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“Study on the treatment of vulnerable groups in EU risk assessment”

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SUMMARY AND CONCLUSIONS

Main conclusions:

- Current practice indicates that the present practice within the different EU risk assessment frameworks (i.e. present use of assessment factors for human variability) sufficiently cover the differences in susceptibility, although it is acknowledged that no appropriate data are available to confirm or disprove this consideration. For practical reasons, the general notion is therefore that the current risk assessment procedures are sufficient to protect potential vulnerable groups. Therefore, at present no need for urgent action is identified.
- In addition to the previous bullet, it is recommended to set-up and maintain a data base with human data on vulnerability, originating from different regulatory frameworks. It is not meant to initiate studies in humans but to gather data from practical experience and health monitoring programs. Such a database can provide alerts for potential vulnerable groups based on e.g. substance-specific data, structural alerts and experience obtained within other frameworks and can provide insight in the appropriateness of the generally applied defaults for the assessment factor for human variability.
- Based on the present study, a “best practice” as such is not assignable. The frameworks differ too much (with respect to scope, aim and type of compounds covered) to allow a direct straight comparison. A few possibilities are given for improvement of the risk assessment for some potential vulnerable groups by making better use of the required data.
- It appears to be premature and not feasible to recommend extensions of data requirements without knowledge on potential vulnerable groups. Therefore, it is recommended on the one hand to make a more optimal use of the already available data set and on the other hand to initiate further developments to obtain more insight in factors relevant for the human variability.
- Specific developments are identified and briefly described that might be useful for the identification of potential vulnerable groups in the foreseeable future. In order to achieve that purpose it is recommended that these developments will be more guided by risk assessment-orientated instances.

The evaluation of current approaches in the risk assessment of potential vulnerable groups revealed that most frameworks address potential vulnerable groups only on a case-by-case basis, if appropriate data happen to be available. In none of the different legislations, publications of scientific bodies of the Commission, major competing economies of EU and international bodies any practical guidance was given for the respective approaches of vulnerable groups.

Furthermore, the generally applied default assessment factor for interindividual variability is in principal already meant to cover the general variability due to e.g. a poorer health status and age (the old and the very young). No data are available to support the assumption that a default factor of 10 (covering a 100-fold human variability) is (or is not) sufficient. It is

generally assumed that most of the potential vulnerable subpopulations are covered and protected by this approach. However, it was remarked that it will be difficult, if not impossible, to detect small or rare health effects in a human (sub-)population and relate these to exposure to a specific chemical. This could explain the absence of reports on inadequate protection of vulnerable groups by the present risk assessment procedures. Thus, for practical reasons it can be considered that at present there is only a need for additional concern with respect to vulnerable subpopulations if the available data do indicate so. However, there still is a need to verify the sufficiency of these default factors.

The main issue therefore is not so much how to deal with vulnerable groups but how to identify them. Which potential vulnerable groups can be addressed is dependent on the requested data within the respective risk assessment frameworks. However, it appears to be premature to recommend to extend dossier requirements by default without knowing what one should look for. Therefore this report primarily focuses on recommendations for optimization of the use of the data already required and on some possibilities to obtain more insight in the human variability in the near future. A strictly legally fixed harmonized approach applicable to all risk assessment frameworks seems not feasible and/or desirable, due to the varying scopes, aims and type of compounds covered in the various regulatory frameworks. The main purpose of the recommendations made is to gain more insight in human variability. On the one hand to evaluate the appropriateness of the default factor of 10 for interindividual variability, and on the other hand to study the possibilities for improvement of the current risk assessment procedures of vulnerable groups by derivation and application of more refined assessment factors for human variability.

Summary of this report

The present report describes an evaluation of how vulnerable groups are dealt with in the current risk assessment procedures of the various EU regulatory frameworks and an exploration of possibilities for improvement. The first step included an analysis of current practises within the EU frameworks, within relevant international institutes and bodies and some major competing economies. Secondly, the scientific literature was intensively searched for new developments and discussion papers on human variability, susceptible subpopulations and related topics. The findings were evaluated and discussed among experts in the various EU risk assessment regimes. The analyses finally resulted in recommendations for improvement of the current risk assessment methodologies on a relatively short-term as well as recommendations on possibilities for improvement on the mid- and long-term that need further development.

