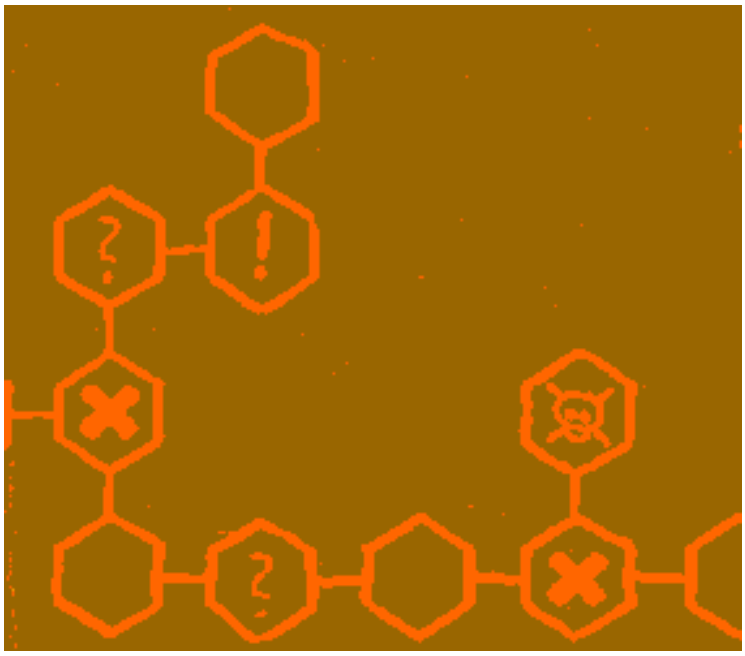
TEKNOLOGI-RÅDET

The non-assessed chemicals in EU

Report and recommendations from an interdisciplinary group of Danish experts



Report from the Danish Board of Technology 1996/5

ISBN: 87-90221-10-9
ISSN: 1395-7392

Preface

About 15 years ago the American National Research Council reported, that no information was available about the possible toxicity of 80 % of the more than 50.000 industrial chemicals in use in the USA. Simultaneously, from Europe it was informed that a vast majority of the more than 100.000 chemicals which by the European Commission had been registered as marketed within the EU, had never been subjected to investigations or evaluations for effects on health and environment, *e.g.* toxicity, carcinogenic properties, global and/or local effects on the environment etc. Any such investigation is technically, scientifically, temporally and economically demanding, and because of the size of the problem, societies were facing a large - almost insurmountable problem.

In the spring of 1995, the Danish Board of Technology decided to initiate a review process dealing with the still unsolved problem of non-assessed, existing chemicals. An expert working group was established to perform a review which should describe/analyse the problem in order to 'promote the understanding and submit the problem to debate'. The Danish Board of Technology asked the question whether:

'... the many non-assessed chemicals pose a risk of a ticking bomb, which constitutes a latent threat to the health of human beings and/or the environment ?'

and the working group was requested

&ldots;to focus on the non-assessed, existing chemicals and to evaluate proposals for strategies towards more fast and earlier investigations of them. The consequences of such strategies should be part of the considerations of the working group, and possibly a plan of action or elements of such plan should be suggested for presentation and discussion in a public debate - primarily in a forum of political decision-makers and interested parties, but possibly also calling upon a broader interested and informed public.

In its review work, the working group should deal not only with the possibility of achieving a highest possible reduction in the workload required for the assessment of chemicals. It should also consider possibilities for reduction of toxic or environmental risks that might result from the use of chemicals.

The working group consisted of:
Finn Bro-Rasmussen, professor, The Technical University of Denmark (DTU) (chairman).

Helle Buchart Boyd, senior consultant, food scientist, The Danish Center of Toxicology (ATV/DTC).
Christian Ege Jørgensen, environmental planner, Centre of Alternative System Analyses, (CASA)
Preben Kristensen, head of department, ATV Institute of Water Quality (ATV/VKI)
Elle Laursen, MD, medical specialist, The National Board of Health,
Hans Løkke, PhD, director of research, Department of Terrestrial Ecology, National Environmental Research Institute (DMU)
Kjeld Mann Nielsen, group leader, Directorate of the Danish Working Environment Service,
and
Johs. Grundahl, project manager representing the Danish Council of Technology.

All members of the working group were appointed individually, and viewpoints expressed in this report do not necessarily represent the viewpoints of their respective institutions.

From the spring of 1995 and until the spring of 1996, the group held 9 meetings during which actual problems were identified and taken up for examination. It was agreed that a final report should refer to the procedures of notification and assessments of marketed chemicals as these had developed during recent years, now being expressed in legislation and administrative practice in the EU. It should thereby refer to schemes of classification, priority setting, and hazard and risk assessments of chemicals.

The result of this work is presented in this report which was first written in the Danish language. In practice, the report was developed chapter by chapter by group members, individually or in pairs, whereafter these chapters were dealt with editorially and merged into the final report. It is noted therefore,

- *in principle*, that such consensus creating process may imply that evaluations and joint statements can occur which does not necessarily and in all aspects cover every individual viewpoint held by the working group members, and

- *in practice*, some overlaps may be found in the report, either resulting from an effort to present single chapters as individually readable, or in order to avoid any suppression, resp. removal of single evaluations or individual viewpoints.

The working group has not attempted directly to answer the question originally raised by the Danish Council of Technology, whether the many non-assessed chemicals is in fact 'a ticking bomb' which constitute a latent threat to human health and/or the environment. It is felt, however, that discussions and recommendations presented in the report, indirectly do give comments and possibly also some answers to the question.

A summary of the report, including discussions of individual chapters and recommendations are collected in the first part of this report. This part is prepared by the working group on the basis of a joint interpretation of the state-of-the-art as described in Chapters 1-6. The first drafted report was presented before a 'midway seminar' and subjected to a detailed discussion arranged by the Danish Board of Technology at Sørup Herregård on 12.-13. March 1996. Corrections and proposals which emerged from this seminar and afterwards accepted by the working group, have been made part of the final report in the Danish language and as it now reads in its English version.

The Danish Board of Technology and members of the working group use this opportunity to thank and to express appreciation to all Danish and Nordic experts who accepted to take part in the Midway seminar. With contributions from all sides, an intense and constructive debate was initiated already on the basis of the first drafted report. This will hopefully create and further stimulate the continued interest in the problems raised.

The Danish Board of Technology

April 1996,

(eng. edition: August 1996)

Summary

Chemicals in society

It has been reported that approximately 11,6 million tons of chemicals are used every year in Denmark, *i.e.* in chemical and other industries, in agriculture as well as in commercial and domestic households. There exists, however, a large uncertainty concerning the actual number of chemicals which surrounds us in the form of products, materials or chemicals *per se* and which may affect man and his well-being, or have an impact on the quality of the environment, either directly or indirectly.

From the 10-15 million chemicals, which are presently known to exist, it can be anticipated that in the order of one per cent of these have a distribution and circulation of some significance in the society. In 1981 the EU registered and numbered 100.106 marketed individual chemicals and listed them in the so-called EINECS list, *i.e.* European Inventory of Existing Chemical Substances. In spite of this registration process there is still large disagreement concerning the exact number of chemicals which are actually found on the market of the EU today. Different estimates vary between 20.000 and 70.000.

In case more accurate estimates are wanted on the number of actually marketed (existing) chemicals, it is pointed out by the working group as a possibility - although not directly recommended - that a new registration of existing chemicals could be carried out.

Existing chemicals which are registered in the EINECS list shall not be further notified and a general submission of data to National or European authorities is not required. This means, that the vast majority of the 100.000 chemicals on the EU lists -whether they are used or not - are not assessed for hazards or risks to man and the environment, or they may be short of data for their proper assessments. This is in contrast to the requirements for so-called 'New Chemicals', *i.e.* all chemical substances that are brought to the European market after the EINECS-list was finalised. Presently this amounts to approximately 1500 individual chemicals which since 1981 have been individually notified to the so-called ELINCS-list, including submission of all information specified as relevant to their possible classification and hazard/risk assessment.

The major problem for new as well as for existing chemicals is that generally we have only poor knowledge about the impact and effects of chemicals on health and environment. This is true, not only for individual chemicals, but also for chemical mixtures, irrespective of their use *e.g.* in production or in products, or of their distribution in waste or in wasted material.

In the legislation on environmental chemicals, including chemicals in and around the working place, rules are established for the protection of health and environment against adverse effects resulting from the use of the chemicals. The Danish chemical legislation regulates the classification of chemicals and products which are found to be toxic, explosive, inflammable or otherwise dangerous to health or the environment. More specifically, it also deals with approval, use regulation and/or control of certain specialised product types,

such as pesticides. Detailed use regulations are further enforced for chemicals which are in use *e.g.* in foods, as pharmaceutical products or (partly) in cosmetics.

Suppliers of dangerous chemicals and products which are new (*i.e.* if first-time in use at a Danish workplace after 1. April 1983) must notify these before the Danish Working Place Inspection Service for registration in the so-called *Product Register*. This register is a shared responsibility of the National workplace and environment authorities, and it represents an activity which is only practised in a few EU countries, especially the Nordic countries, but it is found recommendable that similar registers are established in other countries as well.

Today, only chemicals classified as dangerous have to be notified to the Product Register. However, an extension by which *all* chemicals and products are included would increase the possibility that the register could be applied in general assessment and possibly use regulations.

Principles of chemical regulation

Chemical regulations, nationally and/or in the EU, include *e.g.*:

- notification of (new) chemicals
- classification, labelling and directions for use of chemicals which are dangerous to health and the environment
- use regulations, incl. procedures of approval, possible use restrictions, or prohibitions
- selection and prioritisation of chemicals, as well as risk assessments
- regulation of point source discharges of chemicals
- waste disposal, waste treatment, including transportation of dangerous waste
- voluntary agreements
- green purchasing policy

As a member of EU and of OECD, Denmark in its legislation of chemicals is highly dependent of any agreement and/or principle of regulations which are established internationally. This includes a number of the regulation systems already mentioned, especially classification and labelling, administration of notification schemes, hazard and risk assessment, establishment of limit values, specified individual prohibitions, voluntary agreements as well as taxes.

Regardless of the regulation systems chosen, it is a requirement that the systems do not infringe neither the EU treaty, nor any directives and regulations of the EU.

The chemical regulation is rather extensive, probably one of the most closely, harmonised areas of the EU. In practice, therefore, the possibility for enforcement of separate, national legislation is extremely limited, at least in questions where the marketing of chemicals are involved. Such possibilities only exist if they are in accordance with specified rules, and generally only as temporary, stricter Danish rules. One optional possibility, however, is mentioned, namely the use of the so-called the '*Environmental guarantee* ' given by the EU Treaty (Article 100 A, par. 4).

The area of chemical regulation is often characterised by conflicting interests represented by considerations and demands for stricter protection of health and environmental qualities on the one side, and requests - mostly industrial and commercial - for free mobility of products on the other side. Any Danish (or other national) rules concerned with imported products, although dictated by considerations of environment and

health, may be considered a technical hindrance to trade in case such rules are stricter than in the producing or exporting countries. This may create disagreements or conflicts relative to existing minimum or maximum rules in the EU, *i.e.* dependent on the degree of harmonisation or uniformity which is aimed at by those rules.

It is found satisfactory that discharges of effluent and treatment of waste materials from manufacturing processes in industrial installations increasingly seem to be regulated by way of minimum rules.

Even though regulations for the working environment according to the EU treaty states should be based on minimum directives allowing countries to enforce stricter rules, there is presently a tendency to draw the field of the working environment into the sphere of EU regulations, *i.e.* as a legislative object for total harmonisation. Directives dealing with restrictions on the marketing of chemicals are in Denmark considered to be minimum directives, a viewpoint on which Denmark seemingly stands alone.

According to the Danish legislation concerning regulations for the working place, new chemicals or products which are introduced to workplaces in Denmark, must be notified to the *Product Register*. Information must be given about product identification, physical, chemical and toxicological properties, composition of the product, hazards and risks connected to expected patterns of use, and also the anticipated quantities of sales. All of these will make it possible for authorities to give priority or select individual products or chemicals as subject(s) for specific regulation.

Minimum directives may give individual EU countries the possibility to make stricter rules, while maximum rules expressing total harmonisation, implies that the rules of EU must be abided to even though single countries, *i.a.* Denmark should want stricter rules. Maximum rules are the results of political negotiations and decisions in the EU. They can only be altered by political re-negotiation as the instrument for revision of the EU rules in question.

Examples are given that Denmark has maintained stricter rules than those of EU, but it is also known that Denmark has been forced by long negotiations to submit to the rules of EU resulting in a Danish adoption of the harmonising rules of the EU. The former situation is illustrated by the fact that stricter Danish rules on banning of ozone depleting chemicals, the so-called CFC-gasses, was accepted by the EU, while the Danish adaptation in general to EU regulations on pesticides exemplifies the latter situation.

Tools and concepts applied in chemical assessments

When expressing the hazard potential of a chemical, a number of characteristic properties must be described, *e.g.*:

- toxicity to humans, animals or other living organisms
- explosivity
- inflammability
- danger of corrosion
- ability to cause damage in any other way.

In order to assess the hazard potential of chemicals, any relevant, adverse effect which may be caused by the chemicals are measured. On this basis, the chemicals are classified and ranked numerically according to the degree of dangers - first of all in relation to hazards towards human health, including often also the workplace situation, and in recent years further the environmental hazards.

Dissipation and distribution of a chemical into the environment may occur as a result of its use and it may have to be evaluated, depending on a number of external conditions, *e.g.*:

- the amount or volume used,
- the locality or compartment into which it is released, and
- other circumstances of application.

Distribution of a chemical in the environment may lead to exposure of humans, animals or other living organisms which can be measured as a concentration or as a load, and it may be evaluated as an impact through/on the environment.

It is the measurement and the evaluations of these properties and conditions, that determine the risks connected to the use of a chemical. Thus, the risk is expressed not merely as a *possibility*, but rather by the *probability* that a chemical may actually cause (adverse) effects. The necessity for clarifying these concepts is important, as they determine:

- which data are needed in order to assess, or possibly predict the potential impact on health and environment of a chemical resulting from its application in practice
- which priority we must assign to the chemical concerning its significance for health and environment, including the workplace environment
- which kind of safety measures, including degree of certainty we wish to achieve in our safeguarding towards the threats or impacts deriving from production, application and/or waste disposal of chemicals, and
- which regulations are found on these grounds to be justified/imperative.

Referring to these needs, the demands for scientific investigations and the requirements for socio-technical documentation can become extremely large. Efforts, therefore, have been taken to standardise and to harmonise requirements during recent years, not the least through:

- development of rules for classification of the danger of chemicals, nationally [1] as well as in a Nordic context [2] and on a European scale [3],
- proposals for priority setting and selection of 'most dangerous' chemicals [4]
- preparation of Guidelines for the testing of chemicals as developed through activities within OECD [5], and
- development of rationale and technical guidance for chemical risk assessment [6].

Classification and priority setting

The classification of chemicals according to their hazard potential is normally considered the preliminary step in legislative practice when dealing with the evaluation of hazard and risk assessment of chemicals. The classification scheme includes guidelines for the labelling with risk and safety phrases. As a whole, *the process forms the background for all further evaluations and assessments of a given chemical*, including restrictive measures, specific use regulations or possibly substitution practices.

Classification can take place as an approval of a chemical to be included in a so-called '*positive list*' serving special applications, *e.g.* when approved as a food additive or for pesticidal purposes. Only chemicals which are approved can be used for these specified purposes. Thus, it is the function of the positive lists to determine whether a chemical may be marketed for the specified applications, and to a varying extent also

to give details on accepted application patterns.

Positive lists are well-known as a means of chemical regulation in the fields of pharmaceutical chemicals and food additives. In these cases, the documentation requirement for classification and approval can only be met by comprehensive information about physical/chemical, pharmacological, toxicological and environmental properties and characteristics, including long term studies *e.g.* on side effects, reproduction failures etc. Classification and approval of chemicals for use as pesticides follow principles similar to a 'positive list' regulation, either via special directives or as in Denmark under a special ordinance authorised via the general Law on chemical substances and products - *cf.* Chapter 7 of Danish chemical law [7].

Normally, however, classification of chemicals is merely serving the purpose of ranking individual chemicals in broad classes according to their degree of danger and to label them accordingly, as *e.g.* toxic, harmful, dangerous to the environment etc. The principle behind such *negative lists* is that any chemical in fact freely can be produced and brought to the market, unless evidence is presented on hazardous properties or on hazards which are obvious and connected to normal use patterns. Thus, restrictions on sales or uses are *only* imposed on those chemicals for which evidence is given or suspicion is substantiated that they may create damage or adverse effects under normal use conditions.

In practice, this process of classification follows a scheme established by an EU directive [8]. It is based on available data from measurements carried out by relatively simple methods, involving basic physical/chemical, toxicological and environmentally relevant properties and characteristics.

For chemicals which are registered as existing chemicals in the EINECS list, but not until now has been classified and listed on official lists of dangerous substances, an obligation for so-called self-classification is normally carried by producers and/or importers. This will follow the same simple rules as for other chemicals, but information about details of the practice and outcomes of self-classification is presently limited, both as far as its extent and as the underlying documentation is concerned. It is noted, however, that producers/importers are asked to perform their classifications on the basis of available data, only. They are not obliged to create new data for the classification process, unless this is individually specified and requested by the authorities.

An inventory of available data and the creation of a new database - IUCLID, International Uniform Chemical Information Database - has been initiated in recent years by the EU. It serves the subsequent risk assessments, and it is expected to expand the information available for classification procedures. The development of the database is presently in progress, although it includes only those few thousand chemicals which are marketed and sold in amounts exceeding 1000 tons per year. It is planned, however, as a phase 2 that producers/importers before medio 1998 shall submit (limited) documentation also on substances marketed in amounts above 10 tons per year in so far as data is already available.

It is pointed out and outlined by the present report that all chemicals on the EINECS list could be included in a common classification system by systematising them in groups, blocks or clusters of chemicals. Such groups, blocks or clusters should be created on the basis of structural, chemical, biochemical and/or other specified relationships, and defined in such a way that all chemicals within a group/block are to be classified identically. It is anticipated that the procedure could enable all non-assessed chemicals

- to be classified on a compulsory basis, and that it could create incentives
- to procure the necessary data for a classification, and also
- to increase the speed drastically of assessing all relevant chemicals (see section about Recommendations).

In the opinion of the working group, the EU should further initiate a classification activity covering also the large, but presently unknown number of chemicals, which are not included in the term 'marketed chemicals', *i.e.* they are not listed on the EINECS list, nor are they characterised as 'new' chemicals. Undoubtedly, thousands of chemicals are likely not to be identified as targets for the EU regulation of chemicals, because they are not directly marketed. This may be the case for substances which are used as processing aids or known only as intermediates *within* industries, or they may not have been notified as constituents of *e.g.* imported products etc. (see section about Recommendations).

The testing of chemicals

It is a part of the notification scheme for *new chemicals* that documentation in the form of a 'base set' of data is submitted as the basis for a classification and 'first assessment' procedure. Following notification, the chemical can freely be placed on the market, and it is the responsibility of the authorities to justify and to make request to the producer/importer in case any additional information should be submitted or made available. Such additional, more comprehensive information will normally require that more testing and studies are performed which for a new chemical can be rather extensive and time consuming. It is said, however, only to be demanded in relatively few cases.

For all *old chemicals*, *i.e.* those listed as 'existing' chemicals in the EINECS list, no similar demands for testing and evaluation are enforced, in so far as they are *de facto* placed on the market and thereby used in a variety of applications. A complete test of all these chemicals individually and in accordance with the requirements of the testing of new chemicals would require enormous resources - in working hours, in economics, and in form of materials as well as in efforts required for analyses and experimental animals.

The EU strategy for all chemicals on the EINECS list is to give priority to the testing and evaluation, including provision of necessary data for a so-called 'realistic worst case' risk assessments of

- those chemicals which are produced and used in large amounts (HPVC or High production volume chemicals), and

- those which are evaluated to be carcinogenic, to have mutagenic effects, or - not least - to affect reproduction and foetuses.

Further possibilities of testing and assessment can be based on *e.g.*:

- the use of a stepwise test strategy, implying that a full testing is not demanded, unless effects of concern are indicated in initial stages,
- an extended use of in vitro methods and other short-time tests,
- an expected further development and use of (Q)SAR methods, and
- a higher degree of integration of human and ecotoxicological test methods.

As an important observation, the working group points out that any testing of chemicals - even very extensive ones - have drawbacks, unnoticed limitations and lack of knowledge when it comes to the prediction of the effects and potential hazards of chemicals.

On this background, it is suggested that any modification or new field of application for chemicals on the EINECS-list, as well as the use of chemicals newly notified and registered on the so-called ELINCS-list, should be followed by a 'post-marketing surveillance'. This would involve a systematic registration of effects which the chemicals might produce on humans and/or the environment. As it is the case for *e.g.*

pharmaceuticals, it could be made compulsory, that the first marketing of any chemical should be carried out in a controlled manner. This would make it possible during a specified 'period of trial' immediately after marketing, to observe not only the development of use pattern(s) and sales of the chemical, but also to note any signs on deviations that might occur from toxicological and environmental predictions (see section about Recommendations).

Hazard and risk assessments

The presently accepted classification scheme is based on the most important hazardous properties and characteristics of a chemical, *e.g.* toxic and ecotoxic effects, potential to bioaccumulate, persistence etc. These are also the characteristics, which primarily determine the position of the chemical on a hazard scale or on 'scoring lists'.

However, for a more exhaustive description of the qualitative and quantitative hazards of the chemical further investigations, more data, and a more thorough assessment are required in order to understand

- harmful effects of the chemicals,

and to explain how

- circumstances,
- amounts or
- concentrations

may influence the assessment of these effects. This will include requirements for studies and results from extensive physical/chemical, toxicological and ecotoxicological investigations, which should be required additional to classification requirements in cases that limit values have to be established on the basis of so-called zero-effect-assessments.

Generally, the hazard and risk assessments will specify the kind of damages and the types of effects or diseases that can be induced by a given exposure. Distinction is made between hazards to health and to environment, both in the practice of testing and in the assessment of data, namely:

-*health hazard* which refers to damaging effects, including acute as well as chronic effects on humans, *e.g.* acute poisoning, neurological changes, cancerogenic effects, reproduction failures, effects measured over full lifetime or for generations, including inherited malformations, as well as more specific effects, such as hormonal disturbances etc.

- *environmental hazards* are normally tested and considered in a less profound manner, as it mostly deals with lethality only, *e.g.* of fish and birds. Only a few non-lethal tests, *e.g.* on growth or on reproduction of various, primitive species such as Daphnia are considered on a routine basis. Less emphasis is placed on *e.g.* mechanisms and development of (eco)toxicological effects, although scientifically attention is increasingly drawn to effects on both functions and structures of ecological systems. Important in this respect are effects over time and place, *e.g.* when resulting from persistence and/or accumulation of chemicals through food chains, or from distribution to other compartments or geographical localities.

Information and data valid for these assessments normally arise from toxicological and ecotoxicological laboratory tests or investigations, but also from accidents, epidemiological observations or from further sources, such as chemical or biological monitoring in the environment, in the workplaces etc.

As part of the assessments of effects, information can be included about degradation and fate of a chemical

in a living organism, and accordingly also about its exposure directly on organs, cells or genetic material. Such information may often be of importance for the prediction of toxicological effects also in other species/populations or under other circumstances.

However, as for the more precise predictions and assessments of *e.g.* secondary or indirect effects, it should be realised that these are only rarely possible to achieve. This is true especially for changes in lifetime expectancy, or when evaluating qualities of life against individual stress situations. Similarly for environmental effects, it is difficult or almost impossible from the present system of single-species tests, to predict any complex interspecies effects, or 'cascading' side effects which may occur over time in natural ecosystems.

Limit values and uncertainties

Limit values are used to describe the amounts and/or the concentrations of a chemical, which can be accepted, respectively allowed in *e.g.* foods, drinking water, working environment, air, sea and fresh water or in soils.

The limit values are normally established assuming that the chemical is used under normal use conditions and ordinary, external circumstances, and it is the expectation that human health and/or environment should be protected against any harmful effects, which generally implies that the values shall not exceed a so-called *Zero-effect-level* (NEL).

If a limit value is set at a value higher than NEL, it is expected as a consequence that a risk situation can arise. This implies, that safety precautions and/or protection measures should be initiated, *e.g.* by protection of the workplace environment, alteration of technology, substitution for less harmful chemical etc. If on the other hand, the limit values are established at a value lower than the NEL-level, this is an indication that a safety margin has been implemented. The latter situation is seen most frequently as a practice in connection with protection of food, water or other media directly exposing human beings.

Limit values are set on the basis of professional/technical valuations, but administrative and/or political elements may most often be included in the decision process. Values can be established as mandatory, or they can be set as guideline levels only. Dependent on circumstances and on points of interest or profession, the limit values can further be regarded as only scientifically based, or as politically decided, or they can be considered to be scientifically as well as politically determined.

Through the setting of limit values is expressed:

- a *quality standard* - as for most environmental limit values
- an *accept limit* - as for additives permitted for use in foods, or
- a *tolerance* - as for residue contents, *e.g.* of pesticides, accepted as unavoidable, and they may thereby serve the further purpose of information :
- about a *degree of purity* compared to a situation of pollution, or
- whether the *presence* of an intentionally added chemical is *acceptable*, or
- whether the presence of a chemical can be *tolerated*, when humans and/or the environment *unintentionally* are exposed to the chemical.

For the establishment of limit values for individual chemicals, it is necessary to possess knowledge about short-term as well as long-term effects on humans and animals, but also about special effects such as

carcinogenicity, and of effects which may arise from the chemical when appearing together with other chemicals. The latter may be important in several assessments because most chemicals in actual fact are used in combinations. However, in most cases it is extremely difficult to obtain reliable knowledge on combination effects, and or it may be even impossible as when secondary chemicals are unknown, or when they give rise to formation of further new chemical substances.

