Structure-Biomagnification Relationships (QSBMR) as outlined in phase 1. An important part of this work will be the development of relevant and interpretable descriptors for chemicals with diverse chemical/physical properties.

Project #12: Chemical synthesis. In phase 1 several of the NewS projects needed help and advice in matters concerning chemical analytical problems. In phase 2, one laboratory will be responsible for that part as well as for supplementing reference compounds, standards and labelled/non-labelled material required for toxicity testing etc. This work may require methodological developments of the synthesis procedures.

Project leaders

Bengt-Erik Bengtsson, assisting project leader. Professor of ecotoxicology at Stockholm University, who has specialized in combined effect studies and test strategies for single substances and industrial effluents in fish, invertebrates, and plants. (Project #5, Development of invertebrate tests.)

Åke Bergman, professor of environmental chemistry at Stockholm University. His main research areas are risk assessment through chemical analysis, biotransformation, and synthesis of persistent and semi-persistent substances. (Project #10, Persistency and project #12, Chemical synthesis.)

Ingvar Brandt, professor of ecotoxicology at Uppsala University. His main research areas are tissue disposition, metabolite formation, tissue- and cell-specific toxicity, and developmental toxicity in mammals, birds, and fish. (Project #7.2, Mechanisms behind functional anomalies of the CNS and endocrine organs.)

Magnus Breitholtz, PhD in marine ecotoxicology at the Institute of Applied Environmental Research at Stockholm University (Project #5 Development of invertebrate tests).

Per Eriksson, professor at Uppsala University. His research is primarily devoted to developmental toxicology in mammals, with emphasis to the fetal- and neonatal periods. (Project #7.1, Mechanisms behind functional anomalies of the CNS).

Lars Förlin, professor of zoophysiology at Göteborg University. His research is devoted to fish health and toxicology. (Project #6, Development of fish test.)

Sverker Gustafsson, professor of political science at Uppsala University. His research is focused on political and administrative processes in the European Union (project #4, The EU decision process)

Sven Ove Hansson, professor of philosophy at the Royal Institute of Technology, Stockholm. He has specialized in decision theory and the philosophy of risk, with an emphasis on applications to toxicological risk assessment and risk management. (Programme director, phase 2.)

Agneta Oskarsson, professor of food toxicology at the Swedish University of Agricultural Sciences, Uppsala. Her research is primarily devoted to lactational transport and neonatal effects of toxic substances and to the availability and transport of cadmium. (Project #8, Breast milk contaminants). Project was concluded in 2004.

Dietrich von Rosen, professor in statistics at the Swedish University of Agricultural Sciences, Uppsala. His primary research interests are multivariate statistical analysis, linear models and applied linear algebra (Project #3, Biometrics).

Christina Rudén, PhD in toxicology. Her research is devoted to regulatory toxicology. She is a member of the same interdisciplinary research group at the Royal Institute of Technology, Stockholm, as the programme manager for phase 2. (Project #1, Synthesis).

Mats Tysklind, professor of environmental chemistry at Umeå University. His research is primarily devoted to chemical analysis of persistent pollutants and their transformation products. (Project #11, QSAR as a regulatory tool).

Ulrika Örn, is a PhD at the department of Environmental Chemistry, Stockholm University. (Project #9, Sources and materials flow).

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