Knowledge about the effects and potential hazards of a chemical is most often obtained from experimental studies with animals, but of course also from observations (*i.e.* epidemiological investigations) of humans, by analogy from existing data bases, or by calculation from mathematical models. For the setting of limit values, it is assessed whether the chemical has a so-called threshold value, *i.e.* a dose or a concentration below which no harmful effects can occur (Zero-effect-value). As a case of particular interest, carcinogenic chemicals are considered normally not to have a threshold value.

Large uncertainties are attached to the setting of limit values. This is not only due to the uncertainty following the interpretation of data from animal experimentation and transfer of results to be used on humans (or on natural environmental systems). It is also tied to the fact that experiments with animals are carried out under laboratory conditions, *i.e.* under conditions of life, with a uniformity in choice of food etc. which in no way resemble the situations for humans (or natural ecosystems). Further uncertainties - or even direct lack of knowledge - concerned with effects assessment may spring from overlapping exposures to other chemicals, including of course the usual limited information about the fate and effects, including degradation and metabolism of the chemicals in the natural environment.

In recent years, these circumstances have caused a new and critical attitude towards the use of (un)certainty factors - or assessment factors. Explicitly expressed, there is a need to obtain a wider understanding and a clearer definition of the scientifically based, 'calculated' uncertainties, and the necessity to integrate these with a more general, 'politically' phrased '*precautionary principle*'. This is currently of special interest, *e.g.* for pesticides in drinking water in which case 'a lowest measurable limit value' are requested, or for certain food items, such as dairy products and meat which are expected to be 'kept free of residues'.

The requirements for data as a basis for the setting of limit values differ widely depending on the type of value, such as

- ecotoxicological limit values - serving protection of populations, species and environmental biota in general,
- human toxicological limit values - for protection of individuals, or
- limit values directed towards the workplace environment - for protection of humans in the variety of situations characterising the workplace.

Generally, the demands for testing and for data in the setting of limit values for chemicals are more extensive, when it concerns the potential for effects on humans, than is the case for ecotoxicological testing or for data used in environmental relations - qualitatively as well as quantitatively. In both cases, but definitely more so in environmental matters, estimated calculations or statically based extrapolations from simple test systems is the rule rather than the exception, as opposed to thorough studies and assessments of direct measurable and theoretically described effects/no-effects. Thus, environmental limit values which are set on the basis of such assessments, can often be seen to rest on rather meagre documentation.

Discussion

Introduction

The number of man-made chemicals which are put into use and circulation in our societies, are not precisely known. They originate from industrial production and uses within industries, from commerce and domestic household uses, and they form part of general housekeeping under the generic term 'household chemicals' - which in Denmark amounts to more than 11 million tons per year. From these, approximately 25% are used in the retail consumption, while 5% (or more than ½ million tons per year) statistically constitute the actual, domestic household chemicals.

In the official EINECS inventory dated September 1981, the EU Commission registered a total of 100.106 individual chemicals designated and marketed as 'existing chemicals'. The significance of this registration is, that all chemicals listed can be produced and used without any immediate demands for further notification or for assessment, such as this is required for all new chemicals. The number does not coincide with the number of 20-30.000 chemicals which are estimated by the Danish National Agency of Environmental Protection and the Danish Working Inspectorate to be registered via the specific Danish Product Register. On the other side, the large amount of semi-manufactured materials, of intermediates, or of processing aids which are produced and handled within chemical industries do not form part of these marketing statistics. Also, the number does not include those numerous degradation and transformation products, which are formed in nature and/or in society as part of dissipation and distribution, or substances which are constituents of imported materials and products (e.g. in textiles, electronics, motor vehicles etc.).

The actual number of chemicals, which may have a possible, harmful influence on health and on the environment, seems realistically to be counted somewhere between 50 - 100.000, an order of magnitude which is in clear contrast to that fraction of chemicals on which we actually possess information concerning their potential for being dangerous to man or hazardous to the environment.

It should be noted that the number of chemicals continuously is increasing. New chemicals, which are continuously being produced or imported and first sent on the market, are presently given to be in the order of 200 individual substances each year.

Out of this ' universe of chemicals', only a few thousands are presently classified, *i.e.* investigated and found to be dangerous, whereas the majority of all other chemicals are presently found beyond any classification and/or assessment. This is due to the fact, that they

- **neither** have been individually identified as dangerous in practical situations and circumstances,
- **nor** have they - which is probably more frequently the situation - been tested at all, *i.e.* studied and/or assessed specifically for possible adverse and environmentally harmful effects.

In the EU and OECD, resources for chemical evaluations are presently concentrated to the assessment of exposure and effects to health and environment, including a defined risk assessment for a total of only 50 existing chemicals per year. In contrast to this situation, therefore, the concern of actual chemical regulation directed towards the consequences of chemical uses should not only deal with *chemicals individually*, in so far as these are considered dangerous. A similar and primary interest should be given to the impact and consequences of the *amount and number of chemicals*, which in combination contribute to the totality of stress situations on humans and exposures of the environment.

Assessment of chemicals

Chemicals on positive lists

Out of the total number of chemicals which are in circulation today, and which are listed in the EINECS inventory, only a small part - *viz.* a few thousands - are accepted, possibly certified, and approved for inclusion in 'positive lists'. These are additives to foods, pharmaceutical products and medical specialities, and pesticides. All of these are individually approved for their specified purposes, and it is an integrated part of the requirements that they before their approval are comprehensively tested and individually assessed for toxicological hazards (and increasingly also environmentally), and that they are or can be submitted to detailed regulations as far as use patterns are concerned.

Positive lists have been accepted as instruments in the protection of health and of the environment within their respective fields of application, but with special emphasis on the areas of food and food production. Directly dangerous chemicals have been removed from earlier uses, and a considerable number of doubtful applications been reduced. Furthermore, many chemicals which were earlier freely at disposal, although often insufficiently assessed, have now been abandoned from uses in food.

The number of chemicals which are today listed on Danish positive lists, is definitely lower than it would have been in case of a 'negative list'-regulation, prohibiting only the dangerous or the most doubtful chemicals. Irrespective of fears often expressed publicly as to the safety and risks of some (or all) food additives, or of pesticides in agriculture and gardening, there is no doubts that it has been possible through legislation to secure a higher quality and a more thorough testing of individual chemicals by way of their regulated assessments and officially recognised use patterns. It is typical in this connection to note, that the ca. 250 pesticide chemicals now approved in Denmark, actually constitute less than 20 % of that number, which by the relevant industries and agriculture are recognised and advertised publicly as biologically active for world-wide usage.

Notoriously, therefore, it is expected that a system of positive list regulation would involve considerable reduction in numbers of marketed chemicals. With a reduction in numbers to 'a needed minimum', the individual chemicals remaining on a positive list could be subjected to extended investigations and assessed more safely for health and environment hazards, as opposed to the present situation in which a large number of chemicals are brought to the market and used on a meagre and uncontrolled basis.

In a public debate, however, reference to a general use of positive lists may be found objectionable. This is connected to the observation that positive lists, as a system of regulation can be apprehended as less flexible than marketing systems, in which restrictions and prohibitions for individual chemicals can only be introduced on the basis of presented evidence for hazards and risks. Further more the system might be more resource demanding.

On that basis the working group expresses, that there is hardly no foundation for a recommendation of positive lists as a solution to be accepted generally for the regulation of all chemicals. It is still noted, however, that a regulation of *e.g.* cosmetics during recent years has been carried by *combination* of a prohibition principle in form of a negative list (directed towards several, mostly allergenic chemicals), and an approval scheme in form of a positive list (implying permission and use regulations for some cosmetic chemicals) (*cf.* chapter 3, section 3.2.1.). This seems to indicate, that the possibilities for introducing positive lists are not exhausted. In recent years we have experienced lively, scientific discussions, and suspicions have been expressed concerning *e.g.* the risk of oestrogenic (hormone like) activity from both man-made and naturally occurring chemicals. This might well be taken as another indication, that more

restrictive regulation schemes, including positive lists may still become relevant for further branches of trade or for other chemical uses, *e.g.* cleaning agents, detergents and plastic materials.

Chemicals on negative lists

A most critical problem connected to regulation of chemical substances and products is associated with the large number which are produced and marketed - *cf.* their inclusion in the European EINECS list - substantially without any regulating surveillance or restrictions on their use. For the vast majority of the EINECS chemicals there is hardly any detailed regulation at all, and the documented knowledge about potential fate and effects is small - most likely it is non-existing.

In the diagram (fig. 1) shown below, it is illustrated how the EU and the member countries have tried to develop a system of test rules and assessment principles, which is discussed in more details in chapters 1 - 6. In principle, it is a 'negative list system', which is characterised by:

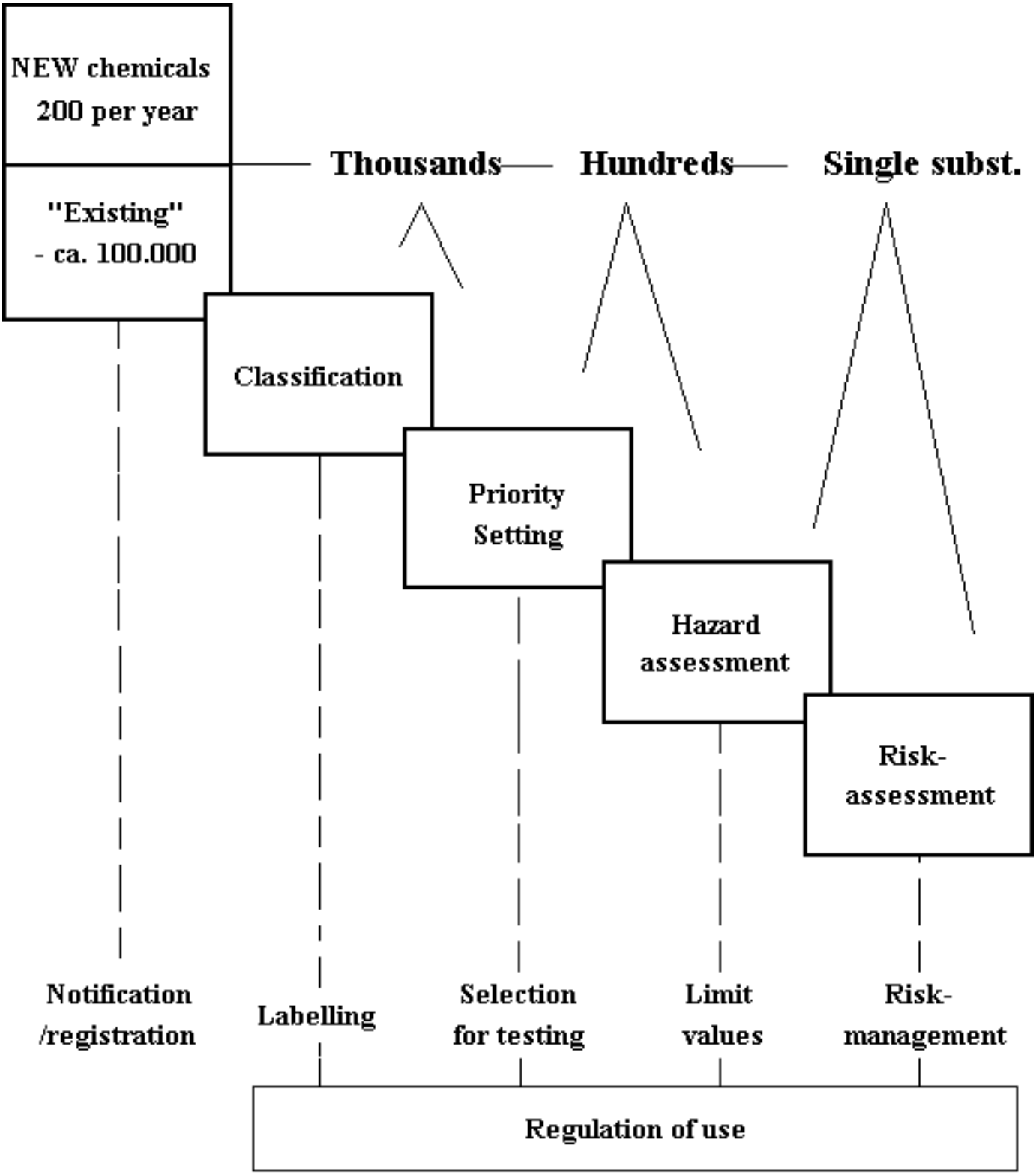
- a free marketing of all chemicals that are registered in the EINICS list as 'existing', or have been notified to the ELINCS list as 'new' chemicals,
- a requirement for classification for those chemicals which are found individually to be harmful to man or the environment, including possible risk- and safety labelling, and by
- the fact that *only* those individual chemicals for which evidence are given on hazardous properties (or uses), restrictions are considered as means of regulation of use, consumption and/or disposal.

Classification according to the general rules (*cf.* chapter 3 and 4) has been carried out for those chemicals, which are accepted on official *Lists of dangerous chemicals*, which in Denmark presently include approx. 2100 entries. For chemicals outside this list, producers/importers have the responsibility to perform so-called 'self assessments' and 'self classifications' and to make these known, *e.g.* by labelling. For this process, however, only presently available data is required. No demands are detailed or enforced for the creation and submission of documentation in addition to the already existing in order to update or provide information of more recent knowledge.

Chemicals which are 'self classified' as dangerous, must be notified to National authorities. So far this amounts to approximately 5800 notifications in Denmark. It is not informed, however, which kind of documentation constitutes the basis for this number of assessments, or in how many cases the same chemical is classified differently by different producers or importers, or whether the actual assessments generally are apprehended as satisfactory.

Within the principle of 'negative lists', regulation starts with the classification based on standardised test results and data. Subsequent use regulation or other restrictions connected *e.g.* to consumption or disposal are imposed individually, and then only on basis of indications from these standard tests. These individual and stepwise submissions of data and documentation, can be interpreted as a 'network catching dangerous or the possibly most dangerous chemicals' to the extent and in a sequence determined

Figure 1 Flow sheet illustrating the regulation of chemicals in the EU



by frequency and succession of observations, *and* by the 'mesh size of the data network'. Logically, it is only a small number of individual chemicals, *i.e.* maximum in the order of a few hundreds which are actually brought through to a 'full' series of comprehensive testing and hazard/risk assessments confirming their hazard potential.

Classification

Consequently, it is the classification which constitutes the preliminary basis for any further steps in the danger and risk assessment of chemical substances. This includes also subsequent use regulations or further

interventions towards dangerous chemicals. For the daily 'household situations', the importance of a classification process can be illustrated by the fact,

- that the public ordinarily are not allowed to buy chemicals which are classified as 'poisonous', unless they are holders of a license or have special permission
- that persons under 18 years of age are not allowed to work with dangerous chemicals, and
- that an 'eco-label' of goods and products, such as *e.g.* textiles, paints etc. will not be given, or can not be expected in cases that chemicals classified as dangerous to man or the environment have been used (*e.g.* carcinogenic).

Actually, it is only for a very limited part of the EINECS-chemicals that data are available to the extent that a complete classification can be carried out, *i.e.* comprising all classifiable properties. At best, but even then not completely, this concerns:

- those approx. 2,100 chemical entries, which are included in the *official list of dangerous chemicals*, and
- an additional group of oil- and coal-chemicals, which recently are accepted and classified specifically for their *ability to cause cancer*.

In addition to these, there exists a not-defined number of chemicals (estimated to a few thousands), for which *data fully or partially may be present*, but without giving rise to a classification as dangerous.

It is the lack of data and of documentation on properties and characteristics of chemicals in general, which has forced the EU Commission via its European Chemical Bureau (ECB) to call for data on all HPVC-chemicals (*i.e.* High production volume chemicals, which are produced in amounts of 1000 tons or more per year per producer/importer) to be submitted from producers and importers before 1.7.1995. Similarly, data on all chemicals which are produced in amounts of 10 to 1000 tons every year shall be submitted before 1.7. 1998.

Following its intention to obtain further data, the EU Commission has required that only data which are presently available must be submitted for inclusion in the IUCLID database. No demands for development of presently missing data or for initiation of new test activities are made. Thus, even though a submission of relatively large amounts of data and informative documentation are presented, it is not to be anticipated that the problem of 'missing data' will be solved from this action. This is due to the fact,

- *that* bottle-necks are already described directly as a severe lack of basic data, but also are expected to develop in the form of insufficient resources for the assessment of submitted data,
- *that* the data which will be submitted, expectedly will coincide with the documentation already applied in the 'self classification' process mentioned above, and
- *that* the submitted data only partly can be expected to fulfil normal demands for data documentation and quality assurance (*cf.* testing by OECD methods, authorisation of testing laboratories etc.).

The insufficiencies connected to data documentation in the existing classification system, is especially of concern when dealing with:

- the fundamental lack of data, which concerns the large number of 'existing chemicals', among these also a part of the HPVC chemicals, but of course mostly for the large number of chemicals, which are marketed in smaller volumes only, and
- the fact that the classification historically has been dependant on relatively unstructured chemical descriptions and tests, that were carried out by the producers/importers, and on which only

insufficient documentation were available.

It is on this background, that proposals are made in the present report (*cf.* chapter 3, section 3.3) that the classification practice should be modified in such a way:

- that **all chemical substances** on a compulsory basis are placed in a registration system, which **allocates each chemical into detailed groups, blocks or clusters of substances** which are all **defined on the basis of their chemical/biochemical, structural and other relationship**, and

- that every chemical is **assigned to a group classification, i.e. together with the most strictly assessed chemical in the group/block** (cf. chapter 3, section 3.3.), and

- that a group-bound hazard classification of a chemical **can only be altered to an individual classification and labelling** provided this is fully justified by a comprehensive set of data submitted for assessment by producer/importer.

This would further imply:

- **that all** presently non-assessed chemicals are drawn into the hazard classification system on the basis of their identified relationship, *e.g.* demonstrated through so-called QSAR tests, or by analogy to earlier decisions for other compounds etc., until individual studies and/or assessments made by the producer/importer is produced as documentation for the individual classification,

- **and that** the practice of labelling chemicals prior to their marketing are simultaneously made compulsory, and that the present practice should be adjusted and supplemented in order to include information, *e.g.* on

- chemicals, which are classified in accordance with the group classification, but *without being individually tested and/or assessed for hazards* to health or environment.

The proposal that chemicals are classified on a group- or block-basis has obviously to be managed in a way, which ensures that guidance for safe handling of all chemicals is directed by a 'precautionary principle' and by referring labelling requirements to the 'worst case' evaluation(s) of chemicals in each group/block. Irrespective of possibilities for so-called 'over-classification' it must be foreseen, that any following regulation of use or of disposal of chemicals must be handled on the same group- or block-basis - unless, of course, documentation is produced justifying the individual classification.

Priority setting

A modified classification practice will not alter the need for a constant attention to or surveillance of the most dangerous, individual chemicals or groups of chemicals. Definitely, it will also not alter the situation that a priority setting shall take place, *i.e.* a process of selecting the most relevant and obviously threatening, single substances for further studies and evaluations.

The presently described proposals and models for priority setting, not the least the European IPS-model inspired from the Netherlands and now adopted by the EU Commission, try to account for this

- by including both hazard and risk aspects of assessment, *i.e.* properties, and characteristics of the chemicals *per se* as well as fate and effects following the use of a chemical, and
- by allowing the use of 'default values' and standardised scenarios as substitutes for actually measured

values, when these are missing.

In practice, the prioritisation process is carried out as a 'scoring process', in which chemicals are arranged in an order of 'ranking their hazards/risks'. The ranking becomes a tool for selection of chemicals, which should be called for more intensive studies and more thorough testing, while the process is less accurate and therefore less useful for final assessments and decision processes.

There are, however, still good reasons for emphasising the kind of predictions, which can be achieved by prioritisation processes and selections based on a concept of 'incipient suspicion'. Such predictions can continuously contribute to a setting of course and direction for future chemical assessments, including a potential for use regulations - a situation which is presently of significance when dealing with the selection of 'pesticides suspected to be polluters of subsoil aquifers and/or groundwater'.

Testing of chemicals

It was one of the major achievements following the revision of EU and National chemical legislation in the late 1970'es, including the succeeding EINECS registration of 'existing chemicals', that new chemicals and selected priority chemicals should be subjected to laboratory testing and hazard assessments. This has now resulted in a situation, characterised by an increased, but unfulfilled demand for routine tests and evaluations, clearly contrasted by an insufficient capacity to fulfil this need.

In a matter of 'balance' between supply and demand for chemical investigations, it is characteristic, that the individual test methods (physical/chemical, toxicological and ecotoxicological) on the one side

- is so far standardised and limited in number that it serves a routine, often low-cost investigations,

but on the other side, that exactly the standardised, stepwise test and assessment procedures

- present a limitation which can obstruct or hinder a sufficient fulfilment of the investigations which are needed for a satisfactory health and environmental evaluation.

The basic tests, which are demanded before the marketing of a new chemical, will normally only permit a simplified classification to be made on health and environmental hazards. They can be performed in a matter of approx. 2 man-years per chemical with a cost level in the order of 100.000 ECU.

For the use of a wider, more comprehensive hazard assessment, *e.g.* as required for the preparation of setting of limit values and/or for detailed risk assessments, demands will increase exponentially - requiring from 2 - 10 years of investigations and with costs which are said to vary from 2 up till 15 mill. ECU for the most requiring chemicals, as for instance for approval of chemicals for positive lists of food additives or for pesticides.

Thus, theoretically it may be said that,

- a completed, individual classification of all chemicals listed in the EINECS register could well amount to the order of 7.000 million ECU,

- while the additional investigations for *e.g.* 1000 prioritised chemicals from the list of dangerous substances, selected for comprehensive hazard/risk assessment for a variety of practical applications, would undoubtedly amount to costs in the same orders of magnitude.

Figure 2 Chemical testing - Estimated time and

resource consumption per chemical substance

Human toxicology		Ecotoxicology		Test basis and levels of assessment -			
Time	**Economy**	**Time**	**Economy**				
1 year	*New chem.*: 50.000 ECU *Exist. chem.:* 75.000 ECU	3 - 6 months.	*New chem.:* 25.000 ECU *Exist. Chem.:* 50.000 ECU	*Base-set*	Classification	*HEDSET*	Generic risk assess-ment
=> 2 year	=> 750.000 ECU	1 year	75-150.000 ECU	Supple-mentary tests	Hazard assess-ment		
2 - 10 year	2 - 15 mill. ECU	2 year	?	Compre-hensive test level, incl. epi-demiology	+ establishment of limit values		Risk assess-ment

Additional to these estimations it is noted, that the hazard/risk assessments related to human health normally are significantly more demanding than the environmental assessments, probably in a ratio of 2 - 3 times larger. Similarly, it seems to be a rule rather than the exception, that testing and assessments (or reassessments) of existing chemicals are more costly than for new chemicals, probably due to the needs for covering a greater variety of already established use situations by relevant risk assessments.

It is to be expected, that the demands for testing of chemicals will increase considerably in the years to come, in order to fulfil a still increasing concern for the protection of health and environment. The environmental field may be in greatest need, as it is presently indicated through the wishes for supplementary test methods expressed from individual countries, especially towards the OECD. An increased pressure, both scientifically and environmentally, also seems to be excerted calling for field investigations, monitoring and even additional surveillance of regional as well as global pollution.

Classifying hazards - prioritising risks

Since the introduction in the late 1970'es of the notification requirements for new chemicals and the revision of the classification and labelling schemes, the most significant steps in development of European interests and evaluation of chemicals seem to be related to:

1. the development of concepts for setting limit values and environmental quality objectives, which implies that the impact from chemicals should not exceed the so-called *Zero-effect-levels*, and
2. the adoption by the EU Council of Ministers of rules and by the EU Commission of guidelines concerning development of so-called '*generic*' *risk assessment**) for both new and existing chemicals.

The establishment of limit values and/or environmental quality objectives requires extensive and detailed information based on measurements of effects and on assessments of hazards for each individual chemical. This is normally considered more demanding than the classification of the same chemical.

For the health related limit values, a certain practice has been developed over the years to accomplish the setting of so-called ADI/TDI values**) . These serve as the basis for limit values, and much experience has actually been developed in the practice of transferring the scientifically based ADI/TDI-values into limits or maximised concentrations for chemicals in food, water, air etc.

*) 'Generic risk assessment' refers to the so-called PEC/PNEC-ratio, now accepted in EU regulations and directives. The term is objectionable and should be distinguished from (comprehensive) risk assessments in which risk is interpreted as the probability for an (adverse) event to occur. It requires therefore that assessments are referred to clearly defined and described situations, localities etc. - which is exactly what is avoided by referring in the 'generic assessment' to conceptual and simplified scenarios, only.

**) ADI = Acceptable Daily Intake; TDI = Tolerable Daily Intake

As a parallel to this, environmentally relevant limit values (or *quality objectives/standards*), are now being established for certain priority chemicals 'taking into account the Zero-effect-levels' (*cf.* Annex 1 to EU directive 79/831/EEC - ref. 8), which are then serving as a baseline for the assessment of the environmental hazards. However, in this area there is still a lack of fully acceptable practices. This is mainly due to a continued lack of relevant data, but it is also tied to the frequent poor quality of data. Consequently, this is followed by a significant uncertainty in the assessment of environmental hazards, and by fluctuating demands for safety and for decisions on safety margins to be applied in order to meet the needs of environmental protection.

Similar considerations can be made for the 'generic' risk assessment, which has to be carried out for new chemicals and for selected, existing HPVC-chemicals (high production volume chemicals) from the EINECS list. This has been initiated by the European Chemical Bureau (ECB, at the EU Joint Research Centre in Ispra, Italy) in accordance with the requirements of the recent EU regulation no. 793/93 and its subsequent technical guidelines. For this purpose, uniform principles are established for the assessment of effects (hazards) and of general (worst case) exposure levels, mostly related to average application situations. In principle and to a great extent also in practice, however, it seems that the assessments schemes do not differ significantly from schemes and models which are mentioned above, and which are concerned with the process of priority setting.

The development of risk assessment to a certain extent seems to be 'blocked' by the same lack of data and documentation which is the true bottleneck of chemical assessments. Confronted with the huge number of individual chemical substances, it does not constitute a solution to the problem that simplified test methods have been developed, and that 'generic' models are presented as acceptable. The requirements for documentation and data and for filling in our gaps in knowledge are vast. The demands are by far exceeding the resources which have been allocated to their fulfilment.

In the working group it is a clear expectation for the future, that a considerably increase in the demands for better basic investigations will arise, that studies must be intensified for obtaining knowledge and data to comply with the increasing requirements for hazard and risk assessments, and moreover that practices are developed for a safer setting of limit values including larger safety margins. It is a reflection of this, that the working group recommends that demands for chemical testing and assessments are made more stringent, in order that

> **not only new, but also all existing chemicals are included in a notification and regulation system extending from the present practice, in which chemicals are classified individually for hazardous properties and characteristics independently and individually.**

But in so doing, it is accepted

> **that decisions for aligning all chemicals into chemical groups, blocks or clusters are made by analogy or calculation from one chemical to another, from chemical/biochemical or structural relationships (*cf.* QSAR) etc., and**
>
> **that 'the most dangerous' chemical in each group shall be the determinant for classification of all group chemicals .**

Following a detailed outline of this principle, it can be expected that incentives will develop, and that data and documentation needed for regulation of all chemicals will be created considerably faster. This will occur

> **because a vast number of individual chemicals guided by an established 'precautionary principle', can be drawn into the regulation schemes merely on the basis of the outlined group or block relationships, but also**
>
> **because producers and importers undoubtedly will be increasingly motivated to create the necessary data and to develop the experimental and more profound documentation needed for their individual assessment and regulation demands.**

A thorough planning will definitely be needed in order to encourage a development of chemical testing and assessment in a direction as proposed here. The working group, however, has desisted from going into further details in this report, taking also into account the variety of interests, considerations, and uncertainties which have to be presented as partners in such planning.

Recommendations

Today there is only inadequate knowledge about numbers and amounts, as well as fate and effects of that majority of chemicals which substantially without restrictions are being produced and marketed, and continuously are put into circulation in the society. The consequences for human health and environmental quality of the production, use and disposal of these chemicals are also inadequately described and regulated. Similarly, the procurement of data and need for documentation is immense - time-wise and as far as resources are concerned.

In the light of this, and on the basis of reviews and discussions presented in this report, the working group recommends:

General remarks

> *1. The collection and preparation of data for use in the assessment of hazards and risk to human health and the environment must be further developed*, initially with focus on the basic properties and characteristics, which are essential for the classification and labelling, but also on subsequent more comprehensive hazard and risk assessments, including details of use regulations.
>
> *2. All chemicals, i.e. newly notified as well as chemicals listed as existing on the EINECS list, should be organised in a data-system*, in which chemical/biochemical and/or structural (so-called QSAR*)) relationships shall direct all chemicals into groups, blocks or clusters, and thereby determine classification and labelling for the individual chemicals on the basis of group classifications.

3. Adapting the classification system to such practice, it must be a leading principle, that any chemical *which is without data or inadequately documented within a group, block or cluster, shall be classified and labelled for hazards similar to those of the most hazardous chemical* represented in the group.

4. For the preparation of a revised classification system it must be ensured, that hazardous characteristics presently not included in classification requirements - such as *oestrogenic (hormone-like) effects, or properties which are significant for the chemical threat to subsoil aquifers and groundwater - are made parts of future schemes.*

*) (Q)SAR = (Quantitative) Structure Activity Analysis, i.e. a method for calculating characteristics of chemicals, including biological effects based on the knowledge of molecular composition and structure etc. (see chapter 4, section 4.2.2.).

Dangerous chemicals / harmless chemicals

5. All chemicals, which are presently produced and marketed without having been subjected to tests and/or assessments within a full classification scheme, *should be labelled accordingly, e.g.* as 'not completely tested and assessed' or 'not tested and assessed', in either case with possible reference to general safety precautions related to human health and/or to environment.

6. The existing Lists of dangerous substances must be developed and extended substantially, in order to prioritise not only the currently dominating HPVC chemicals (*i.e.* high production volume chemicals), but with the demand that it includes all marketed chemicals, irrespective of their production volumes, and irrespective that classification may be incomplete, as it will frequently be the case within group-classified chemicals.

7. Probably a major part of all chemicals in society are marketed and found as constituents in products and preparations. Special efforts should be made, therefore, to *demand that classification and environmental labelling schemes are developed and expanded to cover also composite products and preparations*.

8. It shall be possible to delimit special-purpose chemicals with a view to '*classification (and approval) of chemicals for defined application areas*', *i.e. following a positive list principle within specified branches*. This may reduce (or restrict to a minimum) the number of chemicals which are used within specified field(s), and it may further enable that improved test and safety demands are made for the individual chemical, while at the same time each chemical assessment expectedly will be more resource-demanding.

Data demands and testing of chemicals

9. The collection of physical/chemical, toxicological and ecotoxicological *data and development of documentation from chemical producers and importers must be accelerated considerably*, and the presently enforced 'self-classification' of chemicals should be altered in order that all individually classified chemicals must be notified, and must meet demands similar to those for 'new' chemicals, concerning submission of relevant data to accessible databases.

10. Danish (or Nordic) requirements for *notification of chemicals to the Product Register shall be extended and enforced to cover all chemicals*, *i.e.* not only those which are listed as dangerous.

11. The use of in vitro test systems, QSAR calculations, chemical/biochemical and structural analogies etc. in classification, should *be accepted as test strategies in classification as well as in priority setting*, but methods should not be accepted without further quality assurance as valid and sufficient foundation for the further scientific assessment of chemical hazards and risks

12. In the ordinary test and assessment programmes for chemical hazards and risks, a *time limit should be introduced in the arrangement for notifications, in order to enable that new tests or reassessments can be claimed in the light of general new knowledge, e.g.* after 8 or 10 years, irrespective that production may not have changed to exceed the amount which was valid at the time of notification.

13. Support should be given to the development of a so-called 'post-marketing surveillance' of chemicals, which may give opportunity to follow and scrutinise possible consequences or side-effects of new chemicals, when they are being introduced to the open market - similar to an existing practise in the area of pharmaceuticals.

Implementation

14. Supporting the implementation of the above mentioned proposals, the working group recommends, that *legislative initiatives are taken to ensure the development and implementation of the proposed classification and labelling system for all hazardous chemicals*. This includes the efforts for having the principle of group classification accepted, developed and used within and by the EU .

15. Within the EU, efforts must be made to establish and to develop the product register system in all countries, ensuring that it does not remain a matter for Nordic countries only.

16. Alternatively, Denmark must use other management systems, which within the framework of EU directives will *widen the options for limitations and restrictions to be imposed on marketing and use of hazardous and/or non-assessed chemicals*. This could be developed in co-operation between Nordic countries, and possibly including other similarly disposed countries, and if found necessary, the '*Environmental guarantee'* of the EU treaty (*cf.* art. 100A, par 4) should be used.

17. It is recommended that National and Nordic, as well as international *activities are encouraged in support of exchange of information and that co-operation concerned with the regulation of chemicals* is promoted, and that these are given high priority.

Chapter 1

Chemicals in society

1.1. The number of chemicals

It is presently not possible to predict the number of existing chemicals and products. Inventories, chemical annals and handbooks suggest that the number has passed 10 millions during recent years - possibly on its way to 15 millions. Smaller, but suffering from a similar lack of precision, is the number of individual chemicals which surrounds us in our every day life. Industrial, agricultural and household chemicals are all produced, marketed and applied as chemicals, or in preparations, products and/or materials, and they are circulated, transformed or degraded in continuos chemical and biological processes - in our environment and/or in the individual human being.

Estimates of the number of chemicals which are of direct interest due to their potential for affecting human health and environment, fluctuate drastically. Based on several official, semi-official or unofficial statements figures are mentioned between 20.000 and 140.000. In 1986, the number of chemicals which were produced intended for marketing in industrialised countries, was given by OECD to approximate 70.000 [9]. According to information from the EU Commission [10] names of 100.106 chemicals are officially registered by 18. September 1981 in the so-called EINECS database, *i.e.* 'the European inventory of EXISTING chemical substances'. These are listed as individual chemicals and as chemical categories with specification of their international and EU codes, their chemical names and formulas as far as structures are known.

The inclusion of a chemical in the EINECS register imply, that at the time of registration, the chemical was accepted as marketed without requirements for any further data or documentation, unless circumstances or later indications should give rise to demands that further information had to be submitted for proper assessment.

No later revisions have been initiated of the EINECS list, but all chemicals marketed first time after 1981 have been officially notified and registered in supplementary, so-called ELINCS lists, *i.e.* 'the European list of NEW chemical substances'. All new chemicals must be notified by the producer or importer prior to marketing in the EU and possibly assessed on the basis of the submitted data. At the present time approximately 200 new chemicals are notified each year, or in total about 1500 substances since 1981.

It is an open question, how far the presently registered chemicals are those actually being marketed in the European region. Between 1979 and 1981, *i.e.* during the preparation of the EINECS list, there was taken no steps to control the registration process, and in the years to follow it has often been openly discussed whether registered chemicals were actually marketed, or - on the opposite - whether chemicals which had been produced and marketed in the preceding period of 10 year were correctly registered. The real number is most often said to be considerably smaller than those registered in the EINECS list. This is connected to the observation, that the chemical industry was said to 'throw' many chemicals into the registration process prematurely, because a later notification of the same chemicals as *new* would be tied to requirements for detailed information about the physical/chemical, biological and toxicological properties and characteristics serving a possible classification and labelling.

From the National Agency of Environmental Protection [11] and the Directorate of Danish Working Environment Service it is estimated, that only 20.000 chemicals substances are of significance as the source to the flow of chemicals in Denmark. This is based on assessments from the Danish Product Register [12], in which approximately 80.000 chemicals and products are registered with information on where and how they are used, on amounts put in circulation, and with data on physical/chemical properties and relevant health characteristics. These estimates are in fair agreement with figures unofficially given from the

European Chemical Bureau (ECB) [13] who at the EU level is actively engaged in the assessment of approximately 30.000 chemicals which are of interest in the continuous priority process.

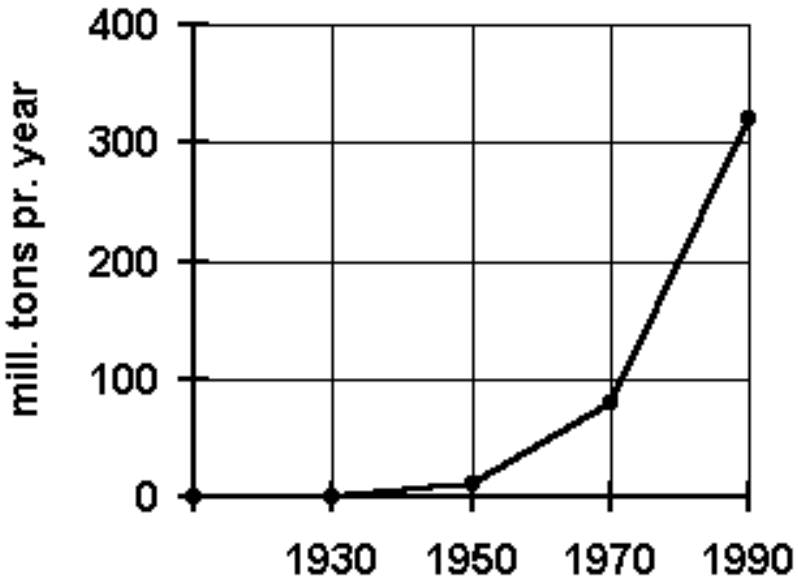
In comparison to other international assessments, however, some of these figures may be underestimated. *E.g.* in the order of 18.000 chemicals are registered in the EINECS list as marketed and with the label that they are: '.. of unknown or various composition, complex reaction products and biological material', while it is presently not known whether these chemical entities are known to the Product Register. Similarly, there is no account on the thousands or even tens of thousands of degradation products, chemical metabolites, technical intermediates and impurities, which are generally kept out of registration for marketing, in spite of their often significant contributions to the circulation of chemicals in the society and in the environment. The same apply when dealing with imported materials and products (*e.g.* textiles, electronics, cars etc.) for which there are no registration, *e.g.* in a product register.

As it appears, large uncertainties are connected to any counting the numbers of chemicals, whether individually or in combination, and whether they are of significance or not for their impact on human health or environment. It might be considered to initiate a renewed registration procedure in order to improve this situation, but for the time being it seems that also such approach will be futile. It seems prudent, therefore, to accept the basic registration represented by the EINECS list, and to continue the reference to its official number of 100.000 chemicals. The list still holds the legal status of defining 'existing chemicals', and it serves as the starting point for several priority and assessment processes. Further, it has to be kept in mind that all chemicals on the EINECS list at any time freely *can* be marketed and distributed in EU countries - without further notification, excepting only the special requirements in some countries for notification to Product registers (*cf.* working environment demands, section 2.2.1)

1.1.1 Production and application of chemicals

The global production of chemicals has developed explosively in this century. Without including the statistics for 'heavy', inorganic chemical, such as building materials, glass, ammunition, iron/steel and metals or fertilisers, the production of synthetic organic has increased from approximately 1 million tons each year to more than 300 million tons during the years from 1930 - 1990 (*cf.* figure 1.1) [14].

Fig. 1.1 Global production of synthetic organic chemicals



In the former West Germany taken alone, an amount of 25 million tons, or 400 kg per capita were produced in 1980, or corresponding to 100 g per m^2. As an illustrative comparison, this is in the same order of magnitude as the natural primary production (*i.e.* the annual growth in the plant world), which varies from 100-300 g per m^2 in industrialised countries.

The variety of uses for chemicals and chemical products are as numerous and varied as is the number and characterising properties of individual chemicals. In practice it concerns chemicals or household chemicals in:

- *the chemical industry*, *i.e*. the inorganic-chemical industry (*cf.* sulphuric acid, chlorine, fertilizers, metal salts, sodium carbonate etc.), or the organic-chemical industry, noted for its large supply of 'fine chemicals' (*e.g.* photo-chemicals, medical and pharmaceutical products) and of intermediate products which serve as raw materials (*e.g.* in the plastic industry, for production of pesticides, dye stuffs, synthetic fibres).
- *other industries* producing chemical preparations, products, materials, and manufactured goods in which a large variety of chemical substances may serve as additives or processing aids (*cf.* metal, plastic- and building materials, wood processing, textile and food industries etc.),
- *the agricultural sector*, which by volume is a sizeable consumer of chemicals, espec. fertilisers or pesticides, and
- *the* '*household*' *sector* in which an explosion of retail trade with 'manufactured goods' has taken place, bringing chemicals into households *per se*, to small industries and crafts, traditional trades etc. (*e.g.* cleaning materials, preparations for surface treatment, cosmetics, utensils and car-cleaning preparations etc.)

The National Agency of Environmental Protection [15] in Denmark has in 1990 reported on the total consumption of so-called 'household chemicals', based on statistical surveys made by Danmarks Statistik and on information from selected trade organisations, industries and individual distributors of relevant

products (*cf.* table 1.2). Including the consumption in the industry and commerce, the Danish use was estimated to a total of 11.6 million tons each year. Retail uses - *i.e.* consumption, which takes place in actual households or under similar circumstances - constituted approximately 2.6 million tons, corresponding to 23 % of the total consumption..

Summing up a number of individual, heavy commodity groups, such as cement, mortar, lime, motor fuel, incl. gas, petrol and diesel oil, these constituted approximately 95 % of the total consumption or 92 % of the retail consumption. Ignoring these, the remaining 'small-scale' uses which are mostly characterised by a high degree of diffuse distribution, constituted approx. 0.5 million tons each year, from which 40 %, or 200.000 tons were distributed and consumed via the retail trade each year.

The chemical commodity groups, which are presented here as household chemicals, are in other contexts often being produced, marketed and distributed under the term 'chemical goods and products'. It is emphasised, therefore, that a list of individual chemicals only characterising these categories, will not cover the number, nor the amount of chemical compounds which are in circulation today. Not included either, are for instance *chemicals under special regulation,* such as:

Table 1.2 The use of so-called household chemicals

in Denmark (1985-86)[*)]

Commodity groups - given by field(s) of application	Total consumption (tons / year)	Retail consumption (tons / year)	Retail / Total (in percent)
Cleaning/washing	145.000	70.000	48
Metal polishing	200	< 100	< 50
Dehardening	45.000	2.000	4
Textile treatment	142.000	50.000	35
Impregn. & leather treat.	1.100	250	23
Wood & metal surfaces	107.000	22.000	20
Adhesives, fillings	42.000	< 4.400	< 10
Furniture- & floorpolish	500	150	30
Car utens. & clean. Aids	116.000	100.000	86
Photographic chemicals	2.700	30	1
Motor fuels	3.840.000	<2.062.000	< 54
Swimming pool chem.	3.900	345	9
Pesticides [**)]	7.200	40	1
Fertilisers	2.100.000	17.500	1
Cement, mortar, lime	5.000.000	275.000	6
Artistic dyes and colours	< 50	< 50	100
TOTAL	11.552.600	2.603.815	23 %

*) From N.E.P.A. project no. 152 (ref. 15) - all figures are approximate, referring to amount of products.

**) Use volume is presently under reduction - influenced by official reduction plans and changes in use practices.

a) additives in foods

b) medical &
c) pharmaceutical products
d) cosmetic

or non-marketed chemicals, such as:

e) chemical intermediates, technical additives produced and applied *within* industries, thus being without interest in relation to marketing
f) chemicals substances, which are resulting from degradation or side reactions in industrial processes, or found as waste products from production, combustion or clean-up processes, and
g) imported chemicals contained in manufactured goods.

These areas often attract attention in relation to chemical impact and the need for assessment of chemicals in relation to human health and environment, incl. the work place environment. This may be due to the fact, that they (*cf.* a, b and c above) are thoroughly described, assessed and possibly even use regulated, or on the contrary that they as non-classified chemicals are poorly defined as well as difficult to control (as it is the case for categories e and f). Concerning category d) it is noted, that cosmetics since 1992 have been placed in a category regulated by a negative list (or prohibition) principle, and as positive list chemicals (*cf.* section 3.2.1).

1.2. Danish regulation of chemicals

With the exception of special chemicals used as foods additives, pharmaceuticals or cosmetics etc., all chemical substances are regulated according to general rules, as follows:

Law on chemical substances and products from 1980 (including later revisions) [16]. By and large this law replaced the former 'law on poisonous substances', and for any individual chemical it regulates

- classification according to health and environmental hazards, including risks of explosion and/or fire,
- packaging, labelling, sales and storage

and in special cases, such as for pesticides (*cf.* chapter 7 of the law), also

- approval, application and control.

The Statutory order of 1982 on substances and materials from the Danish Ministry of Labour, which direct all suppliers of new, hazardous chemicals and materials (= products) to notify these to the Danish Product Register. This is an official register established in 1981 on a legal basis (*cf.* reference 12) as a means of registering all information on chemicals and products of primary interest to commerce and industry.

Irrespective of the difficulties which are tied to the exact definition and delimitation of the individual chemical areas, these laws and regulations are taken as the legislative and administrative basis to which this report refers in its review of chemical testing and evaluation, including discussions on non-assessed chemicals registered in the EINECS list.

The establishment and functions of Product registers are primarily known from the Nordic countries. Beyond this, it is an essential feature of the laws mentioned above, that they are based on the principles

which are established in the common EU legislation on chemicals [17], meaning that the individual member countries in general will be obliged as partners in the European harmonisation process.

These principles are discussed in the following chapters. They imply:

- that a common concept of *environmentally dangerous chemicals* has been independently defined,
- that the demands for *classification and labelling of environmental hazards* has been developed and detailed [18] in parallel to the already existing rules of classification and labelling of hazards to human health,

and as more recent activities

- that priority lists [19] of all chemicals which are dangerous to human health and to the environmental are being prepared, anticipating
- that assessment and possibly reductions of risks to man as well as to the environment [20] shall be carried out according to the latest EU Technical guidelines.

Chapter 2

Principles of chemical regulation

2.1. Control systems

For the control of chemical impact on human health and the environment, different systems and tools of regulation can be applied, such as :

- legislation
- voluntary agreements
- introduction of cleaner technology
- taxes and levies
- 'green purchasing policies', eco-labelling based on *e.g.* LCA- or life-cycle assessments.

Legislation is the traditional control system in widely use, in Denmark especially since the Chemical Law from 1979. Governing today is further the statutory order of 1982 from the Danish Ministry of Labour concerning chemicals and materials used in workplace environment. Most important at the EU level are directive 76/769 on Restrictions of the marketing and use of certain chemicals as the basis for the EINECS inventory list from 1981, as well as the 6. and 7. Amendments to directive 67/548 on Classification and labelling of dangerous chemicals.

Voluntary agreements between authorities and chemical producers/importers have occurred in recent years, especially in the 1990´s. Such agreements have been initiated in relation to PVC-plastic and so-called VOC-chemicals, *i.e.* volatile organic hydrocarbons. These hydrocarbons are regularly found as air pollutants evaporated from motor fuels during transportation, relocation or handling.

The concept of cleaner technology has since 1987 been given official support.

Taxes on chemicals have been used since the early 1990´s, *e.g.* on CFC-gasses, pesticides and chlorinated organic solvents.

The principle of '*Green*' *purchasing policies* was adopted as an official Danish strategy in 1991, but in practice it has only just recently been initiated.

Environmental or eco-labelling has been under development since the late 1980´s, but contrary to Germany and the other Nordic countries, it has not been successfully introduced in Denmark.

2.2. EU regulation

The legislation on chemicals is probably the part of the environmental field, which is most closely regulated at the EU level. For an evaluation of the regulation of chemicals in a EU member state, therefore, it is necessary primarily to observe the EU regulation system and then the national regulation, which has been adopted in accordance with the EU regulation. This is a situation which will influence not only the possibilities for establishment of national legislation in Denmark, but also for the dealing with other means of regulations, *e.g.* voluntary agreements, public green purchasing policy etc.

It is often stated that environmental rules of the EU are minimum rules, *i.e.* allowing the individual member countries to have stricter rules. In principle, however, this is not valid for environmental demands for merchandises, such as products and manufactured goods which are or can be transferred or marketed in and between the EU countries, *e.g.* chemical products, foods, machines, fuels, building materials and so on. For these, the maximum rules corresponding to total harmonisation will apply. It is a major part, therefore, of the chemicals which are circulated and consumed in such way that rules stricter than the harmonised maximum rules cannot be enforced, in spite of their potential for damaging effects on health and environment.

From a Danish point of view - and for other countries holding a high environmental standard - problems on EU environmental policies are connected to directives and provisions in the Treaty which open up for possible collisions between the drive for increased environmental protection on the one side and the demands raised for free mobility of marketed products and goods on the other. This situation may develop anytime when environmental requirements are imposed on products or goods, which are characterised by being transboundary. It has become even more critical in recent years, as environmental management and public controls and measurements has been enforced on waste and discharges from production processes of chemicals. This leaves the use and disposal of industrial products containing hazardous substances as the main environment problem today. Increased productions has been accepted and permitted for products which in the end creates increasing amounts of waste materials, and which are contributing to the increased circulation in the society and distribution of chemicals having an impact on man and the environment. The weight of environmental problems in the highly-industrialised countries have moved from processes towards products.

The concept and strategies of cleaner technology expressing that it is 'better to prevent than to cure' has found its way into the debate. This implies that it is essential to substitute the potentially damaging chemicals in products with less damaging chemicals, in order to avoid *e.g.* not only that accidents occur, but also to minimise requirements for waste water or smoke treatments, if and when an accident eventually does occur. These are areas, however, in which the EU is aiming at total harmonisation, and only in the incitements of industries or through more indirect regulations, therefore, is it legally possible to initiate

environmentally relevant activities which are not in contrast to the EU rules.

2.2.1. Types of harmonisation

In table 2.1 is given a survey of some important EU and National regulations dealing with chemicals. As chemical laws are widely harmonised in the EU, and as total harmonisation is a dominating tool, member countries can neither maintain, nor implement stricter rules, unless this is done with reference to the so-called '*Environmental guarantee*' of the EU Treaty (*cf.* art. 100 A, par. 4). However, the extent to which this guarantee can be applied is still uncertain. In the interpretation of the EU Commission, local problems as for instance heavy groundwater pollution, must be clearly demonstrated for acceptance of the use of the guarantee - a situation, however, which is not directly evidenced from the only the judgement of the EU Court in the field, namely in the trial from May 1994 concerning PCP (Penta-chloro-phenol) used in wood preservation.

In addition to this, the so-called 'safety clause' exists which makes it possible for member countries to implement *provisional* rules, only, in case these are stricter than the rules of EU. Such rules can be altered by a new voting among the member countries, whereas in the case of objection to the use of the Article 100A, par. 4, this can only be altered by decision from the court.

As it appears from table 2.1, chemical regulations can be divided in several groups according to the type of EU regulation:

Classification and labelling	Total harmonisation
Notification of new chemicals	Total harmonisation
Use restrictions (prohibition, approved uses)	Total/min. harmonisation
Hazard and risk assessments of chemicals	Total harmonisation (?)
Discharges of chemicals, treatment of waste	Minimum harmonisation

Whether total harmonisation or minimum rules are used, depends on whether the free mobility of goods is involved, which can most often not be decided unambiguously. On this basis, there are often disputes about and different interpretations of which type of regulation should apply. Obviously, all rules concerning *classification and labelling* of chemicals and products and on *notification* of new chemicals are totally harmonised. From this follows, that not only chemicals mentioned specifically in annexes to the directives, but the field as a whole is totally harmonised.

The EU rules for classification and labelling of chemical substances (dir. 67/548 including amendments no. 6. and 7.) and chemical products (dir. 88/379). Both include provisions for dealing with human health hazards, whereas only the former will include the subject of environmental hazards. As by far the major part of industrial chemicals are marketed as constituents of products, the classification and labelling of environmental hazards is not widely practised in the EU.

As far as notifications are concerned the demand for total harmonisation is only valid *if marketing is the reason* for the notification. This implies, that chemicals used as intermediates or semi-manufactured products are exempted from notification as an EU practice, although they in a Danish system may have to be registered in the Product Register (*cf.* the National Danish rules demanding notification of products and dangerous new chemicals when used in Danish workplaces).

In table 2.1 is shown the most important fields of EU directives and their legal significance for member countries, *i.e.* their legal position when implemented and whether they are constituted as minimum rules or as total harmonisation. Among these, directives are found which will result in total harmonisation, although

they are not yet filled in with detailed 'implementation directives'. In such cases, there is still some room for national regulation for a certain period of time. This includes *e.g.* situations following the agreement on 'uniform principles' for approval of pesticides where, however, actual decisions on individual active ingredients in pesticides have not yet been taken.

Even in the field of total harmonisation, degrees of harmonisation may exist. While the classification, labelling and notification of chemicals is harmonised for *all* substances, this is the case in the directive on Restrictions of the marketing and use of certain chemicals and products (dir. 76/769). Only those products or uses of products, which are explicitly mentioned in the directive are subject to total harmonisation. This is the case for *e.g.* PCB (polychlorinated biphenyl), asbestos, PCP (Penta-chloro-phenol), arsenic and mercury for wood preservation, cadmium, nickel in jewellery, and a number of carcinogenic substances or chemical mixtures (*e.g.* creosote). For some products or uses of products not mentioned in the directive, Denmark has been

Table 2.1. The most important fields of EU directives and their legal effects in the member countries

	Harmo-nised	Total or min. *)	National regula-tion	Notes
Classification and labelling		total		
Restriction of marketing and use, in general	X	total a)	X	a) dir. 76/769 - interpreted in Denmark as being 'minimum-like'
Restriction of uses in the working environment	X a)	min.	Xb)	a) dir. 88/364/EU - prohibition of some carcinogenic chemicals b) Separate Danish regulations
Limit values in the working environment	X a)	min.	X b)	a) dir. 91/322/EU - fewer chemicals than in Danish list b)All chemicals not listed in dir. 91/322/EU
Producers' Safety data-sheet	X a)	total	X b)	a) *cf.* dir. 91/155 =. 'daughter-dir.' to the preparat. dir. 88/379 b) Danish rules are maintained after 1.7.1995
Employers' Safety Data-sheets			X	
Approval of pesticides	X	total	(X)	Main directive is decided - implementation directive(s) (*i.e.* detailed lists) are not developed
Notification of new chemicals, marketing	X	total		
Notification of chemicals and products, industrial use			X a)	a) Danish rules only. Uses must be notified to the Product register

Assessments of existing chemicals	X	total ? [a)]	X? [b)]	[a)] Reg. 93/793 total harmonised - interpretation not clear [b)] For chemicals not yet assessed by EU + list 2 chemicals
Ozone depleting substances	X	min. ? [a)]	X	[a)] Reg. C4 0131/94 minimum rule - unless national rule collides with Treaty
Discharge of dangerous substances into the aquatic environment	X	min		

*) i.e. member countries are allowed to have stricter regulation

able to make national regulation. This is *e.g.* the case for formaldehyde in chipboards and plywood, mercury (except for wood protection) and lead in some specified fields (*e.g.* lead-containing bullets). The directive is therefore interpreted as being both 'harmonised' and 'nationally regulated' as it is indicated in table 2.1.

Generally, rules about *Restriction of marketing* include total harmonisation when a 'global' restriction is involved. But it is only those dangerous chemicals (or products containing dangerous chemicals) which are mentioned in the Annexes of the directives, which are total-harmonised. Thus, member countries are free to make national regulations for other dangerous chemicals or products. In such situation, however, the Commission has to be informed on the specific national rules, and it will hereafter decide whether harmonised rules shall be proposed for the field in question. The possibility is open for the Commission to postpone the national rules for up till one year, while it is being considered, whether to suggest harmonised rules.

As an example, a statutory order was issued in 1994 in Denmark concerning products containing mercury. This was at first postponed by the Commission, but later accepted, because the EU harmonised rules for mercury are specified for batteries and for mercury in wood protections, while no general ('global') rules are enforced in this case.

When it comes to use restrictions for use of chemicals at the *work places*, a minimum harmonisation is applied. When no general product regulation is in force at the time of marketing, a national restriction concerning the use of the product at the work place can be established. This may, however, give rise to difficulties of interpretation, *e.g.* in case the claim of the national rule is that the chemical or the product shall be completely banned at Danish work places. As an example, *Creosote* is allowed for professional uses according to an EU directive, whereas it is prohibited for housekeeping purposes. In Denmark, however, it is prohibited for uses at the work places as well. This is interpreted by the commission as a complete Danish ban, which is in defiance of the harmonisation in the EU, and can probably only be allowed, if it is covered by Article 100A, 4 of the treaty.

The main directive (dir. 76/769) concerning marketing restrictions for certain chemicals, is in Denmark considered to have character of 'minimum directive'. But all other member countries disagree and find that the directive provides total harmonisation as far as the more recent revisions and amendments of the directive are concerned. These revisions include *e.g.*: asbestos (no. 5), Penta-chloro-phenol (no. 9), cadmium (no. 10), nickel in jewellery (no. 12), and creosote (no. 14).

It is a different situation, when it concerns the EU regulation of ozone depleting substances (C4 0131/94).

This is based on the article 130 A of the Treaty on environmental protection, and being therefore a minimum rule it has a potential to create a technical barrier to trade in case of stricter national rules in individual countries. According to the Commission interpretation of these rules, a member country is not allowed to set limits for the import of chemicals, which are still permitted by the EU. Reference is here made to article 130 T of the Treaty, *viz.* that any rule must be in accordance with the treaty, especially article 30, following which technical barriers to trade must not be created (see section 2.4. 'Examples').

In spite of these considerations, the Commission has chosen not to bring Denmark before the EU court on the cause, that the Danish plan for phasing out the ozone depleting substances is stricter than the common EU rules (*cf.* statutory order no. 974 of 13.12.1995). This might be based on the fact that by choosing the article 130 A - the environment article - as their authority in this case, the Council of Ministers has obviously clearly signalled, that the environmental perspective should be given the highest priority - more so than the single European market.

When it comes to the working place, Denmark has introduced a number of limitations and restrictions on the use of chemicals, such as:

- notification to the Product Register about marketing of new, *dangerous* chemicals and chemical products
- requirement for pre-approval of specific carcinogenic chemicals
- prohibition of the use of specific carcinogenic chemicals in specific product types
- a code numbering system for paints, varnishes and lacquers, incl. corresponding guidelines and regulations on use
- compulsory training programmes etc. as a requirement *e.g.* for the use of epoxy and polyurethane products
- limit value maximising free chromate in cement products

These are all strictly national regulations.

The recently introduced rules concerning *risk assessment* of chemicals has no direct connection to the concern for free exchange of products and goods, but they are established with reference to art. 100 A of the Treaty, *i.e.* as a total harmonisation in respect of the 'internal market'. It is still unclear, however, how this will be interpreted. It might be the Commission - not the member countries - who will have the competence to make suggestions for regulating use(s) of individual chemicals. But in such case this will only apply to substances which are being assessed in the framework of the EU. Furthermore for chemicals in relation to the working environment, it is noted that these are not covered by the competence of the Commission.

Rules and regulations on point source *discharges of chemicals* and on *waste treatment* are always minimum rules. This has, however, not been clear all the time. At several occasions, the Commission has suggested to the Council of Ministers, that rules within this sphere should be adopted by referring to articles on the single European market. In one example from 1991 concerning directive on discharge and waste treatment in relation to the titanium industry, the EU Court of Justice endorsed the opinion of the Commission. Contrasting this, in another example, the Court agreed with the Council of Ministers in 1993, that the Framework directive on waste materials should follow the Environment article (art. 130 S), *i.e.* have function as a minimum rule, which presently seems to be the legal status when dealing with discharges and waste treatment.

2.2.2. The EU and chemicals at the workplace

There is an increasing tendency, that chemical regulations in the EU shall include aspects of working environment under the concept of total harmonisation. This is contrary to the intentions that this area should be maintained as a field of minimum regulation (art. 118 A) by allowing member countries to make stricter rules. Development has shown, however, that various chemical directives are accepted as total harmonisation (especially art. 100 A), and in consequence with influence on national rules within the field of working environment.

An example of this is the directive on 'Safety data-sheets ' (91/155/EU) according to which member states shall introduce rules on so-called *Supplier's safety data sheets*for marketed chemicals and products which are dangerous according to two similar EU directives. These instructions include chemicals from the EINECS-register as well as from the ELINCS lists. Since 1983, Denmark has made similar demands. They differed, however, by requiring other types of information and by setting requirements for a larger number of products, than those which are classified as dangerous according to the EU system.

By the implementation of the directive in 1995, therefore, Denmark has revised its existing rules on Suppliers safety data sheets, but has maintained its requirements for safety data sheets of the same number of products as specified in the earlier regulation. Further, the extent of information is also maintained at the earlier level, *i.e.* higher than in the directive.

2.3. Rules of notification

The National Agency of Environmental Protection, as well as the Directorate of the Danish Working Environment Service administer rules concerning notification of chemicals. The main purposes of these are to provide information about new chemicals and continuously to ensure an up-dating of existing information about old and new chemicals.

In the EU, information about any new chemical must be submitted by producers/importers as part of their notification of the chemical before bringing it to the market. This is a consequence of the rules introduced by 6. Amendment of directive 67/548 on notification and classification. It includes requests for toxicological and ecotoxicological properties and characteristics, and in such way that requirements for information will increase with amounts of a chemical (*cf.* chapter 4). Based on the submitted documentation, the authorities will make its first evaluations, which eventually can lead to a demand for further toxicological and/or ecotoxicological information to be provided by the supplier.

Until November 1995 only 5 new chemicals have been notified in Denmark. This is obviously due to the requirement that producers must 'first time notify' a new chemical to the authorities of the country, in which the chemical is produced.

Pesticides have to be notified and also to be approved for the specific applications before for their marketing. In Denmark a further time limit of the approval of 8 years is valid, which is not the case in the EU notification scheme for new chemicals. If a pesticide chemical have been evaluated in the EU or by national authorities, and no specific arrangements or requirements are settled on the basis of the submitted information from the notification, is it *not* possible for these authorities later on to demand renewed tests or information from the producer, unless the chemical is marketed in larger amounts than anticipated.

In order to ensure the relevance for the working environment of the information which is submitted, the

Directorate of Working Environment Service administers a special set of notification rules for chemicals and products. According to these rules, the marketing of a new dangerous product must be notified with full, qualitative and quantitative information on the composition, on amounts which are expected to be marketed in one year, as well as expected uses and use patterns of the product etc. Toxicological data are not demanded, unless the notifier already possess this information, whereby it is indicated that the notifier is not obliged to initiate toxicological studies additional to those which are already at hand.

The notification rules for dangerous chemicals and products which are established by the Directorate of the Danish Working Environment Service are strictly national without any background in the EU regulation. The term dangerous is applied on the basis of specifications laid down in a statutory order after agreement between the partners who conventionally represent the labour market. It has now been extended to make it valid in relation also to the EU rules on classification and labelling.

About 32.800 notifications of different chemicals products are presently listed in the Danish Product Register. Compared to the situation in most other countries, it is evaluated, that a much larger knowledge on commercially available chemicals and products is thereby presented for the Danish authorities. Information is included on composition of products and preparations, as well as on the branch(es) of trade or types or products in which the chemicals are used.

According to the Danish legislation on the working environment, producers/importers are obliged specifically to notify carcinogenic substances as well as preparations containing such substances before marketing take place.

2.3.1. Harmonisation and national regulation

According to the Danish chemical law, authorisations are given to the minister to develop and issue special regulations within a number of specified areas related to chemicals and products. Most of these authorisations are corresponding to similar rules established by the EU. In practice, however, it is neither the number nor the character of such authorisations in a Danish law, which determine whether Danish activity in the field of chemical protection is sustained and further developed. A drive may rather be determined by:

1. the possibility of obtaining majority in the EU for stricter rules, including the prioritisation of international co-operation, the need for increased exchange of information, as well as direct agreements with the most progressive EU countries.
2. the willingness to 'approach the limit' and utilise all options and opportunities in interpretation of the EU rules for supporting the national Danish initiatives.

re. 1. From Danish side great effort has been made to propagate knowledge which is available in Denmark (and other Nordic countries), and to advocate a proper labelling concerned with health hazards connected to the exposure with *organic solvents*. Generally, however, Denmark could do a lot more in this direction. In recent years a certain prioritisation have been given to the publishing in English of results and strategy proposals by the Danish authorities, but it still seems as if this is much less than similar activities in some other countries, especially the Netherlands.

re. 2. Generally, Denmark is most reluctant in its use of Article 100A, 4 in spite of the efforts which was made from Denmark to have it included in the Treaty in 1986. This is also the case when it comes to adoption of restrictive interpretations that might end up in the EU Court of Justice. Only after Germany had

won - at least partly - a case concerning PCP, Denmark has also used Article 100A, 4 on PCP, and later on creosote.

On the other hand, it has happened that stricter national rules were chosen in Denmark, even though it was pointed out by the EU Commission, that uniform rules should be awaited. This has *e.g.* been the case for regulations on cadmium and mercury, as well as for ozone depleting substances, esp. such as CFC-gases. In the last case Denmark decided a quicker phase-out of ozone depleting substances and a more specific regulation presented as time-limits for the different fields of application. EU has a more general regulation and longer time-limits, especially for the so-called 'soft' HCFC-gasses, but also for methyl bromide which is used as insecticide in fumigation processes.

Other ways of 'taking the lead' may be information campaigns and introduction of environmental management, including 'green purchasing policies' in governmental and other public institutions. It should be made possible and be encouraged not to select certain dangerous chemicals and products, even though they may be permitted according to EU rules. It is noted that the National Agency of Environmental Protection in agreement with the Ministry of Industry and Commerce have refrained from being restrictive in this sense. It is a consequence, that purchasers in public institutions *e.g.* are not allowed to make stricter demands on imported products than those given by the EU directives, even when environmental problems can be related to the production process, or to the finished products as this is presented to the purchaser.

2.4. Examples

There are numerous examples of collision between Danish rules and the corresponding EU rules concerning chemicals and chemical products. This can be exemplified as follows:

Pesticides

- The existing Danish scheme for pre-marketing approval of pesticide chemicals is presently confronted with the demand for development of a common and uniform EU approval scheme. Following this, a pesticide can be approved in the EU by a majority voting, and the harmonisation will remove the present Danish possibility for banning a chemical referring to the fact that a less hazardous alternative is available.

Thus, the result may be that Denmark - apart from the possibility of enforcing a national delay clause of 5 years - may have to accept pesticide chemicals which are otherwise found unacceptable, *e.g.* in order to protect Danish ground water resources. The EU countries still does not have a common position on protection of ground water. Contributing to this conflict is the fact, that agricultural commodities and produce have their own procedures in the EU according to which the Article 100A, 4 is not valid, without regard to their environmental implications.

Cadmium and PCP

- The EU allows uses of the heavy metal *cadmium* and the wood protection *Penta-chloro-phenol (PCP)* to a much larger extent than the Danish legislation. Cadmium is prohibited in Denmark (and Sweden) with a few exceptions (positive list) while in the EU, cadmium is only prohibited or restricted for certain applications (negative list). Formulations of PCP may contain dioxins, and it may further give rise to formation of unacceptable amounts of dioxins when incinerated. It is totally prohibited in Denmark, Germany and in the Netherlands, while in the EU it is permitted for industrial pressure impregnation of wood.

Creosote

- The EU will allow commercial uses of carcinogenic creosote for wood protection. In Denmark the use of creosote has not been approved since 1991.

PVC

- In the EU a packaging directive has been adopted, which allows free exchange of *PVC-based packing material*, whereas in Denmark there is a voluntary agreement providing a substantial reduction in the PVC uses. In PVC a major constituent is chlorine, which will give rise to formation of hydrochloric acid during incineration, and which furthermore may contribute to the formation of dioxin(s).

Organic solvents

- In the EU the majority of countries has not accepted the scientifically based claim, that long-term exposure with o*rganic solvents* will cause brain damages, and there is therefore also no acceptance of continued proposals that classification and labelling criteria are introduced in order to express risk warning and safety guidelines. In 1987, Denmark single-handed introduced a risk labelling by using the so-called safety clause in the EU classification and labelling directive. This clause, however, only makes it possible *temporarily* to introduce stricter rules, as the Commission can meet these by calling member countries for a new voting. This has been the case for most of the actually discussed organic solvents, whereby Denmark has been outvoted with the result that the Danish risk warning labelling had to be abandoned.

As for the *white spirit* a rather peculiar compromise was reached. This product is labelled as hazardous to health - as requested from Denmark - but without the specific warning on the actual long-term effects which cover brain damage (*re* R-phrase no. 48: 'Risk of severe effects after prolonged exposure'). As a matter of fact, the solvent is labelled as if it is a potential cause of acute effects (*re* R-phrase no. 22: 'dangerous when consumed')

Ozone depleting substances (CFC, HCFC etc.)

- The EU regulation of *ozone depleting substances* allows for a relatively long period for the phasing out of uses of the so-called 'soft' CFC-gases (HCFCs) and of methyl bromide, *i.e.* chemicals which in spite of their lesser potential for ozone depletion, are all going to increase in contribution and significance as so-called ODP-compounds when the CFC's are phased out. In Denmark a faster process of phasing out the HCFCs has been adopted, which has been opposed directly from the EU. So far, however, Denmark has taken a firm stand on this issue, and it seems that the Commission has decided not to bring the case before the court.

Chapter 3

Classification and priority setting

3.1. Classification

3.1.1. Classification and approval for specific applications

Today, extensive safety requirements are made for some *specific groups of chemicals*, which are applied *e.g.* as additives to foods in the food production, as pharmaceuticals, or as pesticides. Such requirements are made to secure that these chemicals as a background for their applications are *harmless*, which further involves that they have to be *classified and approved for their specific applications*.

For these chemicals, importance is attached to the information on the physical/chemical, pharmacological and toxicological properties and characteristics of the chemicals, although today an increasing demand is noted also for information on environmental properties. Obviously, information about actual use patterns and information about possible side effects, must be available. The needs are for exhaustive assessments of hazards as well as for definition of no-hazards qualities, but also for detailed assessments of risks - for man as well as for the environment.

The outcome of these assessments can result in use restrictions or in demands for substitution, or possibly even prohibitions. The requirements for data and documentation can be rather extensive - to the point that it may set a practical limitation to the number of chemicals which are actually placed on the market. An example of this situation, is the present '*Positive list' for Additives in Foods (from 1973, latest revised in 1995)* *[21]*, by which a pronounced reduction in number of actually applied colouring agents, preservatives, antioxidants etc. has emerged since the preparation of the list.

Another example is the demands for classification and approval of *pesticides* [22], which has functioned as a limiting factor for number as well as for amounts of applied pesticides up till the present day. This is due to the fact, that the burden of proof, not only for the efficiency of the chemical, but also for its harmlessness apart from the pesticidal effects, lies with the producer/importer regardless whether the application is commercial or private.

Through the procedure of classification and approval, including use regulation via the positive list, producer/importers are obliged to provide and submit to the authorities a much larger amount of data and documentation. Additional to the health and environment related properties and characteristics, the documentation must include detailed information about the specific use patterns for the chemical product, and measures of precaution by handling, mishaps, accidents etc.

These demands seem gradually, though not unexpected to be increasing, concurrently with the increasing attention to hazards to humans and animals, as well as with the knowledge on risks of contamination of food, groundwater, the working place etc. In the pesticide field these demands have undoubtedly been contributory to the fact, that there is today only about 250 active pesticide chemicals, which have been assessed and accepted under Danish conditions, out of those ca. 1300 individual chemicals which are world-wide being recommended in an agricultural context [23].

3.1.2. Classification of new chemicals

Contrary to the circumstances for specific positive list, the general assessment of chemicals and chemical products will normally only include the identification of basic physical/chemical, toxicological and some ecotoxicological characteristics (*cf.* statutory order no. 829 of 15.10.1993 from the Danish Ministry of the

Environment),

As for the *new* chemicals (see section 1.1), these characteristics must be described and submitted by the chemical producer or importer as a part of their notification of the chemical to the authorities. The process of classification includes an initial hazard assessment on a first, so-called base-set level (see next chapter). It is related to the *normal* (*i.e.* intended) handling and application of the chemical, and it does not in itself involve establishment of further use limitations/restrictions. Only in case chemical(s) at the time of marketing are identified as hazardous, a classification is demanded, which will include labelling with instructive R-phrases (for risk) and S-phrases (for safety), and attention must be given to those characteristics which are identified as dangerous (*cf.* figure 3.1, below).

Today it is a part of the harmonisation process in the EU:

- that the general classification scheme for chemicals is based on a standardised, rather simple set of information - *the base set* - comprised by data, which include the most essential physical/chemical, toxicological and environmental parameters,
- that this base-set is used to

  - to define the *characteristics*, which can (or must) be included in the classification and
  - to detail the *danger classes*, which in a uniform way shall characterise the individual hazard parameters of a chemical.

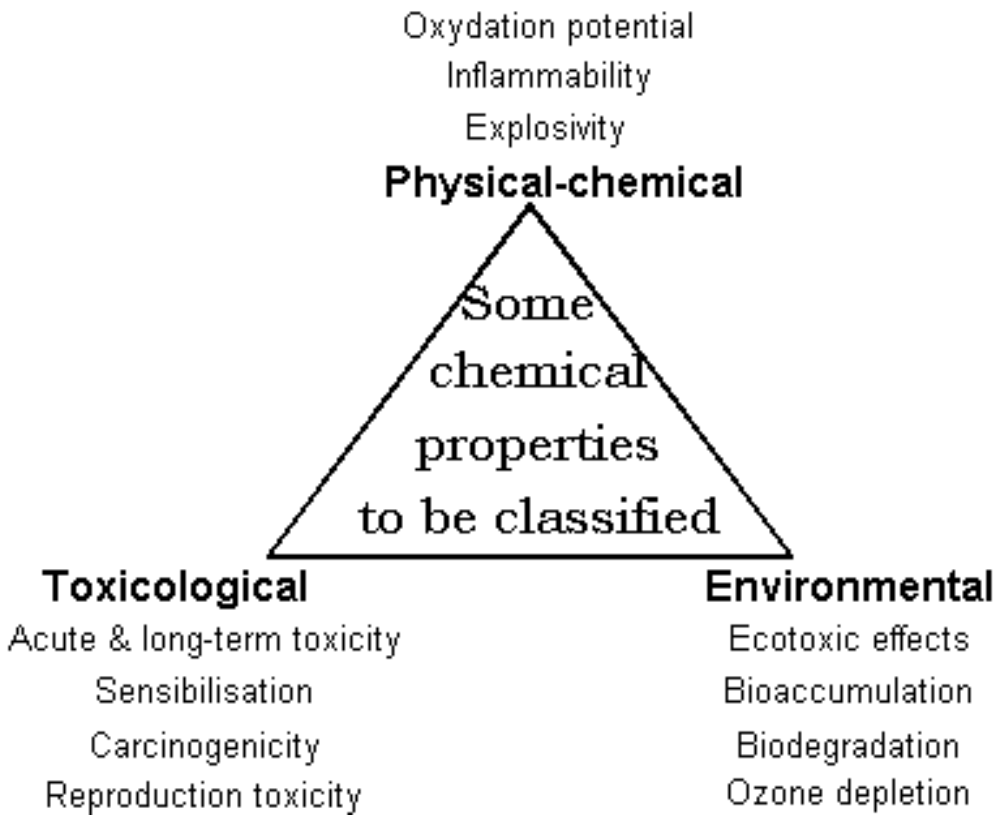
The uniformity of these rules are of course serving the free movement of chemicals, without giving rise to technical barriers to trade within the EU internal market.

Only those characteristics, which are included in the classification diagram (and in the subsequent 'generic risk assessment'*) - *cf.* chapter 5), are today included in the routine studies of *new* chemicals. It is a common feature of those characteristics, that they are relatively simple to describe, and their assessment are based on relative simple test methods. It is therefore connected to difficulties and it is time demanding, if further and more complex characteristics should be included in the routine classification.

*) The term ‘generic risk assessment' refers to the so-called PEC/PNEC-ratio. It should be clearly distinguished from normal (comprehensive) risk assessment.

Figure 3.1 Characteristics, which are included in the general

danger classification of chemicals



This is a matter which has been discussed in relation to *e.g.* hormone-like effects of some chemicals (for which a suitable base-set methodology hardly exists today), or in relation to the mobility of pesticide chemicals in soil (which is significant for groundwater protection - a field, which may be included in future environmental classification schemes of the EU on the basis of an expected German proposal [24].

3.1.3. Classification of existing chemicals

According to the most recent EU rules on classification and labelling [25] and on risk assessment for chemicals [26], it is the same criteria for 'classifiable' properties and characteristics which shall apply for existing chemicals as for new.

The problem is of course, that these characteristics are not described for the major part of existing chemicals, such as these are listed in the EINECS register. This situation will further be described and discussed in the chapters below, but it is mentioned here, that the individual base-set properties (to the extent data and documentation exist) will be scaled or related to hazard classes in a way similar to the practice for new chemicals, *i.e.* based on the same relatively simple, but standardised measurements, such as:

explosive	<=>	*inflammable*	<=>	*fire nourishing*
very toxic	<=>	*toxic*	<=>	*harmful health*
accumulative		<=>		*non-accumulative*
persistent	<=>	'*not easy*' *degradable*	<=>	*easy degradable*

It is information of this kind, which has to be labelled directly on marketed products, in sales documents etc. As a useful user/consumer information additional warning symbols and instructive R-phrases (for risk) and/or S-phrases (for safety) must be applied..

In the latest edition of the *List of dangerous chemicals* [27] a total of approximately 2100 individual chemical entries are included. Among these are a major part of the ca. 250 active pesticide chemicals, which are approved for use in Denmark. Also included are most of those 541 chemicals, which were recently selected in a Nordic project and assessed in relation to a possible classification as *dangerous to the environment* [28].

In this Nordic project, the chemicals were selected because they were defined as:

1. 'high production chemicals' (HPVC), *i.e.* chemicals, which are marketed in amounts larger than 1000 tons per year,
2. 129-chemicals on the so-called List I, which by the EU Commission in 1981/82 were selected as 'dangerous to the aquatic environment',
3. chemicals included in the Nordic countries on national lists of dangerous chemicals
4. a number of chemicals which for other, individual reasons have been identified in Nordic countries as cause(s) to problems.

342 of the 541 chemicals were identified as being of special interest to the Nordic countries, while only 199 were found on international priority lists. It was found, that a data base quantitatively sufficient for implementation of an environmental hazard classification could only be provided for 400 chemicals (or 74% of the total). Approximately 50 % of those chemicals which were assessed had a qualitatively satisfactory data base for an additional effects assessment. In conclusion, less than 50 % of the most problematic chemicals could be carried through to an initial environmental assessment. And further, there is not necessarily a coincidence between the lists of highly prioritised chemicals from the EU and corresponding lists from individual member countries.

3.2. Priority setting

It is remarkable, that approximately 50 % of the more than 2100 chemicals, which are included on the Danish *List of dangerous chemicals*, are also categorised as HPVC chemicals. For this HPVC-group it is a further estimate, that only half of the data which are needed for their classification and additional hazard and risk assessment are presently available*).

*) This information was first given to the IPS Working Group in 1992 from ECB, European Chemical Bureau, Ispra. It is later (1996) confirmed from ECB with only slight amendments (cf. last column of table 3.4,).

The principles, which have until now determined the priority setting and the selection of chemicals for various priority lists selection, are to a large extent empirical. They have been based on existing information about individual chemicals or groups of chemicals, and the lists are developed by empirical identification of unwanted and/or dangerous properties supplemented with experiences provided from accidents, mishaps or actual damages and risks related to the practical use of chemicals.

Only in recent years it has been tried to develop methods and activities for a more systematic assessment of the significance exposure and effects of chemicals on health and environment. This is to a large extent a reflection of the pressure from a continuous increase in number of chemicals and a still more complex use pattern of these.

As a starting point for considerations on the need for and the burden of assessment, including the question on how to accelerate the test activity or - alternatively - how to reduce the burden by proper selection of

chemicals and methods, it is important to decide if the chemical regulation shall be based on a:

Positive list principle, i.e. that permission to use the chemical is required prior to marketing, and that this has to be given on the basis of pre-investigations and pre-assessments for the exact purpose, or a

Negative list principle, which involves that marketing and use generally is free, unless individually selected chemicals are given specific restrictions (or prohibitions) based on evidence and evaluation of hazard potential or individual risk assessments.

3.2.1. Positive lists

Chemicals which must be approved and accepted for specific uses according to a Positive list principle are said to be 'classified for a specific purpose or field of application'. A selection of chemicals for the positive list must include

- *both* an acceptance for the purpose,
- *and* a detailed description of properties and characteristics contributing to potential hazards,
- *and* an assessment of risks connected to the specified applications

- all of this as part of the actual approval. In principle, the approval procedure has automatically the function of a prioritisation procedure, not least if authority is given for substituting individual chemicals/preparations for 'less hazardous' alternatives as a part of the approval procedure.

The most critical question in this procedure is of course:

How many or which chemicals can be justified, i.e. are necessary or interesting enough to be accepted as part of the general 'housekeeping'? The question should be answered on the basis of

- a documentation of the demand for each individual chemical in the defined field of application,
- a classification and assessment of health and environment hazards, including toxicity, reactivity, general or specific biological concern etc., and finally
- a controlled use regulation, including risk assessment in relation to zero-effect-level, vulnerable exposure situations etc.

Some examples of the use of this principle of classification and further regulation are well known today:

- *additives for foods*, in the continuously revised 'Positive list' as published from the National Food Agency [29],
- *medical specialities* and *pharmaceuticals* products [30], and
- *pesticides*, *cf.* general law on chemical substances and products, including statutory order setting criteria and requirements for approval and control [31],
- *cosmetic chemicals and products [32]*

It is characteristic for these specific types of chemicals that every individual chemical are defined and classified for the purpose by the authorities via the legislation, possibly with a general approval, but often with details of a regulated use pattern based on the claims, information and documented data submitted by producer or importer. The submitted documentation must be adequate for hazard as well as risk assessment, and it must include technical information in order to make a following use control possible.

Interesting in this relation is the relatively new regulation of cosmetics (Danish Statutory order no. 502 of 9.6.1992), in which is included *both* a list of chemicals, which are *not* permitted as components of cosmetic products, *and* lists of chemicals, which can be applied for specified purposes (*e.g.* colouring matters, preservatives), but only under certain circumstances and with specific use limitations. This is obviously exemplifying a combination of the 'positive list' and the 'negative list' principles, although still with relatively few rules of labelling and control.

3.2.2. Priority setting for 'Negative lists'

The negative lists, which work according to a prohibition principle are dominating chemical legislation in Denmark, as well as in other European countries on chemicals. Characteristics are:

- that all chemicals registered as existing on the EINECS list (indicating that they have been marketed for a period of 10 years before September 1981) can freely be produced, imported, marketed and sold, *unless* this is altered by regulation or prohibition. In actual cases, such regulation can only take place on the basis of evidence presented on a hazard potential or actual risks, which increasingly have to be presented following uniform test principles (see chapter 5), and/or upon request and documented demands from a member country;

- that all new chemicals freely can be marketed based on a written notification from the producer/importer including information on identity, properties and characteristics of the chemical and with statements on expected fields of application. After the notification marketing is free, and intervention can only take place on the basis of presented evidence and risk assessment (see chapter 5), which are carried out following similar uniform test principles.

The establishment of lists of dangerous chemicals or the selection of individual chemicals, which should be given priority, is a necessary but often widely discussed basis for a vast majority of decisions taken about chemical safety and development of chemical regulations in relation to the protection of health and environment. In a 'universe' of freely marketed chemicals the *demands for data* are very large. In comparison, however, the amount of information which is presently available for the evaluation of these is limited, and the central issue is therefore:

- *which chemicals and how many* can be identified as dangerous, *i.e.* toxic or in another ways threatening to health and/or environment
- *which chemicals and how many* should be categorised as the *most* dangerous, and thus unacceptable as potential polluters? and not least
- *how is it possible to prioritise and select* these chemicals as being the most critical.

For answering these questions, the existing data bases are very incomplete. It is noted, however, as a move in the right direction when EU countries in the late 1970'es revised their chemical legislation, extending it with demands for standard test methods and introducing requirements for uniform data in relations to health and environment. It represents a follow-up of this work, that *the European Chemical Bureau (ECB)* (since 1995 in Ispra in Italy) has been established and that further initiatives have been taken to call for data and documented information from the chemical industry. Such calls have been made for all HPVC chemicals on the EINECS list (before the end of 1995) and for further 'grey zone' chemicals (before the end of 1998 (see 3.2.3.).

Data which are submitted and accepted, are stored as an updating and supplementary to existing databases (*cf.* the IUCLID, International Uniform Chemical Information Database at ECB, Ispra). Regardless,

however, of these efforts, there is still a considerable lack of information in relation to the needs for evaluating the large number of EINECS chemicals. The process of assessment of priority chemicals is undoubtedly progressing, but according to the information given, only with about 50 chemicals per year - which is in fact less than the rate of notification and marketing of new chemicals, said to be approximately 200 new chemicals added to the ELINCS list each year.

As examples of the use of the 'negative list' principle is mentioned:

- *The selection of chemicals for establishment of control rules and setting of limit (or so-called M.A.C.-) values by the Directorate of Danish Working Environment Service [33] ,*

- *The List of Dangerous Chemicals* [34] *from the Danish Ministry of the Environment*, which includes more than 2100 selected entries*) listed for their classification and labelling requirements, and
- *A number of specified prohibitions or use restrictions* which are established for chemicals, that have been identified individually as dangerous for a variety of specific reasons. Examples are PCB/PCT, Penta-chloro-phenol, certain heavy metals, CFC gases, Atrazine etc.

*) The Danish list corresponds closely to the list of dangerous chemicals from the EU (cf. Commission directive of 19.12.1994 about the 21. adaptation to Council directive 67/548). The only differences are the inclusion of petroleum (white) spirit in the Danish list, and further the establishment of a separate list (volume 2) of all chemicals from coal and oil, which are assessed for their carcinogenic characteristics and their aspiration pneumonic properties

Among international 'negative lists' based on a selection by priority related to the environmental hazards, the following are mentioned:

- The lists of US Environment Protection Agency, EPA on 'Priority Toxic Pollutants' which includes approximately 130 chemicals. The lists were prepared in the years 1979-1982 through a systematised expert activity [35] which was authorised by the American Toxic Substances Control Act (TSCA), a legislation which in fact preceded the 1979 - revision of the EU chemical directive (79/831/EU, also called 6. Amendment of EU/67/548).
- The so-called BUA lists which include approximately 700 chemicals. They were prepared in Germany in the years 1985-88 as a co-operative effort between the German chemical industry and the Federal environmental authorities (UBA) [36].
- The EU List 1, also called the 'list of 129 chemicals' which are prioritised and selected for an assessment as dangerous to the aqueous environment. The selection was authorised by the Council directive 76/464/EEC [37] and based on expert judgements during the years of 1979-82.

3.2.3. 'Grey zone' chemicals

There are fundamental differences between on the one hand, the identification and approval of individual chemicals for specific purposes of the positive list, and on the other hand, the specification of chemicals which are included on negative lists of dangerous chemicals or which are separately prohibited or regulated. It is obvious, that by far the largest number of individual chemicals are left un-assessed between the extremes of the two principles, *i.e.* unclassified and without any clearly specified demands of regulation.

The number of such '*grey zone chemicals*' is very large, representing the majority of chemicals known from the EINECS list. It is within this immense field, producers/importers are requested to make their 'self classification' of chemicals as required in the statutory order on classification. It is also for chemicals in the

'grey zone', that the EU Commission via the *European Chemical Bureau (ECB)* in these years are calling for submissions of data and documentation from producers and importers, in order to expand data bases. This is done in accordance with the EU Council regulation on risk assessment of existing chemicals (EU/793/93), and a deadline has been set that data for chemicals produced in amounts between 10 - 1000 tons per year shall be submitted before the middle of 1998. Data for HPVC chemicals were similarly collected in 1994-95.

For the time being there are no estimates of neither quality, nor amount of the data, which in this way is collected for a number of EINECS chemicals. Also, evaluations are not available on the prospects for an exhaustive assessment of the incoming data to be carried through. The potential for actually reducing the burden of investigations as well as the burden of assessments is therefore a question of considerable importance. Of course, this is also the case for the possibility of limiting the uncertainties connected to the consequences for health and environment,.

It can hardly be doubted, that temporary, most often simplified assessments will continue to occur for a long period of time and for a considerable number of chemicals, based as they will be on analogies from other and more well known chemicals, or on theoretical estimates (*cf.* section on QSAR, chapter 4). Furthermore, it can be expected that data bases, classifications, and hazard/risk assessments will refer to chemical groupings (in stead of single chemicals) of chemically or biologically related chemicals to a much larger extent than earlier.

A rather interesting proposal, which has not yet been tried out extensively, is the possibility of aggregating and assessing a number of petrochemicals [38] in groups. This procedure operates through so-called *threshold effects* for groups of chemicals. A larger number of chemicals can be ascribed to a *uniform* '*hazard potential*' which is determined with less accuracy, but refers to a uniform and relatively restrictive level of protection. The level should be decisive for a restricted use practice, and deviations shall only be permissible in case a more thorough documentation and chemical assessment has been submitted from the producer/importer.

It is in continuation of this proposal, that it has been considered by the working group that controlled group-classifications should be carried out in a more systematic way, in order that

- *all chemicals on the EINECS list* are distributed and positioned into a large number of groups or blocks chemicals, which are based on chemical, biological, structural or other 'relationships'. This will reduce the present need for data - and consequently also the burden of assessments - as this will be determined by the number of groups in stead of the number of individual chemicals, and that

- *all chemical in a group* can be classified identically, following the classification of the most dangerous/critical chemical present in the group.

3.3. Proposals for the group classification

As discussed in more detail in chapter 5 below, a chemical assessment will generally consist of a hazard (effects) assessment, starting with a classification, and followed by an exposure assessment, in order that these can be included in a risk characterisation process, according to the latest EU-terminology.

In case it is wanted to accelerate this process, **a strategy should be chosen, which will primarily**

accelerate the hazard assessment, and that this should be initiated by the classification, bearing in mind that any subsequent assessments, including possible use regulations, undoubtedly will have to follow thereafter.

Serving this purpose, the working group recommends that a revision is initiated of the present practices, by moving from the present *less structured* '*hazard classification, including self classification*' *of individual chemicals* to a more systematic and controlled *process of* '*group-classification*'. The strategy is to distribute all EINECS chemicals into groups, which shall be defined on the basis of their chemical, biochemical, structural, or other resemblance or relationship. The groupings must be developed by using analogies to other, more well known chemicals, QSAR calculations, knowledge of functional groups etc., all of which may be significant for the toxicological and/or ecotoxicological effects of chemicals.

Chemicals in the EINECS list are presently categorised into a numbered group system, which, however, is far from being sufficiently detailed to a system to be used in group classification. The list consists of approximately 150 groups, which are categorised in two main series, and all are labelled with a 3-digit code constituting the first part of the full code number. The two main series are:

1. 103 groups refer to inorganic chemicals which are ordered according to the most important element. The experience shows that this division must be further elaborated. As an example, the metal *chromium* exists in two types of compounds (*cf.* Cr^{III}-and Cr^{VI}-compounds), which must be classified separately due to their significant toxicological/ecotoxicological characteristics. In another example it might be necessary to refer the classification of the chemical *fluor-sulphonic acid* (presently positioned in group no. 016, sulphur), to two groups, namely fluorine compounds and sulphonic acids, and to classify by a relevant combination of classifications from the two group.
2. Organic-chemical compounds in the EINECS list are presently grouped in 18 groups with some sub-groups. These groups are all too broad, and most often they are not clearly defined. Questionable, for instance, is whether the chemical c*hlorophenol*, should be placed among 'halogen substituted hydrocarbons' (group 602), or as 'phenols and their derivatives' (group 604)? - or preferably as a separate group of chlorophenols. Similarly, *PCB* and *PCT* are placed together in a present group no. 602, even though they would be better placed in separate groups, which is also the case when dealing with the chemicals *cyanates* and *iso-cyanates*.

The use of a group division of organic chemicals can be further exemplified as follows:

- Different types of *phenols*, for which data are missing or documentation is incompletely assessed, can be grouped by reference to molecular moieties (substituent(s)) which are determinant for their most hazardous characteristics.
- *Chlorinated phenols* could be placed in group together with Penta-chloro-phenol, while *alkylated* and *ethoxylated phenols*, which might be suspected of having oestrogen (hormone-like) effects, could better be categorised and placed in group together with *nonyl-phenols.*
- *Nitro-phenols* containing more substituents than the nitro-group(s) could most suitable be placed in the same group as the pesticides *Dinoseb* and *DNC.*
- Some dyes or pigments are based on the chemical *benzidine,* which may be a constituent *e.g.* of yellow printing ink and in car enamels. The benzidine structure and benzidine salts are known to be carcinogenic, which is the case also for some benzidine pigments. Consequently, other benzidine dyes and pigments should also be listed and grouped with the carcinogens, even though they have not yet been tested. It is hereby indicated, that a metabolic degradation in the human organism (esp. in the intestinal tract) may give rise to formation of the benzidine.

The practical grouping of chemicals should be understood as a 'technical-scientific' formation, *aiming at a very detailed division, easily leading to a considerable number of groups (1000 - 2000 ?).* It could be developed by a thorough revision of the present EINECS group division, and preferably be carried out as a European project of common interest.

The group classification with its 'built-in' precautions must include all chemicals on the EINECS list in order that the present 'self-classification' can be abolished, and the only means of accepting a classification of a single chemical outside the defined group classification, will be by way of submitting sufficient test data and documentation to justify that an individual classification can take place of the specific chemical. The procedures and the specifications of data required for dealing with such cases must be developed as extensions of the present data requirements, and decisions must be left to authorities whether a submission of data and documentation is sufficient,.

Without going into further details at this stage, the Working group has discussed some preliminary steps to be considered as parts of a subsequent procedure :

- All *chemicals, which are already assessed and/or classified and labelled* maintain their classifications etc., *i.e.* industrial chemicals on the *List of Dangerous Chemicals*, pesticides, biocides, pharmaceuticals etc. according to existing regulations, but as far as 'book-keeping' is concerned they are distributed and positioned within the defined groupings.
- All other - today insufficiently investigated or non-assessed - chemicals are to be distributed into the defined groups, and they *are classified similarly to the most dangerous chemicals of the already placed chemicals*. Deviation can occur, only, if knowledge or documentation exists which indicate either a need for stricter classification, or give evidence for a possibly milder one.
- If an individual chemical has more than one functional group or an overlapping structure, which may often be the case, it will be possible to place the chemical in more than one group, and *the classification should be decided as a combination of the classifications, which are obtained from each of the relevant groups.*

It is predictable, that the suggested procedure, *i.e.* classification in analogy with related chemicals or by the use of a QSAR assessment, may leave a 'rest groups' which cannot be referred to any of the defined groups. Such chemicals should be included in a prioritisation process and possibly be selected for testing or further studies in relation to the use of the chemical. This could lead to the conclusion, that chemicals which - in spite of their potential impact on human health or environment - are neither tested, nor assessed in any detail, could be labelled accordingly, *e.g.* 'Attention, the chemical is not tested' or 'Not completely tested for health or environment hazards', with the further implication that such labelling could only be removed on the basis of documented testing.

Three categories of chemical lists can arise from a procedure as suggested:

- The revised *List(s) of Dangerous Chemicals*, resulting from formally 'valid' and/or satisfying classification procedures - including possibly such deviations from the standard model which have been 'politically' determined.

- *Guideline List(s) of Chemicals which are only partially assessed i.e.* they are evaluated on less data or documentation than standard requirements, and they are 'left' without definite characterisation as 'dangerous', 'harmless' etc. - and can therefore only be classified in accordance with the 'group classification' principle.

- *List(s) of Chemicals*, which have been duly tested and accepted (possibly by 'political'

decision) as 'harmless, *i.e.* for marketing without further notice or by being labelled as 'passed for marketing'.

The working group has desisted from dealing with a more specific and detailed planning for group classification, but some consequences or further considerations have been discussed. If *e.g.* a chemical in fact is more dangerous than the one which is judged to be the most dangerous in the group, the producer will not in the classification find any motivation for further testing of the untested chemical. This equals the existing situation of a presently uncontrolled 'self-classification' and, of course, it should be given special attention. In the opinion of the Working group, however, the group classification will most likely still represent the 'safer' option, due to its acceptance of a 'precautionary principle'.

The group classification may be said to have a tendency for 'over-classification' for single chemicals. Depending, therefore, of the economical importance of such situations, it is expected that an 'over-classification' will create a motivation and stimulus for producers/importers to provide more data and documentation for single chemicals in order to 'gain the right' to an individual classification.

A resulting increase in the rate of submissions of data will, of course, raise also the demand for resources on the side of authorities - not the least because it may develop into a politically 'unbearable' situation, in case producer(s) following their submission of documentation, do not receive an expected 'rectification' due to inadequate resources and capacity available for the assessment.

The working group is further aware of the fact, that a proposal for use of a group classification system is not in itself new. A number of group classifications can already be found on the EU list, such as *e.g.*

- organic mercury compounds
- organic lead compounds (lead alkyls)
- hydrazine and its salts
- dichloro-benzidine and its salts
- Benzedrine and its salts (as already indicated above).

These examples which have come forward during recent years, have already created a precedence. It is known, that they may be said to be 'unscientific' as substitutes for the individual assessments. However, it carries the strength of a standardised assessment, which is used as a uniform principle of regulation, being carried out by analogies between chemicals and grouped on the basis of familiarities, and - finally - in which the *inevitable, but possible and as yet undocumented* differences in toxicological and ecotoxicological effects are managed under a 'precautionary principle'.

3.4. The process of priority setting

For the practical prioritisation and selection of 'most dangerous' chemicals, this is characterised by the establishment of inventories and data bases of chemicals which require specific attention, either on account of their production volume, properties and characteristics, or because of their known or anticipated use patterns. Lists of priority chemicals are to a large extent developed empirically, and normally they are explained from field experience, epidemiological observations, accidents, identification of adverse effects etc. In later years, however, efforts have been made to develop a broader basis for data evaluation and 'predictive' assessments. A more systematic use of an existing knowledge aims at an increased activity of testing and extension of the available knowledge. Furthermore, an improved use of data can be achieved through the creation of Chemical- or Product-registers, and by application of mathematical models.

The assessment of *environmental effects and hazards of chemicals* arises from the chemical laws and legislation, which were developed during the 1970's in the U.S.A. (*cf.* the American 'Toxic Substances Control Act'), and in Europe as a revision of the EU directive on Dangerous chemicals (EU/67/548, including its 6. Amendment from 1979). In Denmark the EU revision was closely followed by 'Law on chemical substances and products' of 23 of May 1979 - most recently revised in 1994. The demand for classification and labelling of the hazardous chemicals which was an immediate result of these regulations, brought forward a strong need for a priority setting and selection of those chemicals, which primarily had to be tested and assessed, and possibly also use regulated.

3.4.1. Scoring systems and models for priority setting

Several proposals and now existing lists of dangerous chemicals have been developed in the 1980´s with the result that numerous national and international models serving the process of selection came to light. Scoring systems became especially popular. They varied in their degree of details, but most often they were referring to base-set data, *i.e.* corresponding to the demands for registration of new chemicals. Conveniently, however, this might be supplemented with some exposure data and/or monitoring results. Thus, knowledge of the following kinds were used:

- *Physical-chemical characteristics*, which are important for prediction of mobility, transport, degradation, accumulation and other parameters determining the fate of the chemical(s) in the environment,
- *Toxicity*, *i.e.* toxic effects on animals and humans, most often including both short-term and long-term studies investigations, but with varying uses of information on possible carcinogenic, mutagenic and/or teratogenic effects,
- *Actual degradability and potential for accumulation* having the possible consequence that chemicals may distribute into the environment and possibly give rise to higher concentration levels in the environment via transfer(s) through food chains or in individual organisms,
- *Ecotoxicity*, *i.e.* toxic effect on other organisms than man and mammals, especially fish, invertebrates and micro-organisms, and in rare cases also effects on plants, adverse effects at the population level and/or on competitive relations which are observed in ecological societies, and even effects on the functional and structural conditions of ecological systems.

Table 3.4 The amount of presently available effect-data for approx.

2500 HPVC chemicals on the EINECS-list*)

Effect	*Available data (IPS - estimate, 1992)*	*Renewed estimate - (ECB, 1996)*
Acute toxicity	90 %	90 %
Sub-acute toxicity	30 %	53 %
Carcinogenicity	10 %	
Mutagenicity	50 %	62 %
Fertility	10 %	20 %
Teratogenicity	30 %	30 %
Acute ecotoxicity (fish or daphnia)	50 %	55 %
Short-time ecotoxicity (algae)	5 %	20-30 %

Toxicity on terrestrial organism(s)	5 %	5 %

*) The two estimates both arise from information given by ECB, the European Chemical Bureau, Ispra - via the IPS working group in 1992, and updated directly from ECB in March 1996. Differences are due to the fact that the EU Commission in the intervening period of time has called for submissions of unpublished information from the European chemical industry.

For *existing chemicals,* the amount of data is often limited or it may even be missing, which is of course essential for the possibility of dealing with the chemical at all in a priority setting process (*cf.* table 3.4 above). In order that the assessment of these chemicals do not develop into pure guesswork, data must be provided:

- *either* by implementation of direct laboratory testing of each chemical, which is a time-consuming, and expensive - and no doubt also an immense project,
- *or* from calculations *e.g.* QSAR (*cf.* chapter 4), which may not always be possible, and generally will be connected to increased uncertainties,
- *or* by a standardised prioritisation process which could be introduced as a 'worst-case' assessment, being based on more narrowly defined data limited to closely related chemicals.

Among the numerous prioritisation models or schemes, which have been prepared during recent years by national authorities or individual scientists, only a few more generally accepted are mentioned, namely:

- *the OTS model* prepared by the US-EPA, Office of Toxic Substances in accordance with requirements of the US Toxic Substances Control Act (TSCA) [39]

- *the BUA/EPS model* from Fraunhofer-Institut fur Umweltchemie und Ökotoxicologie [40], which was predominantly prepared for the aquatic environment and tested on 800-900 chemicals, all included in the German priority list, named the BUA-list (*cf.* also reference 36).

- *the PRISEC model* [41], which is incorporated in the Dutch USES model [42] for Risk assessment of chemicals for human health and environment,

- *the IPS model (Informal Priority Setting* - (*cf.* also reference 4) which was prepared by experts called by the EU Commission from a number of EU countries, following a request of the North Sea Minister Conference in 1990. It has now gained 'status' as the officially adopted EU model [43]. During 1993-95, it has been tested on the 129 chemicals comprising the EU list I, and additionally on approximately 100 so-called 'North Sea chemicals', and on approximately 30 metal compounds [44].

It is noted that comparisons of results from the use of different priority models or schemes are often disappointing in spite of relatively large homogeneity between models. Undoubtedly, this is due to the fact, *that* a wide variety of threshold limits and scoring principles are found among models in spite of many similarities in the choice of parameters, *and also that* no agreements or standards exist on how different hazard and risk elements should be mutually weighted.

3.4.2. The IPS model

As already mentioned, it is the IPS model which forms basis of the prioritisation process now being applied in the EU. Inspiration for that was reached *i.a.* from the Dutch PRISEC-model, and the IPS model has now been introduced to the assessment of all priority chemicals in accordance with the EU Council regulations (EU/793/93) (*cf.* chapter 5).

As it is the case for most priority setting models, the IPS model is based on a scoring principle. It includes elements of 'predicted exposure' and of 'potential (adverse) effect', which are both based on available data at the 'base-set level' (*cf.* the following chapter 4). It is thus targeting at a *first assessment*, following which chemicals can be ranked in an order of precedence *or* be placed in a (limited) number of priority-groups or -categories.

In practice, the use of the IPS model will include the following elements:

- an estimate of the volume of production, and a simplified use categorisation
- an assessment of the distribution of the chemical in the environment and on the workplace,
- a simplified division into hazard-classes or -categories, referring especially to the potential for toxic and other adverse effects.

The scores will normally deal with groups of chemicals scaled numerically, *e.g.* from 1 - 100 with relation to human health or to environment, and with the expectation that the scoring process is temporary, only. Awaited is most often the addition of still missing data including general toxicity data or more specialised effects such as *e.g.* carcinogenicity, mutagenicity or teratogenicity.

3.4.3. The need for data

Especially during the 1980´s, a systematic development of prioritisation tools or models was noticed as a means of preparation for a subsequent activity on chemical assessment. Focus has hereby been placed on the considerable lack of documented information and chemical data. In the OECD and from the side the EU Commission initiatives have been taken in recent years for joint efforts to provide data and hazard assessments of chemicals, primarily the so-called 'high production chemicals' (HPVC), that are marketed in amounts larger than 1000 tons per year, but subsequently (*i.e.* before the end of 1998) also in order to cover chemicals from the 'grey zone' (*i.e.* in amounts between 10 and 1000 tons per year).

Data appearing in this procedure is submitted in the so-called HEDSET format (Harmonised Electronic Data Set), and gathered in the IUCLID database from which the hazard/risk assessments are performed by means of the IPS prioritisation model. This is authorised by the EU Council regulation (EU/93/739), in accordance with which producers and/or importers are dictated to submit their data first on HPVC chemicals (before end of 1995), and then on 'grey-zone' chemicals. The data includes toxicological, ecotoxicological and other defined characteristics, and *all* data which are found to be of sufficient quality are accepted for the IUCLID database, regardless of the fact that they might not fit directly into the demands of the standardised notification procedure for new chemicals.

All individual fields, for which data do not exist, are filled in by means of default values which for instance can be developed via QSAR or as separate 'worst-case' assessments.

Chapter 4

Testing of chemicals

4.1. New chemicals must be tested - what about existing chemicals ?

The revision of the Danish Law on chemical substances and products in 1979 was carried out in close contact to the development of the so-called 6. Amendment of the EU Directive on dangerous substances [45]. As most important steps in this revision are mentioned:

- For all 'new' chemicals were required a *notification* before the first marketing, and as part of the notification it was required that data relevant to the environmental fate and effects of the chemical should be submitted

- The formal requirements for submission of data relevant to the impact on human health were revised and extended to cover both short-term and long-term effects, and also to include special effects such as carcinogenicity, mutagenicity and teratogenicity.

Furthermore, it was emphasised that hazard and risk assessments related to human health as well as environment for *non-assessed, existing chemicals should be given high priority*. In the EU, the so-called EINECS list [46] was introduced (*cf.* also chapter 1) and a total of 100.106 chemicals were defined as 'existing', as these chemicals had all been marketed within the EU countries during the 10 years period preceding September 1981.

Prior to this, chemicals could be marketed with no or at best with limited information about basic physical-chemical properties, such as inflammability or corrosiveness, and with a minimum of knowledge about acute toxic effects. Information on environmental properties and characteristics of the chemicals were practically non existing, and as for the requirement for classification and labelling of environmental hazards, this was not formally required before the 7. Amendment in 1992 [47]. Thus, until then there were hardly any opportunities for authorities to intervene and to regulate on chemical uses if this had to be based on environmental considerations only.

The main target for the new regulations were to be able to pre-assess (or 'predict') harmful effects which chemicals might cause to humans and the environment. Primarily, the rules should address the issue of marketing new chemicals. It was clear, however, that an enormous backlog of knowledge existed concerning the non-assessed, existing chemicals which had been registered in the EINECS list. In the national revision of the Danish chemical law [48] as was the case in the EU directive, this question was given a high priority. Because of the size and extent of the work, it was decided that the 'number of chemicals had to be limited considerably' [49], and the selection of chemicals should be made via prioritisation processes (*cf.* chapter 3), which had to be based on 'effects assessment of both environment and health .. including knowledge of application and environmental distribution/pollution'.

In this way it was a process of prioritisation determined empirically combined with a desire for future risk assessments, which became decisive for the legally required laboratory testing. The actual choice of test

requirements and test methodologies was constantly discussed in the following time, and a continuous balancing was established between what was considered 'economically and technically feasible', and what could be required 'for health and environmental reasons'. The demands for testing were divided into 3 types of investigations, namely:

1. *the physical-chemical* identification, properties and characteristics of each individual chemical,
2. *the human-toxicological* investigations, and
3. *the ecotoxicological/environmentally relevant* testing.

In each of these types a hierarchical set of test method was proposed and developed. They should enable a testing which could vary from relatively simple (and inexpensive) screening methods to more advanced, time consuming and economically more demanding chemical test methods. Methods should be valid for testing purposes and be able to serve in prioritisation as well as advanced assessments.

4.2. Demands for human-toxicological data

For the assessment of the hazard potential of chemicals towards humans, toxicological data is now demanded as part of any *notification of new chemicals*. The types and amounts of these data vary according to the amount of the chemical, that is expected to be marketed. As new chemicals they are registered in the EU on the so-called ELINCS lists (*i.e.* European lists of new chemical substances), and dependent of the produced amounts, data have to be submitted from investigations on three different levels, namely:

Level 0 investigation is demanded for a production of 1-10 tons per year per producer, and it has to be carried out with a *base set* of laboratory methods, which include :

- Acute toxicity, for at least 2 exposure routes, one of which must be oral (*i.e.* through the mouth)
- Irritation of the skin
- Irritation of the eyes
- Sensitisation of the skin
- Toxicity, repeated dose (28 days)
- Bacterial mutagenicity
- Not bacterial mutagenicity (incl. chromosome aberration etc.)
- Reproduction toxicity (screening)
- Toxico-kinetics (absorption and metabolism - assessment only)

Level 1 investigations are additional to the former, being demanded at production rates of 10-1000 tons per year per producer (or more than 50 tons accumulated) in the EU. The following tests are required in addition to the tests of Level 0:

- Fertility studies - one species, one generation (male & female)
- Teratogenicity studies - one species (*i.e.* concerned with inborn/congenital malformations)
- Sub-chronic and/or chronic toxicity studies - one species only
- Additional studies on mutagenicity
- Carcinogenic effects - screening only
- Fundamental toxico-kinetics

Level 2 investigations include testing of chemicals, which are produced in larger amounts than 1000 tons per year per producer (or more than 5.000 tons accumulated) in the EU. The following additional investigations are demanded:

- Chronic toxicity studies
- Carcinogenic effects
- Fertility (3 generations, if this is indicated from level 1)
- Developmental toxicity (at and after birth)
- Teratogenicity - more than one animal species
- Additional toxico-kinetics (bio-transformation)
- Organ-specific or systemic toxicity

It is the responsibility of the producer/importer who places the chemical first-time on the market, to make these investigations and to submit the results to the national authorities, directly or - via the Commission - from another EU country. Normally, investigations are accepted only if they are carried out according to the EU-standardised test methods (or the corresponding OECD tests) [50]. In addition it must be documented, that the testing is carried out according to [51] 'Good Laboratory Practice' (GLP), and rules for Laboratory quality control must be abided to. Generally, however, it is of no concern whether data have been produced in published or unpublished investigations, by public laboratories or as internal studies of an industry etc.

As regards *existing chemicals* (*cf.* the EINECS list of the EU), it is of course desirable that hazard and subsequent risk assessments are carried out according to principles and programs corresponding to those valid for new chemicals. The time factors will normally not permit that, however, and due to the number of chemicals the demands of resources are immense, regarding economy, as well as work-load and needs for experimental animals.

The present strategy of the EU is therefore to give priority to the submission of data for those existing chemicals, only, which are individually marketed/applied in amounts larger than 1000 tons per year per producer (5000 tons accumulated in the EU), *cf.* the term 'high volume chemicals' or HPVC-chemicals. This is presently estimated to a total of 2.400 chemicals*) in the EU for which a full investigation, *i.e.* at level 2, would be required in case the chemicals had to be notified as new.

Due to this demand, priority lists are presently being prepared in order to establish a sequence of testing for providing all the data needed for assessment of these chemicals. Special emphasis and priority is given to those chemicals, for which there is evidence for a potential for chronic effects, or when suspicion exists on carcinogenicity, mutagenicity, and/or toxicity to embryos or off-spring.

Bearing this strategy in mind, it has been decided to carry out health and environmental assessments for a limited, highly selected part of existing chemicals on the EINECS list, and further to do this within a specified time-frame, namely before the year 2000. Obviously, this situation seems to be rather critical, because of the difficulties of meeting the time requirements (it is informed, that only 50 chemicals are assessed per year#), *but also* because a strategy which is based solely on amounts or volumes, may create a risk that chemicals:

*) The number was informed in March 1996 as ‘approximately 2400' (personal information, Bj. Hansen of ECB, Ispra). In OECD the "HPVC-chemicals" was in January 1996 counted to approx. 2800, but now defined as the number of chemicals produced in amounts larger than 1000 tons per country (from a total of 25 OECD countries), or more than 10.000 tons per country in more than 2 OECD countries (personal information from Dr. A. Schmidt, OECD, Paris).

Personal information from ECB, Ispra.

which are only produced or used in small amounts or volumes are left out of the priority programme, and/or

- that significant, but so far unobserved adverse effects are not included and made properly available for assessment.

4.2.1. Possibilities for alternative test strategies

With a view to the tight programmes which have been established for the routine testing of chemicals, both the work-load and the costs in time and expertise are high. It has therefore been considered not to implement all required studies at the same time, but only to perform a partial testing followed by submission of results and risk assessment gradually in a more tiered approach. This will make it possible to give priority to dominating effects that have been observed, as it *e.g*. has been suggested for immuno-toxicological and neuro-toxicological effects and has been practised in relation to observations of carcinogenic effects.

Typically, such procedure is carried out as a 'screening', or a preliminary investigation serving as first identification of possible hazards. This might involve the use of *in vitro* methods, *e.g.* certain tests for mutagenic effects, or simplified standard animal tests, which may enable greater efforts to be allocated to other effects, such as *e.g*. effects on the immune or the nervous system.

It is a characteristic of this strategy, that *level 1 investigations* are only carried out provided that

- the level 0 studies have indicated the need to do so, or
- if suspicion of adverse effects can be advocated on the basis of former experience with humans or animals, or
- if there is resemblance in structure with other dangerous chemicals.

The purpose of a level 1 testing is in this way *to refuse or to confirm* only, whether a potential for effects exist - whereas normally, it does not deal with the exact mechanisms which lead to these effects.

Level 2 investigations, on the other hand, consist of specific investigations, which primarily aim at an explanation of the mechanisms by which the effects may arise, in order to interpret whether the effects can be of any relevance to humans.

4.2.2. QSAR

A promising, but still insufficiently tested methodology which may provide toxicological data on all levels, is the so-called (Q)SAR test principle, referring to the possible *(Quantitative) Structure Activity Relationship* in or between chemicals. From the molecular structure of a chemical, or based on similarity with other known chemicals, it is to some extent possible by this method to calculate, or by extrapolation to estimate some toxicological characteristics.

In the field of human toxicology QSAR can be used in a preliminary assessments, and therefore in a selection of toxicological effects that will be relevant as focal points in predictive investigations. This may *e.g.* justify that chemicals which have structural resemblance with Polychlorinated Biphenyl (PCB) are suspected to cause the same effects as PCB, until anything else is proven.

Computerised programs based on QSAR methods can predict the results of different tests, *e.g*. test for

carcinogenic effects, tests for teratogenic effects, skin and eye irritations etc. This is due to the fact, that correlation in different situations can be found between the molecular structure of chemicals and those effects which *e.g.* are caused by cancer, mutations or allergy. The larger databases and the larger number of chemicals with known toxicological effects, the smaller is the statistically determined uncertainty which is connected to their application. Generally these programmes can today be used for obtaining an indication of the toxicity of the chemical, but at the present time there is not sufficient experience or confidence in QSAR-methods to permit their use as predictive tools in acquittals for toxic effects of chemicals.

QSAR computer models are constantly improved. As an example, following the development of the DEREK system in England [52], it has been possible from a database consisting of 112 mutagenic and 138 non-mutagenic chemicals to predict whether a chemical is mutagenic, with only 2% 'false negative' and with 30% 'false positive'.

When it comes to the potential for chemicals to induce allergy by skin-contact, the QSAR-system has been able to identify 133 chemicals out of 135 as skin-sensitising agents. The remaining two chemicals were not identified, as in these cases it was impurities that were able to cause allergy. The impurities were actually identified as causing allergy.

4.2.3. *In vitro* tests and other short time tests

In vitro methods have been used and acknowledged for the last 20 years. The major advantage of these methods is, that they can be performed within a short time and they are relatively inexpensive in comparison *e.g.* to *in vivo* animal experiments. Of particular interest are the tests showing harmful effects on genes, *i.e.* genotoxicity tests which are accepted as supplementary to those predicting carcinogenicity.

Table 4.2 Examples of *in vitro* methods or cell effects proposed as alternatives to *in vivo* animal toxicity experiments (after E.S.Rasmussen, 1995 [53]).

Animal experiment	Status of alternatives
Irritation of the eye	*in vitro* methods can identify severe irritants, but not mild
Irritation of the skin	*in vitro* methods are expected to appear before year 2000
Sensibilization of the skin	*in vitro* methods are being validated
Acute systemic toxicity	Battery of *in vitro* tests may appear before year 2000
Cell effects	**Possible connection with**
Geno-toxicity on bacteria	Carcinogenic effects, teratogenic effects, senescence, atherosclerosis and possibly other effects
Transformation of mammalian cells	Carcinogenic effects and atheroscle-rosis

In the EU, a number of standard test systems on mutagenicity and screening tests on carcinogenicity are accepted. Included are *in vitro* experiments on bacteria as well as on single cells from mammals or other organisms, and observations are concentrated on:

- chromosomal aberrations and gene mutations
- cell transformations, and
- other DNA damages.

Several, simplified tests with character of *in vivo* experiments are also included in this series of short time test methods, such as:

- chromosome- and micro-nucleus studies (on mammalian bone marrow),
- cell genetic tests (on gametes from mammals),
- transmission of toxicological damages to the next generation (on mice).

Some examples of possible screenings of chemicals for toxic effects are shown in table 4.2. The screenings are made by using *in vitro* methods or by utilising possible connections between cellular effects and *in vivo* toxicity.

4.3. Shortcomings and limitations

Predictive toxicological investigations can never be complete. Some effects known from human toxicology, are not observed in the ordinary animal experiment. This is for instance the case for the serious embryo damages caused by thalidomide, if this chemical is consumed during 6.-7. week of a human pregnancy. This effect is rarely seen in rats and mice, but it is observed to a varying degree in rabbits and hamsters, while in monkeys only certain strains are vulnerable towards the effects of thalidomide. Most similar to women is the female New Zealand White Rabbit, in which embryo damages may develop after thalidomide administration on the 8.-10. day of pregnancy.

Other examples are specific neuro-toxic effects, such as dizziness, lack of concentration, disturbance of speaking faculties, hallucinations, psychoses and loss of the short time memory, which in special cases can be produced in humans by chemical exposure, but which on the other hand are difficult to observe in experimental animals.

Even by very exhaustive predictive toxicological investigations there will be effects, which can not be demonstrated experimentally. The present lot of standard methods are not geared for identification and routine observations of new mechanisms of effect which are constantly discovered, *e.g*. in the immunology. Methods to be used in the immuno-toxicology, are presently still under development. Not until this stage has been passed and experimental methods are re-assessed and accepted, will it become possible to identify the more subtle effects on the immuno-system. [54]

After the introduction of a chemical to the market, there is a possibility to verify results from predictive investigations, provided the chemical is being used for a while by a group of consumers, which is limited in number and can be identified individually. It may then be kept under surveillance for any unexpected effects, as it is already being practised for pharmaceuticals. This is called a '*post-marketing surveillance*', which implies, that a gradual marketing of the chemical to larger groups of consumers is possible in succession of the first period, with the purpose of making a simultaneous and systematic observation of

undesirable effects.

It is not to be expected in such a procedure, that all undesirable effects are revealed. Some effects, *e.g.* cancer will normally not occur until years after (first) exposure. For other effects, which may be caused by other exposures or conditions, such as a variety of chemicals, genetic disposition, lifestyle, state of nutrition etc., such more complicated cause-effect (cor)relations can be difficult to demonstrate.

An introduction of '*post-marketing surveillance*' involves a concession, that laboratory predictive investigations can be/are incomplete. It may be interpreted as a supplementary, 'experimental observation on man'. On the other hand, the situation as it now stands - and as it was earlier for pharmaceuticals, namely a marketing without any registration at all of undesirable effects, such as allergic reactions, possible hormone-like long-term effects of chemicals and products *e.g.* as cosmetics, colouring agents, plastic materials etc. - can be said to have a character of 'full scale experiments'.

In case the situation is left unchanged as in these latter examples, we must satisfy ourselves - as we presently do for all 'existing' chemicals - by being dependant on later epidemiological observations. The results from epidemiological investigations, however, are rarely unambiguous. Only in fortunate cases can clinical observations be supplemented by demonstration in animal models, but also this possibility for demonstrating a correlation between cause and effect is likely to fail when effects are unique for humans.

4.3.1. Alternative ways - toxicology and ecotoxicology in combination

According to the latest EU regulations and directives on risk assessment of existing and new chemicals [55], an integrated assessment based on the conclusions of the otherwise separated risk assessment of health and environment must be carried out (see also the following chapter 5). In this connection it is obvious and recommendable, that not only the predictive toxicological investigations, but also the ecotoxicological data shall be included - in 'generic' as well as in comprehensive assessments.

It is a well-known experience, that chemicals which are accumulated in fish most probably can be found in larger concentrations also in mother's milk, and that this can be predicted from ordinary use and exposure data. Of course, such knowledge will emphasise the need for investigations in the field of developmental toxicity, *i.e.* whether the chemical will/can disturb normal development and health of the weaning child.

Similarly, the most recent scientific experience about the possible impact of hormone-like chemicals on reproduction capacity, must be interpreted in the way that not only human effects, but also observation of effects on wild animal will be most valuable in the further studies of more subtle effects, which can influence human health.

4.4. Ecotoxicological assessments

At the time of revision of chemical laws in the late 1970´s, there was especially focus on the threat to the living organisms in the aquatic environment (*cf.* EU directive 464/76 and its 6. amendment, directive EU/67/548). However, studies on ecotoxicity of chemicals during the following years included both aquatic and terrestrial organisms. The result of these studies together with the degradability of chemicals and their potential to bioaccumulate, as well as the physical-chemical data on solubility in water, volatility etc., were all included in the ecotoxicological investigation programmes at an early stage, and they are today gradually being included in the criteria for classification and labelling of the environmental hazards, and for the 'generic risk assessment*)'

4.4.1. Ecotoxicological testing of new chemicals

In table 4.4, below is given a summary of those data relating to environmentally hazards of a chemical, including its possible release and distribution into the environment, which has to be submitted to the authorities by the producer or importer prior to a notification of a *new* chemical. In parallel to submissions of human toxicological information, the ecotoxicological requirements have to be submitted in a stepwise system comprised by the following three levels :

Level 0 investigation including data produced by use of *base-set* methods. Results from this test level are called when chemicals are marketed in amounts larger than 1 ton per year. In case environmental (or human) toxicological effects of concern are observed, the authorities can - regardless of the marketed amount - request that data from a partial or full testing at the next higher level is submitted. Methods at the base-set level are all considered to be screening methods for preliminary investigations only. They are expected to be carried out on a routine basis, professionally but not necessarily based on a scientific expert experience.

Level 1 investigations include chemicals, which are expected to be marketed in amounts larger than 10 tons per year. A more thorough development of data is required for these chemicals, including especially a number of chronic tests. Chronic tests are expected to meet the requirements of a 'full toxicity study' of a chemical, at least so far that a so-called 'Zero-effect-level' (NOEC) can be estimated, in order to identify concentrations below which the investigated species *are not expected to be influenced* during their life cycle.

Level 2 investigations include chemicals, which are expected to be marketed in larger amounts than 1000 tons per year. The extent and type of studies to be required at this level are still not established. It is expected though, that the investigations will include demands which are especially directed towards :

- the eco-toxicokinetics of the chemical (degradation patterns, mechanism(s) of eco-toxic effects etc.) in the investigated species,
- studies of selected sensitive species of animals or plants,
- effects which are of special interests because they are connected to special exposure situations or to vulnerable compartments of the environment (*e.g.* sediments and waste deposits in which accumulation may take place).

Test methods which are used for the creation of data are mostly standard methods that are included in annex (no. 5) to the directive. They are similar to methods which are developed for and recommended by OECD [56], and they are continuously being updated.

Data which are provided in pursuance of Annex V, will in accordance with the intentions of the directive be used for:

- classification and labelling of environmental hazards of chemicals, and
- the environmentally relevant part of 'generic risk assessment' .

The classification criteria for environmental hazards of individual chemicals were finally settled by the EU Commission in 1993. This is also the case for the environmental risk assessment, which is based on information received about ecotoxicity, bio-degradation, bio-accumulation, physical-chemical data, as well as information on exposure related to the expected production volumes and use patterns (*cf.* chapter 5). The utilisation of these criteria in relation to manufactured products or preparations, *i.e.* evaluation rules for the

combination of mixtures of chemicals in a product are still not adopted. Similarly, the directives do not deal with the possibility of phasing-out individual chemicals due to a classification/labelling of environmental hazards (or an environmental 'generic risk assessment').

As a matter of comparison, the amount of information demanded for a human health related classification and hazard/risk assessment is significantly greater than the case is for environmentally relevant information. Noteworthy is also the fact there are several weaknesses and shortcomings in the information, especially connected to:

1. expectations on future application,
2. the use of data from the degradation experiments, and
3. the use of data from acute toxicity tests for the estimation of the Zero-effect-levels or -concentrations, due to lack of chronic toxicity studies at the 0-level.

Table 4.4 Standard methods for environmental characterisation of new chemicals

Test characteristics	Level 0 (Base-set)	Level 1
Ecotoxicity	*growth inhibition of algae *acute toxicity - daphnia *inhibition of bacteria in activated sludge (respiration)	*sub-chronic toxicity - daphnia (disturbance of reproduction, growth of offspring) *sub-chronic-toxicity - fish (ear-ly life stages, growth of fish larvae) *tests on animals living on the earth
Bio-degradation	*degradation studies in surface water ('easy degradation')	*investigation of degradation under favourable conditions (*e.g.* in activated sludge - 'not-easy' degradation'
Bio-accumulation	*distribution between fat and water phase (log K_{ow}) estimate of bio-accumulation in fish	*experimentally determined bioconcentration (BCF-measurements)
Physical-chemical data	*water-solubility *specific gravity *vapour pressure *absorption capacity *hydrolysis in water *melting and boiling point	

re 1. The information which is received about future application(s) in the notification of a chemical is often problematic, and in practise it is generally difficult to make reliable predictions of expected exposure concentrations (*cf.* PEC-values applied in risk assessments - see next chapter). It is normally assumed, that in the order of 0,1 % of the total use volume

may be released/discharged into the environment for chemicals that are used in 'closed systems'. As it has already been exemplified in several cases, however, it is often difficult (or impossible) to confirm or to control that a chemical during several years of consumption has in fact been kept within the closed system. It is recommended, therefore, that the use of chemicals are calculated conservatively, *e.g.* by assuming as a rule rather than the exception, that the total or the majority of a chemical will end up in the environment.

re 2. Information about the degradation of chemicals can also be problematic. The degradability data which are submitted in the notifications are based on bacterial tests, and they normally only reflect an 'easy degradability', as this may be seen under laboratory conditions.

Generally, industries tend to utilise types of bacterial flora which have the highest capacity for degradation of their specific chemicals, *e.g.* by sampling test cultures from sewage treatment plants. It is required therefore, that bacterial cultures must be selected from plants, which are not (or only to a minor degree) loaded with industrially discharged waste water. Such demand is included - but not controlled - in order to prevent, that the applied bacteria can be 'acclimatised' to the decomposing of the actual chemical. The degradation may therefore be more efficient under test conditions than in normal practise. As for the discharge of waste water from normal households this situation is less critical, because it will normally contain a broad and less specialised mixture of chemicals. But generally speaking, the test systems used for studies of 'ready or easy degradability' in waste water treatment, are not very good simulations of the actual conditions valid for the fresh water or the open sea.

In the same way it may be questioned, whether the laboratory temperatures of 15 - 20^{o}C are relevant in relation to the ambient temperature in Denmark, or whether the number of bacteria, which are permitted in the test systems, is unrealistic high when compared to the situation in actual surface waters - all of which, of course, may contribute to an exaggerated interpretation of the ease with which a given chemical can be degraded under non-polluted conditions.

re 3. The short-term toxicity tests of the base-set are carried out on 3 species representing 3 different types of organisms, each of which are selected as a reflection of their life-forms and nutritional classification. The tests are intended to determine the concentration levels of a chemical which might be harmful to the three species. This may initially give indication of a possible impact of the chemical on ecological function and structure in a fresh water environment, but in subsequent assessments, it is the further intention to indicate quantities or concentrations, *under which no harmful effects are expected.*

For practical purposes, this assessment is made by the use of extrapolations (*cf.* chapter 5) the rationale of which are developed by statistical considerations from a relatively large number of already tested chemicals. By a number of reviewers this practice have been found to be conservative, *i.e.* with a protection level which has then been recommended as acceptable. All these tested chemicals, however, are characterised by having a general toxic - often named narcotic - effect on the organisms, whereas there are no examples presented which justifies that protection level should be sufficient also for chemicals with a more specific effect mechanism, *e.g*. hormone-like chemicals, neuro-toxic effects etc. It seems to be a serious draw-back, that none of the ecotoxicological tests used today are adequate for studying effect mechanisms or of measuring toxicokinetic transformations etc.

There is no doubt that the data bases which are presently used for the assessment of new chemicals are rather inadequate, almost primitive in the light of the natural conditions and the complex interactions, which are simulated in the laboratory testing. Considerable deviations are expected, mostly towards a weakening of the reliability and an increase of the uncertainties of the following assessment of environmental dangers and risks. Furthermore, the assessments are limited in their scopes compared to the environment as a whole. Neither the aquatic environment nor the protection of ground water are included in the assessments based on notified base-set data for new chemicals - a situation which must be characterised as most unsatisfactory, considering also the parallel shortcomings connected to the assessments of existing chemicals.

4.4.2. The basis for assessment of existing chemicals

The desire of assessing *existing chemicals* in the same way and to the same depth as *new chemicals*, *i.e.* classification/labelling, hazard and risk assessments based on a similar demand for data and for assessments at the same level, is well understood. It has to be expressed for the human health as well as for the environmental assessments. It is a matter of fact, however, that for the vast majority of chemicals on the EINECS list, there exists only very little information and data coming from the producing industry, beyond a limited, often 'casual' information to be found in scientific literature or in other reports.

Furthermore, the data which can in fact be provided, will often have a most questionable value. This is due to the rather insufficient documentation about methodologies and laboratory standards, not the least for the testing of chemicals which are difficult to handle under normal laboratory conditions, because of *e.g.* volatilisation, large adsorptivity to surfaces, or degradation. Only lately - and slowly also - an understanding can be noted for the fact, that exposure analyses are essential not only in the physical-chemical milieu, but also as part of biological analyses in order to obtain reliable dose-response correlation and to establish trustworthy *Zero-effect* concentrations.

It is on this background understandable, that only a few, significant data-bases on ecotoxicological effects can be found today for existing chemicals, including publicly accessible data bases, *cf.* the American AQUIRE and CHEMBANK databases.

4.4.3. Alternative test methods

QSAR: In recent years a relatively vivid development has been witnessed for the use of QSAR - *i.e.* the Quantitative Structure Activity Relationships of chemicals - as a tool in the assessment of toxicity and bio-accumulation of so-called generally toxic - or 'narcotic' - chemicals. On the other hand, this has not been the case for chemicals having a more specific effect mechanism (as for hormone-like chemicals). A reliable use of QSAR will require, that not only the exact chemical structure is known, but also that the effect mechanism of the chemicals is described. It is noted, therefore, that American authorities (US-EPA) for the time being are especially active in their testing of a large number of chemical groups for their specific effects on fish, exactly in order to accelerate a development of QSARs for more and broader groups of chemicals.

The CBB (Critical Body Burden) concept: Recent scientific results show, that the 'critical dose' which may cause harmful effects in an organism is relatively constant, when it concerns generally toxic, *i.e.* 'narcotic' chemicals. This observation can to some extent be used in screening experiments for distinguishing specific from generally active chemicals.

In-vitro tests for the identification of chemicals having specific toxic effects are today included in cases *e.g.*

where mutagenic, neuro-toxic and oestrogen-like properties characteristics have to be added to the screening methods as a part of ecotoxicological characterisation. It is, however, an important limitation of the present methodology that only known mechanisms can be tested, and it is still premature to evaluate the possibilities of the methods. As for the oestrogen (or hormone-like) chemicals is it an immense project to screen for all possible hormonal effects, and even by limiting efforts to sex hormonal effects *in-vitro* tests alone will not be sufficient.

In-vivo test systems: The existing simple, aquatic (screening) methods utilising algae, crustacean and fish prescribe measurements of the concentrations, which are unambiguously attached to (easily) observed effects, such as *e.g*. mortality, growth inhibition, reduction in litter-size etc. Further, however, there is a demand for registration of other effects, which might be caused by the chemical in question. Such observations are rarely included in the systematic assessment of environmental hazards and risks, in spite of their possible value as indicators of other effect types. As examples, histological observations could well be required as parts of long-term studies on large organisms (*e.g.* fish), as could reports be demanded on the internal doses which are evaluated to cause *low-effects (LOED) and zero-effects (NOED)*, respectively. This type of data could also be used in the interpretation of similar observations in field monitoring - *cf.* the CBB-concept mentioned above and the today still sparsely known term: 'eco-epidemiology'.

Biomarkers normally refer to sensitive, biological methods, which can register if or when a given organism is exposed to a chemical (or other external stress factors), *e.g*. in the form of changes in normal function(s) or response mechanism(s) of the organism. Most biomarker methods do not give direct information on the significance of changes or the importance of effects for the organism *per se,* or for the survival of the species. They do register, however, that an exposure has occurred, *e.g*. by an increased activity level of a specific enzyme systems or by development of a stress situation. They are called 'exposure biomarkers', therefore, as opposed to 'effect biomarkers', and it is obvious also, that most *in-vitro* methods can be characterised as biomarkers.

4.4.4. Testing of complex mixtures

Ecotoxicological testing of complex sewage waste streams present a special, and rather complex field of problems, not the least in relation to industrial plants that are handling large numbers and volumes of chemical substances. This is still an almost unexplored field. On a practical level, some documentation exists of the fact that the toxicity measured from mixtures of chemicals *e.g.* in industrial effluents or in connection with waste disposals, is close to the result of an additive process resulting from a summing up of contributions to toxicity from the individual chemicals.

Such empirical knowledge may be of significant interest in the screening process for interactions between chemicals in mixtures, and also in cases that degradation products can be traced to special chemicals. It may further become useful as a priority setting tool within individual branches dealing with special chemicals having similar structures and/or functions. They do not, however, give any assurance whether other (underlying) reactions may be present from individual chemicals in a chemical mixture.

Chapter 5

Hazard and risk assessments

5.1. The effects assessment - potential of hazard

For the performance of an effects- or hazard assessment the so-called dose-response correlation is central, *i.e.* to analyse and describe the relation between on one side the dose or the concentration of a given chemical and on the other side the frequency and strength of the effects which are caused by an exposure. Normally, animal experiments are serving this purpose, as epidemiological observations or field assessments of environmental damages are rarely available.

Different dose-response correlations can be expected in case a certain chemical can cause more different toxic effects. Each of these effects must of course be included in the assessment, when a *zero-effect-level* has to be evaluated. It is the experimentally *observed low(est)-effect*- or the *zero-effect*-levels or concentrations (abbr.: LOEL/LOEC & NOEL/NOEC) which are recalculated in order to express a *predicted no-effect level/concentration* (PNEL/PNEC). This is done by extrapolation or by introduction of an 'uncertainty factor', such as :

$$\text{PNEC} \approx \frac{\text{LOEC resp. NOEC}}{\text{Uncertainty factor}}$$

or as

$$\text{PNEL} \approx \frac{\text{LOEL resp. NOEL}}{\text{Uncertainty factor}}$$

The calculation from *measured, experimental* data is necessary, as larger populations, or complete ecosystems are not included in the laboratory experiments, and they will be without (or with less) protection, unless a correction is made. The calculation can imply different types of scientific uncertainties and it has to include a number of untested assumptions which are most often difficult to evaluate, each of them possibly implying choices which may be interpreted as 'political', equally well as scientific.

In the setting of limit values, it is - or it should be - unambiguously required that the limit values are respecting the zero-effect-level. In practice, however, this principle is administered in a variety of ways depending on the norms and standards which have determined the development of the use of limit value in the different sectors of society (*cf.* also the discussion in chapter 6).

5.1.1. From danger to risk

The initial, environmental hazard of a chemical is first of all determined from the acute toxicity, but also considered are a number of physical-chemical and additional biological characteristics, such as degradation/persistence, ability to bio-accumulate and mobility, *i.e.* the ability to move within and between environmental compartments. These characteristics are all of importance for the potential of the chemical to pollute and/or to create damages in the environment, including of course the possible effects of exposure of

man.

Risk is defined as the probability that one or more of the predicted adverse effects determined for the hazard assessment do in fact occur. To obtain a complete risk assessment, demands are made for information on both frequency and character of harmful effect resulting from actual or expected exposure. Thus, the risk assessment should as a minimum include the following elements :

- a description of the (or those) *specific scenario(s), i.e.* location, circumstances and conditions of the target area(s) etc., where the exposure takes place,
- qualitative as well as quantitative determination of *discharges/emissions*, which are the source of exposure,
- qualitative as well as quantitative assessments of the *environmental and/or human exposure*,
- identification of the *environmental and human health related effects*, which can be caused by the exposure
- an assessment of the probability of the occurrence of any such *effects/damages*.

Obviously, this makes the risk assessment a very data demanding process, and several efforts are made to rationalise it and to make calculations possible by means of mathematically expressed models. In reality, however, even relatively simple risk assessments of chemicals are today carried out rather few cases. The term 'risk assessment' for individual chemicals is today mostly related to the so-called 'generic' risk assessment (*cf.* section 5.2.1.), which on the basis of a number of simplifications tries to calculate (or predict) maximum discharge data and approximated pollution situations. The predicted so-called 'worst case' situations are then evaluated by direct comparison to the potential harmful effects.

5.2. Risk assessment includes evaluation of both effects and exposure

It is via the inclusion of exposure measurements and assessments of pollution situations, that assessments of the dangerous chemicals develop into risk assessments. Data must be provided about the chemical impact on the individual human being, *i.e.* the total exposure of a chemical measured as doses/amounts that are consumed via food and water, in addition to indirect exposures via other routes of pollutants in the environment. It is therefore important to have access to information about emissions or discharges to the environment as a whole (incl. the workplace environment), as well as to distribution and degradation of the chemical in the individual compartments of the environment.

Considering the variety of natural ecosystems and variability of external environmental conditions, *e.g.* under geographically and biologically different circumstances, it is obvious, that uncertainties in analysing any actual exposure situation inevitably will become large. Assessments which compare individual scenarios, and transfer of results from one analysis or situation to another, almost become impossible. Actually measured environmental concentrations vary over several orders of magnitude, which is also the case, when the chemical impact is considered at the workplace environment or as a result of chemical pollution from marketed products and preparations. It is the credibility of predictions which fails, unless requirements are established for confirmatory measurements and maintained through surveillance programs. In actual fact, such programmes become most important tools and support for the evaluation of exposure situations for existing chemicals.

5.2.1. Risk fraction or danger fraction

It is the result of the recent standardisation and simplification of the 'generic risk assessment'*), that an assessment scheme presently is developing to come into focus as a routine tool when assessing industrial and household chemicals. The principle of the assessment - which is illustrated in the figure 5.1 - is laid down with reference to the the Council regulation no. 793/93 of 23 [57]. March 1993 in a set of harmonised Technical Guidelines which are valid for all EU countries [58].

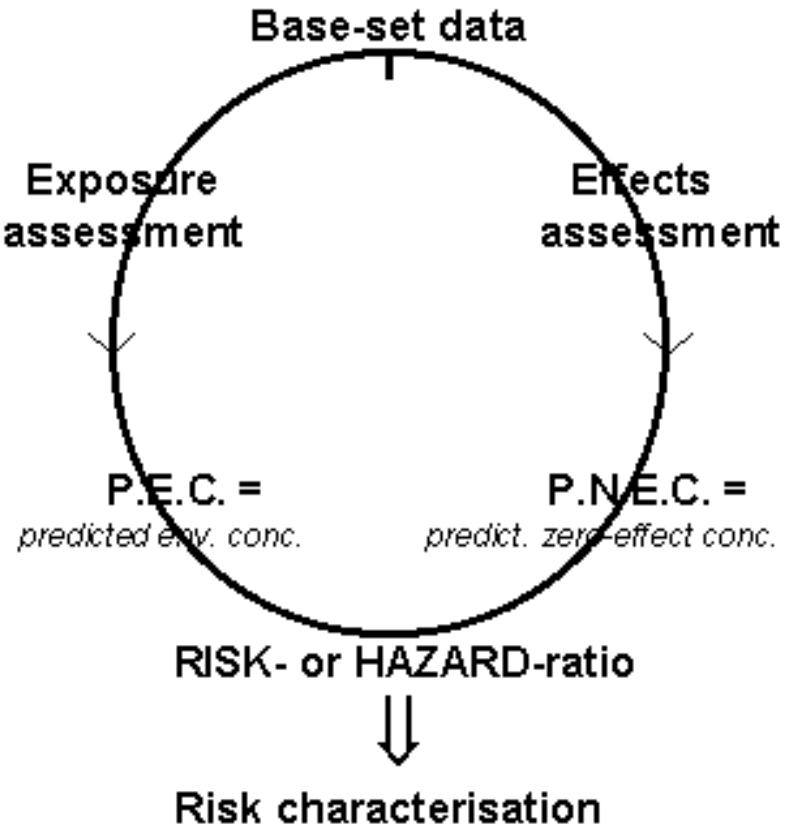
*) 'Generic risk assessment' refers to the so-called PEC/PNEC-ratio, now accepted in EU regulations and directives. The term is objectionable and should be distinguished from (comprehensive) risk assessments in which risk is interpreted as the probability for an (adverse) event to occur. It requires therefore that assessments are referred to clearly defined and described situations, localities etc. - which is exactly what is avoided by referring in the 'generic assessment' to conceptual and simplified scenarios, only.

This implies, that the hazard and risk assessments must be carried out according to the accepted principles, and that these shall apply to:

- all new chemicals in conjugation with their notification and classification, but further also for
- existing chemicals, which have been identified in the EU as priority chemicals (see chapter 3), *i.e.* as *potentially dangerous.*

This is for the time being limited to the so-called 'high production chemicals (HPVC)', and to chemicals which have been included as a result of specific requests from individual member countries. As a matter of progress, decision has further been taken that industry (producers and importers) shall submit their 'presently available data' for chemicals produced/imported also in lower amounts than HPVC-chemicals (*cf. chapter 3)*

Figure 5.1 Diagram on 'generic' risk assessment*)



*) 'Generic risk assessment' refers to the so-called PEC/PNEC-ratio, now accepted in EU regulations and directives. The term is objectionable and should be distinguished from (comprehensive) risk assessments in which risk is interpreted as the probability for an (adverse) event to occur. It requires therefore that assessments are referred to clearly defined and described situations, localities etc. - which is exactly what is avoided by referring in the 'generic assessment' to conceptual and simplified scenarios, only.

The key parameter which 'defines' the 'generic' risk assessment*) is the so-called *risk (or hazard) ratio*,

$$\text{Risk- or hazard ratio} \approx \frac{\text{PEC}}{\text{PNEC}}$$

which is expressing the relation between :

- a calculated (predicted), so-called 'realistic worst case' exposure concentration (PEC), and
- an estimated (predicted) zero-effect-concentration (PNEC).

This ratio is most often referred to as the PEC/PNEC relation, and it is used as a first estimation whether a *calculated concentration of a chemical in the environment can be expected* to become larger than, the same as or smaller than *an estimated, predicted zero-effect*. The estimate will function as a trigger for possible requests for further investigations (testing) of a chemical, or in extreme cases provisions.

The PEC/PNEC relation is said to be a 'measure of a *generic* risk' which has to be distinguished from 'full', comprehensive risk assessments, as no considerations of variations over time or space are included, and because the aim is not to achieve any statistical or measured probabilities for effects. Taking into account the uncertainties resulting from the limited databases, the PEC/PNEC relation can be understood *only* as an expected ranking - a score - on a scale, which allows a relative order of precedence of chemicals, processes

and/or technologies in the handling of chemicals.

Beyond such function as a standard guide and 'trigger' for authorities when chemicals are notified and assessed, the 'generic' risk assessment may also be applied as a tool for priority-setting in substitution processes and for selection of less dangerous alternatives as part of environmental management or in development of *cleaner technologies.*

5.2.2. Risk assessment *vs.* acceptance of risk

An obvious purpose of extending the chemical assessment procedure into a risk assessment scheme by inclusion of both exposure and effects assessments, is the possibility of having a tool which more directly can be fitted for use in risk management. An observed risk is hereafter to be evaluated as: *acceptable,* or *non-acceptable,* or possibly as *tolerable,* and the question is opened whether a *risk reduction* should be carried through, *e.g.* by a change in use pattern(s), by provisions or restrictions of marketing and sales, or even directly by banning the chemical.

No actual guidelines or accepted procedures for such process exist. It is an issue which is being discussed among interested parties, and it is not the least concerned with the question whether an actual assessment and the possibility for management of a given risk shall depend solely on evaluations and judgements of the data which are presently in focus as the scientific basis for chemical assessments. Fundamental in this connection is the *concept of acceptance, i.e.* whether the issue is to distinguish and to deal with decisions:

between *effect and/or no-effect,* or
between *pollution and/or no-pollution.*

Thus, the application of the risk assessment as a tool in questions about *acceptable risks* exceeds the limit for the scientific/technical-scientific knowledge, and demands are made for more normative assessments, or possibly even for decisions related to social, political needs and developments etc.

As an example is referred to the assessment of pesticides/biocides, which are generally considered to be under more restrictive regulations and assessments schemes than is the case for other chemicals. Since the 1950´s the assessment of pesticides has only to a limited extent been characterised by the necessity to protect a 'rich and diverse flora and fauna' - in spite of this being explicitly required in the law - whereas demands in administrative practice has focused on

- protection from direct poisoning of spraying personal and third persons during application,
- reduction of food contamination resulting from residues of pesticide on harvested crops,
- surveillance of uncontrolled bio-accumulation via food chains or in trans-boundary diffusion/distribution
- protection of specific environmental compartments, such as subsoil or groundwater resources, from contamination with pesticide residues.

In *each of these situations* it has constantly been the aim to develop actual risk assessments and to use these in normative assessment which are then taken as definitions of what are *acceptable* or what are *tolerable* risks. In each of the fields mentioned, a kind of practice/procedure has been developed by which the risk assessment is handled in a step-wise manner, such as :

maximum allowed risk,
negligible risk or
no risk

Such risk levels are primarily used as evaluation tools for assessing whether an intervention must be made, *e.g.* in the form of use regulations, more stringent labelling or even prohibitions. Secondarily, it is often attempted to use the risk levels as a means of 'waving a flag', or 'provoking' a better understanding of use guidelines, including improvements of existing practices in the industry, agriculture etc.

5.3. Risk models

In recent years, large efforts have been made in the environmental field to develop mathematical models as a means of characterising and/or managing chemical risks. The aim is to calculate different distribution patterns and/or 'risk/hazard - ratios' for a chemical which is released, distributed, and eventually transformed in the society or in a natural, ecological system. The calculations result in predicted environmental concentrations (PEC-values), to be compared with zero-effect-concentrations (PNEC-values), which are predicted in parallel for the observed sub-systems.

In their routines, PEC models use average concentrations that refer to a highly, simplified and theoretical 'unit-world' or to similarly, simplified regions or localities (*cf.* the term: Central European standard scenario). Models are normally said to operate on a 'worst case', or a 'realistic worst case' principle, but in fact they are superficial and unrealistic in their structure, when compared to the real world. In nature, the variability of distribution of chemicals in water and in soil can cause effects, which not only theoretically, but also in practise are of a kind that do not permit predictions to be made from the normal average consideration.

PNEC-values are calculated by means of arbitrarily selected extrapolation factors. Empirical data from different laboratory experiments on sensitivity of different test organisms are used in these extrapolations which are most often made at a level corresponding to the base-set in a standard testing of new chemicals. The more advanced, though still simplified models, are based on a number of assumptions which are seldom fulfilled, such as *e.g.*:

- the laboratory data represent normal (or other systematic) distributions,
- the test organisms must be selected at random, representing together a *broad spectrum* of species or organisms (*cf.* plants, animals, micro organisms etc.), and
- at least 5 - 7 set of data should be present for each of the selected species.

The Dutch risk assessment model, USES or Uniform System for Evaluation of Substances [59] is presently the most advanced and most frequently discussed model. In USES a number of known, simple individual models are included as modules in a computerised program, among which also is one module which may calculate missing data from the knowledge of molecular structures and by analogy to closely related chemicals.

The USES program has been presented to the EU, and it will most certainly contribute to the further development of the field within the EU. The model represents first generation, *i.e.* it is still under development, and as for its environmental modules there is definitely a need for more realistic risk models, *e.g.* for calculation of distribution scenarios within complete ecosystems, of probable effects on selected key species and of functional disturbances in complete ecosystems. Models like this are developed in several countries, especially the US and the Netherlands, but also in Denmark, *e.g.* at the DMU, Danmarks Miljøundersøgelser. A large amount of data is still needed to describe the ecosystems, but modern computer technology will undoubtedly make it possible and realistic to develop both large and more complex models,

which may be able to calculate actual risks to a given ecosystem, even under selected meteorological and climatic conditions and when based on a minimum of laboratory information on the distribution, fate and effects.

Chapter 6

Limit values and uncertainties

6.1. Human toxicology

The toxicology explores and describes the effect of chemicals in the human and the animal organisms [60], and generally it serves the purpose :

- *qualitatively* to understand the causes/mechanisms for the development of damaging effects,

- *quantitatively* to establish dose- and impact-levels, referring to amounts or concentrations that are damaging or critical

- *and by this* to create the basis for a further assessment of health related safe levels.

Among these purposes, of course, it is the latter which draws the external attention, not the least for the setting of that dose level of a chemical, which is *estimated not to cause damage*. Normally, this refers to the so-called NOEL (no-observed-effect-level or the zero-effect-level) or the NO(A)EL (no-observed-(adverse)-effect-level), *i.e.* the doses or concentrations which experimentally do not cause any damage to the experimental animals.

The distinction between NOEL and NO(A)EL can seem subtle, but in practice it may be essential. The question may arise, for instance, whether an observed effects is actually accepted as a toxic effects, or merely is a non-specific adaptation or a normal compensatory response, as *e.g.* a reduced gain in weight in response to altered experimental conditions, change in food appearance or consistency etc. By the acceptance of a NO(A)EL assessment it is assumed, therefore, that the cause of possible effects at lower dosages has been explored, and that this has given no indications of *e.g*. secondary adverse effects.

Normally the NO(A)EL values depend on the experimental data which is presently available. The values can vary according to animal species or depending on those effects which are in fact included in the observations. Uncertainties will often influence the estimated NO(A)EL. Typically, effects can be observed *e.g*. in some experimental animals, without these effects being statistically different from observations made in a control group. In such case, the norm is that the effects are not accepted as 'signs of toxicity', but attributed to random, biological variations.

A typical effects can, however, also be seen as *e.g*. when embryonic defects are observed with a frequency which is smaller than that, which according to the experimental design is statistically significant. In such cases, damages will not to be taken into account in the setting of the effect/no-effect level, also because the reporting of data into the scientific, open literature normally is made as a summing-up of data leaving no room for atypical, non-significant effects. Such effects are likely to fall into oblivion, unless special attention is given to a selection and assessment of the speecial details from a large amount of individual

data.

6.1.1. Establishment of limit values

The scientific test methods, which are available for the setting of limit values for chemicals, can be divided into *in vitro* (in test tubes) or *in vivo* studies (in living material). The *in vivo* investigations include animal experiments as well as observations of humans after exposure to chemicals.

The majority of human toxicological limit values are based on animal experiments. *In vitro* investigations are used to a much smaller extent, and as far as effects on man are concerned these are incidental (or accidental) only. When humans by mishaps or accidents have been exposed to a specific chemical (*e.g.* in Seveso, Italy in 1976 and in Bhopal, India in 1984), this will usually involve exposure to larger doses of chemicals and for limited periods of time. Such situations will often contribute with a lot of new and valuable information, but on the other hand not with information of significance for low-dose or long-term exposures or on the significance of exposure from several different chemicals simultaneously. In the following attention is primarily given to the setting of limit values based on animal experiments.

Several procedures exist for the setting of Acceptable Daily Intake (ADI) and Tolerable Daily Intake (TDI), respectively. The term ADI is 'reserved' for use only when a chemical deliberately is added or applied to achieve a defined effect (and it is then used, even in cases when negative side-effects are considered). Additives to foods are mentioned as an example. In contrast, the term TDI is used when the presence of a chemical is un-intentional or considered to be undesirable. The presence of pesticides in drinking water is a dominating example.

The limit values are calculated from ADI or TDI (in identical procedures), and mostly by the so-called NO(A)EL method*), in which an NO(A)EL value for a chemical is divided with one or more uncertainty factors, as follows:

*) By the so-called "Benchmark method" the NO(A)EL is not used as a basis. A lower safety margin is evaluated as a dose, which causes a small change of the effect when compared to the control group. Thus, it is determined by utilisation of the full dose-response curve, and therefore referring to observations from a greater number of experimental animals. In this method lower ADI- or TDI-values are obtained, but the method is presently not used extensively in other places than US/EPA

6.1.1.1. The NO(A)EL method

By the setting of limit values it must preliminary be evaluated, whether a chemical has a threshold value or not, *i.e.* if it can be expected that a dose below this value does not cause any damaging effects, while doses above the value may cause damages. The NO(A)EL method can only be used for chemicals, which are assumed to have a threshold value.

The central question to be answered is the following:

- what is the concentration of a chemical, below which *no* (adverse) *effect* are seen?

and, if no such information exists:

- what is then the *lowest concentration, that causes* an (adverse) effect, LO(A)EL (= lowest observed (adverse) effect level).

An acceptable/tolerable daily intake (ADI/TDI) is obtained by dividing NO(A)EL or LO(A)EL with one or more uncertainty factors (UF), as follows:

$$\text{ADI or TDI} \approx \frac{\text{NO(A)EL}}{UF_1 \times UF_2 \times UF_3}$$

It is noted that the indicated UF-factors only in recent years have been named *uncertainty factors*, because they increasingly are used to compensate for lack of knowledge - whereas earlier they were generally accepted as *safety factors* (= SF).

The first factor (UF_1) is traditionally used to account for the differences between animal and man (the *interspecies* variation). *The second factor (UF_2)* is used to 'cover' the variability among or in-between human beings, considering *e.g.* differences between vulnerable or less-vulnerable groups (the *intraspecies* variation) which are seldom disclosed when using experimental animals in the laboratory. UF_1 and UF_2 are individually most often set at a factor of 10, irrespective of the identity of the chemical.

Beyond factors UF_1 and UF_2, there may be introduced *a third factor (UF_3)*, based on a more specific evaluation of quality and of relevance of the available experimental data. Normally UF_3 is set at a factor of 1 - 10 . In special cases it can be set higher [61], or it can give rise to a discussion on a fourth factor (UF_4) in order to include 'non toxicological' precautions - *cf.* 'precautionary principle' (see section 6.2.1.).

The health related databases and documentation which are applied for the setting of ADI and TDI values are grossly the same, even when used in various contexts, *i.e.* for use in setting limit values for food additives, for contaminants in foods, or for chemicals in the workplace environment. ADI- and TDI-Values are mostly generated from animal experiments, from human observations, and *in vitro* or other short time tests, **but** in the calculation of limit values based on the ADI/TDI for water, food, air etc., respectively, the distribution of the chemical in question have to be considered in relation to each of these different compartments.

In some cases, there may be deviations from a 'normal' procedure when calculating limit values. A limit value can for some chemicals *e.g.* be based on smell or taste criteria. Further, for chemicals such as pesticides in drinking water, the normal practice can be overruled by a 'superior', politically accepted interpretation, namely that pesticides are undesirable as contaminants in drinking water. For the existing limit value (*cf.* Drinking water directive [62]) this is demonstrated by the setting of a 0,1 g per litre limit*) , by which reference is made to an analytical detection limit**) at the time of passing the legislation on drinking water quality.

*) 0,1 g = one tenth part of a microgram or a ten-millionth part of a gram

**) Detection limit = the smallest concentration, which can be observed and can be given within a specified margin of analytical certainty

For other chemicals, *e.g.* nitrate in drinking water, there are reports which indicate, that amounts relatively near to the limit value (*i.e.* 50 mg per litre) may be a health hazard to specific sensitive groups. The limit value is then set by accepting *a smallest possible* (un)certainty margin, while reference is made to the fact that the present knowledge is connected to direct observations of humans. For some further chemicals, such as the air pollutants nitric oxides (NO_x) and ozone (O_3), limit values are established in spite of presented evidence that sensitive persons, *e.g.* asthmatics, may develop breathing problems at the accepted limit value.

The setting of limit values in the *working environment* is based on the same toxicological experience as for the other fields. An especially agreed procedure, however, has been established between the directly involved parties of the labour market, whereby technical as well as economical consideration are directly introduced in the procedures for accepting submitted proposals for limit values. The result, of course, of such procedure may be either higher or lower limit values than those which were first suggested on toxicological considerations - a fact which seems to be justified by the inclusion also of regulation and agreed improvements in the decision process. For the administration of limit values in the workplace environment, weight is further given to the acceptance of a 'good practice', *e.g.* that pollution in and around the working place is generally not acceptable at levels close to the limit value, if it is technically feasible to control the pollution at lower levels, *e.g.* by substitution, introduction of closed circuit systems, improvement of exhausts and ventilation etc.

A disadvantage by using the NO(A)EL method is the fact that the setting of ADI and/or TDI values are only based on single values for (NO(A)EL or LO(A)EL, which is contrary to the so-called Benchmark method - *cf.* footnote in section 6.1.1. Similarly, it is normally an uncontrolled assumption, *that* threshold values in fact exist, *and that* uncertainty factors of 10 are sufficient to cover *inter- and intraspecies* variations. Furthermore it is noted, that the use of an increased number of animals in an experimental testing may result in lower NO(A)EL and thus lower ADI/TDI-values (and vice versa). This implies, that the use of experiments with fewer animals will be found 'rewarding' for those, who may find interests in less conservative risk values [63].

6.1.1.2. Absence of threshold values

If a chemical does not posses/demonstrate a threshold value - which is the situation for genotoxic, carcinogenic chemicals - an ADI/TDI-value will normally be estimated in a risk consideration being based on data obtained in animal experiments and utilising mathematical models. In Denmark a lifetime risk of 10^{-6} is generally accepted, which means that the exposure of a chemical in a given daily amount through out a lifetime might *as a maximum involve only one additional instance of cancer per 1 million exposed* humans.

6.1.2. Human toxicological uncertainties

Uncertainties and the application of uncertainty factors have been known and discussed for several years [64]. During some decades they have been applied in connection with the assessment of various types of chemicals, but in recent years they have increasingly been discussed and considered for a lack of theoretical foundation, at least in their early applications [65], which is illustrated in the following:

a) Transfer of results from animal experiments to humans (see section 4.3.)

For the setting of limit values of chemicals from animal experimentation (most often rats and mice) but with relevance for the human organism, the assumption is that there is a fundamental similarity between the chemical impact on animals and on man.

In order to apply the results from animal experiments, the pathways of absorption and degradation and the mechanisms of toxicological effects in the body should be known, both for the experimental animal and for humans. This is often not the case. A similarity in anatomy and biochemistry can also be assumed for the test animals and humans, which is of course far from being correct, *cf.* the rats not having a gall bladder, or the lack of menstrual cycle in several experimental animals. Furthermore, some effects are difficult to

examine in experimental animals. This is the case for animals not giving information about nausea or hallucinations, and when it is difficult to observe changes of the personality or in sensory capacity of animals.

The laboratory conditions under which experimental animals are studied, are very different from the conditions in which humans are living. They are characterised by animals living in specific and controlled environmental conditions, and animals consuming a fully controlled diet, only.[66]

b) The significance of not-measured and non-assessed effects:

Generally, only those effects which are searched for will be found. In animal experiments, the studies are standardised for testing of simple, easily observed effects, *e.g.* cancer, malformations, weight changes etc. The more discrete and less easily distinguished biochemical and physiological alterations, however, normally remain undescribed [67]. As an exemplification, hormone-like effects are not included within the presently accepted and recommended test methods. They do not exhibit normal dose-response correlations, and effects are not observed until the next generation.

The large number of unknown processes and functions which are characteristics of the human body (and not always found in animals) is an obvious indication that animal experiments will never be able to simulate all effects in the human body resulting from chemical exposures. Secondary effects, or 'cascading effects' *e.g.* influence of environmental stress, of nutritional deficiencies, or of one chemical on sensitivity of another, are also not parts of normal testing procedures (*cf.* variations in concentrations and /or activity of enzymes, development of oestrogen effects by metabolism of ingested chemicals etc.).

It has to be understood, that especially situations like these constitute the background that also professional toxicologists may question how far uncertainty factors can be applied unmodified (and indiscriminately?), irrespective of new effects being detected - or known effects being detected at lower doses due to the introduction of better research facilities and technology, *incl.* molecular biological methods.

c) Life time risks:

In animal experiments, the effects of a chemical are studied for a period, usually for weeks or months, which is limited compared to the life time of a human being. Mice and rats have a life times of maximum 6-8 months and 1.5-2 years, respectively. Such investigation can obviously not give complete information about the effects - and functions of repair mechanisms - on humans, for whom long-term, and even life time exposures can be decades. The knowledge about the effect of long-term stress are still relatively insufficient, and for most chemicals it seems unlikely, that we actually gain sufficient insight in the significance of life time impacts on the human organism.

d) Interactions:

Following several decades of development it has been said, that the toxicology of chemical mixtures will become the toxicology of the 1990´s, as this aspect of toxicology more realistically will reflect the situations to which man are mostly exposed.[68]

As a matter of fact, studies of effects of a variety of chemical mixtures on humans are presently being encouraged (*e.g.* within the Danish Strategic Environmental Research Program [69]). A simultaneous exposure of several chemicals may result in an addition of effects, or a synergism (*i.e.* a mutual intensification of effects), or an antagonism (*i.e.* a mutual inhibition of effects). Because of the large number and large volumes of chemicals which surround us and to which we are exposed (through drinking

water, foods, air etc.) it is practically impossible to investigate all simultaneous effects - not even by restricting ourselves to the study of priority chemicals.

On this basis, the interpretation of the WHO is remarkable, that larger importance shall be attached to effects which are caused by interaction between pesticides than generally accepted, regardless of the fact that it can be most difficult to evaluate the extent and the strength of the effects (*cf.* reference 63).

e) Degradation and metabolic products:

Most chemicals are decomposed or metabolised in one way or another, either

- before they come into contact with the human organism, or
- after they have entered the organism, or
- after excretion.

It is therefore often considered, whether separate effects of related chemicals (or impurities) exist, in case these are ingested into or formed within the experimental animal, and thereby possibly supplement the effects of the 'parent chemical'. As a rule - rather than an exception - it can not be decided whether a given effect is caused by a product of degradation or by the 'parent chemical', unless this is directly studied in a specific and goal-directed testing, aiming at a search for *both* individual *and* interactive effects of the individual components. In practice, only very limited experience exists about the effects of most degradation or metabolic products, because chemicals are normally notified and/or marketed individually, and base-set testing refer to the notified chemical.

This question is further complicated by the fact, that some degradation products can often be formed *in* the environment, under other conditions and in other concentrations/amounts than predicted in the preceding studies. In addition, it is not always clear to which extent the existence of degradation products can be controlled, and/or how they should be evaluated by authorities within the existing legislative rules. Such problem areas are often presented in practice, as for instance in recent discussions about degradation products arising in animal organisms and in the soil from Atrazine, or from pesticides which contain Dichlobenil.

6.1.3. Application of uncertainty factors

Today it is increasingly discussed, to which extent the present uncertainty assessment and application of uncertainty factors can be (or must be) revised, and how this should be done. It is hereby referred to those uncertainties, which are related to the insufficiencies of experimental investigations, as well as to the transfer of results from experimental experiments to the assessment of human hazard and risks.

The application of uncertainty factors, as mentioned above, of 10 in cases of UF_1 and UF_2 for different chemicals is based on a practise developed over a few decades, but for which the background, however, is generally not very well described (*cf.* reference 62).

Renwick [70] has suggested a splitting up of UF_1 and of UF_2 into toxico-kinetic and toxico-dynamic part, respectively (see table 6.1). The rationale is, that both toxico-kinetic and toxico-dynamic elements can contribute quantitatively to the experimental uncertainties and that a control of these individually can influence the uncertainties in relation to the setting of ADI/TDI.

Table 6.1 Uncertainty factors applied in the setting of human limit values (modified from ECETOC, 1995 [71])

	Renwick 72	**WHO** *), 73	**US-EPA** ,74	**ECETOC,** 74
Interspecies *kinetic* *dynamic* *oral intake* *inhalation*	(10) *4* *2.5*	10 *4* *2.5*	10	*4* *1*
Intraspecies *kinetic* *dynamic* *general population* *workplace environment*	(10) *4* *2.5*	10 *3.2* *3.2*	10	*3* *2*
Extrapolation acute subchronic subchronic chronic			1	3 2-3
Extrapolation LO(A)EL NO(A)EL	>1	(1-) 10	10	3
Special effects (*e.g* . cancer)	1-10	1-10	1-10	
Inadequate data base	1-10	1-10	>1-10	
Residual uncertainties (modifying factor = MF)			<1-10	

*) Normally, WHO-experts do not accept uncertainty factors totalling above 104.

Toxicokinetics is referring to the fate and metabolism of the chemical in the organism, including its absorption, distribution, metabolism and excretion, all of which will influence the concentration of the chemical in exposed organs, *e.g*. liver or kidneys.

Toxicodynamics is referring to the mechanism of (toxic) effect of the chemical, *i.e.* the interaction between chemical and functions of the organism. According to the proposal of Renwick, both UF_1 and UF_2 are divided into the sub-factors 4.0 and 2.5. This is based on analyses of quantitative information on inter-species differences and inter-individual variations for some selected chemicals.

For chemicals where no data exist, both UF_1 and UF_2 has up to this present time been set at 10 with an interpretation of default values. Included in the proposals made by Renwick is the application of further, separate uncertainty factors for special effects (*e.g.* cancer) and to account for inadequacies of the data base, respectively, and also for the use of LO(A)EL in stead of NO(A)EL. An expert group from WHO (see table 6.1) has subsequently suggested, that UF_2 (but not UF_1) should be divided into toxico-kinetic and toxico-dynamic sub-factors of each 3.2.

Confirming that similar considerations has been made in the US, it has from the US Environment Protection Agency (US-EPA) (see table 6.1) been suggested to use a uncertainty factor of 10 in cases of extrapolation to a chronic NO(A)EL from animal experiments, in cases that no data have been obtained from chronic exposure (reference no. 71).

In a recent publication from the ECETOC (*European Center for Ecotoxicology and Toxicology of Chemicals*, reference 69) these different proposals has been discussed (see table 6.1), and generally a significant reduction is argued for most of the applied (un)certainty factors. The ECETOC represents the European chemical industry, and it is suggested that UF_1 and UF_2 should not exceed 4 and 3, respectively, and that other more data related factors should be limited to a maximum of 6 (=2 times 3) and 9 (=3 times 3) for extrapolation from acute =>sub chronic=> chronic exposure, and 3 for extrapolation from LO(A)EL to NO(A)EL.

It is in open contrast to this proposal, that presently in Denmark it is discussed to include a fourth uncertainty factor (UF_4) for the calculation of environmentally related limit values. This factor should take into account some of those already mentioned uncertainties, which refer to complex environmental effects, combination effects, persistence and special, often unpredictable effects. Covering such broad both technical and administrative situations, this factor should be set on a case-by case basis with possible variation from 1 and upwards.

6.2. Ecotoxicology

As already mentioned, ecotoxicology is concerned with effects and evaluation of effects of species and populations from the natural flora and fauna, which is unlike the human toxicology, in which focus is at protection of the individual human being. It is considered of minor interest, therefore, to search for effects and effects mechanisms of chemicals at the level of individual organisms. And similarly there is a small tendency, only, to include subtle, though still significant, 'toxico-dynamic' effects in the environmental hazard assessments. Also, today, long-term effects are rarely included in ecotoxicological routines, incl. secondary effects, permanent effects, and/or (cascading) disturbances of natural communities and ecosystems.

6.2.1. Ecotoxicological limit values

Like for human toxicological limit-values, ecotoxicological practice is predominantly based on experimental laboratory testing of chemicals. The aim is to understand - and to protect - the biota, *i.e.* natural flora and fauna in the environment from damaging effects. As a practice developed from the setting of water quality limit values in the EU, it is now the key-issue to establish the so-called zero-effect-value (NOEL or NOEC [75]), and undoubtedly, this will also be the case when dealing with soil quality limit values, in spite of the fact that is still today extremely difficult to establish valid zero-effect-levels for the

terrestrial environment.

As the legal request for the setting of environmental quality objectives (or standards) is 'to take the zero-effect-level' into account [76], and as this level is rarely determined experimentally, but by extrapolation from less extensive data, it may definitely be argued that an application of (un)certainty factors is hardly seen today. Special 'precautions' are seldomly included in the setting of environmental limit values. The fact is, that practice is focused on extrapolation from actually measured effect in order to give 'best estimates' on the order of magnitude of zero-effect-values.

The practice can be described as one of the following methods:

- A so-called *'application or extrapolation factor method'*, according to which measured effects or low-effect levels are transformed into NOEL/NOEC-values by use of factors which are arbitrarily set as orders of magnitude between 10 and 1000, dependant of the availability and quality of existing data (*cf.* table 6.2). The factors are recommended as generally applicable on the basis of statistical analyses of data from the open, scientific literature. In principle, this method is recommended by the OECD [77] and it has with only slight modifications been applied in the EU during a number of years in the setting of common European water quality objectives/standards for List 1-chemicals (*cf.* CSTE, 1994).
- A *distribution-based extrapolation* [78], which statistically tries to determine the concentration level, K_p, which is protecting to a given fraction of organisms (*e.g.* 95 %) against damaging effects on a defined statistical level, *e.g.* 95 %.

Figure 6.2 Factors applied in the setting of environmental quality objectives (according to CSTE [79])

Availability of data	**Extrapolation/Application factor**
The lowest acute LC_{50}-values - when data available are few, or the range of test organisms is narrow	1000
The lowest acute $L(E)C_{50}$-values - when an extensive data base covering a wide range of test organisms,	100
or	
the lowest chronic $L(E)C_{50}$-values, *or* NOEC-values, when few data are available	10
The apparent NOEL-value, when it is based on sufficient and representative data	

In actual trials, it has been demonstrated that these two methods do not give rise to substantially different results. In the first method, a pragmatic effect assessment is carried out on the basis of often meagre databases, but with an inclusion of applicational factors, which are derived from experience gained with a

definite number of other chemicals. In the other method, the assessments are made by a more simplified inclusion of factors and first of all with the advantage of referring to the characteristics of the specific chemical. Being more critical in its criteria and demands for the adequate data, therefore, it has the disadvantage of not so often being applicable due to lack of data.

6.2.2. Ecotoxicological uncertainties

Much experience is still missing for valid comparisons of the principles of these two method, and there are even less (or no) useful experience method uncertainties. This is not least due to the fact, that the largest uncertainties today - and in a next foreseeable future - are connected to the lack of data and inadequacies of existing information in ecotoxicology.

In analogy to the discussions of uncertainties in the human toxicology, however, analyses and - so far theoretical - presentations of elements for the evaluation of uncertainties in ecotoxicological effect/hazard assessment are increasingly being made. Expectedly, it is especially the application of uncertainty/safety factors, and the already introduced series of extrapolation factors, which are drawing the attention.

It is mentioned, therefore, that the scientific literature (especially from the US [80]) increasingly points to the need for an ecotoxicological uncertainty assessment, and that the following should be considered:

- a *systematic assessment of the interspecies variation* to take into account the large species diversity of a rich nature, in stead of the presently used statistical assessments of those few species, only, which are included in the routine test systems,

- an *assessment of the intraspecies variations* with the inclusion of the uncertainties connected to interpretation of effects and impacts of chemicals on *individual species in general* and on *vulnerable, (threatened) species* in particular,

- an assessment of *life-long effects* (and their variabilities) for species/popu-lations, in order to extend these beyond the presently limited reproduction test for daphnia and (sub)chronic tests on a few laboratory fish-species, and

- that *separate assessments of uncertainties related to insufficient data bases* and lacking documentation - apart from the already mentioned uncertainties - are introduced on a routine basis.

6.3. Comparison of human toxicology and ecotoxicology

As it has already been stated, the demands for data from testing and documentation for the setting of limit values are smaller - in number as well as in quality - in the field of ecotoxicology than is the case for the human toxicological testing of chemicals. This is qualitatively illustrated in figure 6.3, which shows the variables and uncertainty assessments that are included in the routines of these two fields of assessment.

The figure refers to the following facts and observations:

- Serving the human toxicological assessment and the setting of limit values all routes of exposure is (or should be) included, *i.a.* directly through food, drinking water and air, but also the indirect/other exposures via the external environment and the workplace environment,

Figure 6.3 Elements and variables, which are included in the setting of human and ecological limit values

	Human toxicolog					Eco-toxicology	
	Foods	Drinking water	Air (external)	Soil	Work-place	Sea/ fresh water	Soil/ sedi-ment
Zero-ef-fect-level	+	+	+	+			(+)
Inter-species variation	+	+	+	+		(+) ***)	?
Intra-species variation	+	+	+	+	(+) **)		?
Further uncertainty factors	(+)	(+)	(+)	(+)		(?)	
Others	GAP, GMP *)	Smell & taste, pesticide	Smell	Smell			

*) GAP = Good Agricultural Practice

GMP = Good Manufacturing Practice

**) Usual scientific foundation supplemented with assessment of technical and economical possbili-

ties

***) The routine extrapolation to NEL-value includes only the variation between the species of the

laboratory testing, and the obtained *nil-effect* is given at a 95 % level of significance.

- It is a limited number of standard test methods, which are available for the ecotoxicological testing of environmental hazards (and the setting of limit values) when this is compared to the collection of test methods available for use in the field of human toxicology (*cf.* chapter 4),
- The ecotoxicological zero-effect-values, which determine environmental limit values (*cf.* section 6.2.2 above) are accepted on the basis of extrapolations from *e.g*. acute measurements or by simple 'screening experiments'. They are set, therefore, with much larger (and unknown) uncertainties than the case would be if based on assessments of experimentally obtained NO(A)EL and/or LO(A)EL-values.
- In our use of ecotoxicological test results and experience we have still not - in spite of these observations - included any procedure for the application of actual uncertainty/safety factors or defined any precautions for the routine practise of setting of environmental limit values.

Abbreviations and explanations

ADI	**Acceptable Daily Intake. The term is used for chemicals, which are deliberately added, *e.g.* to achieve a specific effect such as preservation, food colouring etc.**
biocides	**biologically active chemicals - today mostly designated to 'non-agricultural' pesticides**
biota	**the biological, living part of our outer environment**
carcinogenic effects	**the ability to cause cancer**
detection limit	**the smallest concentration, which can be observed and identified with a specified degree of analytical certainty**
EC	**Effect Concentration(s), *i.e.* the concentration(s) at which effects are observed in experimental animals**
ecotoxicology	**the science of toxicity (or poisonous effects) of chemicals to living organisms in nature or on environmental biota as a whole (normally interpreted as having the aim of protection of species and populations, more so than individual animals), but increasingly also with inclusion of natural communities - flora and fauna - as well as intact eco-systems)**
GLP	**Good Laboratory Practice, *i.e.* principles which are accepted as good standard in the laboratory work, including quality controls,**
GAP	**Good Agricultural Practice, normally including nationally authorised safe methods for use of chemicals *e.g.* pesticides. It is understood, that a desired, agricultural effect *can* be achieved, provided that all valid health related and environmental demands are full-filled.**
genotoxicity	**(adverse) effects on genes**
HEDSET	**Harmonized Electronic Data Set - based on EU/OECD guidelines for uniform storage and retrieval of chemical data within the framework of classification and risk assessment directives of the EU**
HPVC	**High Production Volume Chemicals, *i.e.* chemicals which are produced in large amounts (more than 1000 tons per year)**
human toxicology	**the science of (adverse ~ toxic or poisonous) effects of chemicals on human beings, *i.e.* referring to effects on individual human beings**
immission	**the content of chemicals *in* the atmospheric air, normally used on air pollutants close to the surface of the earth**
in-vitro experiments	**experimental investigations carried out in test tubes without any use of living organisms**

in-vivo experiments	**experimental investigations carried out with living organisms, experimental animals or by observation of human beings when exposed by chemicals**
LC/LD	**Lethal concentration/dose, normally given as $LC50/LD_{50}$ indicating the concentration or dose, which is the cause of death for 50 % of experimental animals**
LO(A)EL	**Lowest Observed (Adverse) Effect Level, *i.e.* the lowest dose level, for which damaging or undesired effects are observed in the experimental animals**
LOEL or LOEC	**Lowest Observed Effect Level or Concentration, *i.e.* the lowest dose level/concentration, for which effects can be seen in animal experiments**
metabolite	**degradation or decomposition product formed within the living organism**
MFO	**Mixed Function Oxidase enzyme(s), *i.e.* enzymes which are part of the oxidation processing systems in the organism**
mutagenic tests	**tests, which show whether a chemical is mutagenic, *i.e.* the cause of alterations in genes**
NEL	**No Effect Level**
NO(A)EL	**No Observed (Adverse) Effect Level, *i.e.* the highest dose level, for which no (adverse) effects are observed in animal experiments**
NOEL or NOEC	**No Observed Effect Level or Concentration, *i.e.* the highest dose level/concentration, for which no effects are observed in animal experiments**
PEC	**Predicted Exposure Concentration, *i.e.* concentration level which can be predicted (by calculation or estimation) as the result of release into the environment**
persistence	**a term which is used to characterise a chemical, which due to its intrinsic stability (recalcitrance) remain unchanged in nature or in natural compartments.**
PNEL/PNEC	**Predicted No Effect Level/Concentration, *i.e.* predicted zero-effect-level/concentration**
SF	**Safety Factor, now mostly substituted for Uncertainty factor (see also UF)**
TDI	**Tolerable Daily Intake, the term is used for chemicals, the presence of which is not intentional or directly undesirable, *e.g.* pesticide residues in foods or water**
teratogenic	**the ability of a chemical (or other external agent) to cause inherited malformations**
toxicodynamic	**effect mechanism and interaction between the chemical and body functions**
toxicokinetic	**processes and metabolic changes, which determine the concentration and fate of chemicals in the body**

toxicology	**the science of toxic (poisonous) chemicals and their effects on the living organism**
threshold value	**a dose below which damaging effects are not expected, while a dose above the threshold value may cause damaging effects**
UF	**Uncertainty Factor, *i.e.* a factor which is used as a calculation tool to compensate for uncertainties of experiments, lack of documentation, or possibly of knowledge**

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