Within the present context the definition of “vulnerable groups” was elaborated. It was felt that the starting definition needed further exemplification for practical reasons. Although it was beyond the scope of the present study to provide a comprehensive review some topics were briefly addressed and a pragmatic working definition was put forward. Topics discussed included among others the meaning of the default intraspecies factor and its point of departure. Within the present project the intraspecies assessment factor is considered to account for the differences in susceptibility between the average and the most susceptible human being.

International regulatory risk assessment regimes both within and outside the EU generally deal with vulnerable groups on an ad hoc basis and by expert judgement. The extent to which vulnerable groups can be addressed within the various EU risk assessment regimes depends on the data requirements within each framework. With exception of the evaluation of human medicines (EMA/CHMP), adequate human data is seldom available. Gender as a factor can be addressed if at least some repeated dose toxicity studies are required while for instance children can be evaluated when an appropriate developmental toxicity study and/or multi-generation study is required. It is noticed that in general the required toxicological data set does not provide information on subpopulations that are vulnerable due to, for instance, genetic predisposition, illness, poor nutritional status or life-style.

The analyses of the recent literature revealed that relevant discussions on the topic of vulnerable groups, investigations and methodological developments are still ongoing. The following items were identified as main recent developments and were considered especially promising for improvement of the risk assessment of vulnerable groups in the (near) future:

- the amount of data regarding children and elderly as age-related vulnerable groups;
- modification/adoption of testing strategies in order to include the special properties of vulnerable groups;
- the possibilities of *in silico* methods, especially of PBPK-modelling to address interindividual variability due to e.g. gender, age, differences in biotransformation;
- perspectives regarding the application of new technologies (“-omics” techniques).

TNO and RIVM experts discussed the results of the inventory and the literature search during a workshop. Three main topics were addressed: the definition of vulnerable groups and the adequacy of the default intraspecies assessment factors, relevant developments and recommendations for improvement.

It was stated that the often used total assessment factor of 100 has proven its merits in practice and that this factor was therefore believed, in general, to adequately protect the human population. Two relevant comments were made:

- It is the overall factor of 100 that provides a “feeling of safety” rather than the factor of 10 for intraspecies variability in itself.
- It will be difficult, if not impossible, to detect small or rare health effects in a human (sub)population and relate these to exposure to a specific chemical. This could explain the absence of reports on inadequate protection by the default factor.

Recommendations for improvement for treatment of potential vulnerable groups included consideration of the possibilities on how to improve the public nature and accessibility of confidential information (e.g. regarding data from drug development and from post marketing surveillance of drugs), of PBPK-modelling as a tool for identification of human subjects or groups that show relatively high internal exposures at the level of the target organ, of the “-omics” technologies and of the development of guidance for a more coherent testing strategy.

The possibilities for implementation of these recommendations were further elaborated. Especially the last recommendation, a more coherent testing strategy, was considered to be a valuable tool that could be implemented within the foreseeable future. It implies a better tuning of the required toxicity tests to obtain more adequate data on potential vulnerable

groups. For instance, relevant information on a potential increased vulnerability during pregnancy and/or lactation might be obtained by studying the most relevant endpoint(s) derived from a (sub)chronic toxicity study in female animals also in pregnant animals in a developmental toxicity study or a multi-generation reproduction toxicity study. Also a more appropriate reporting of toxicokinetic data might add to an improvement of the risk assessment of potential vulnerable groups. It is recommended to elaborate the possibilities and to develop more guidance. Some possibilities for improvement are described for individual potential vulnerable groups for the various EU regulatory frameworks.

PBPK-models are promising tools to obtain more insight on interindividual variability in physiological and toxicokinetic parameters. These models have proven their value in the risk assessment of individual substances. Recent developments show that these models might have interesting possibilities to be used in a more generic way. It is recommended to explore the possibilities for a more generic application of these models to obtain insight in the interindividual variability.

“Omics-” technologies might be able to provide important tools for the identification of potential vulnerable groups in the long-term. However, it is recommended to provide more input by risk assessment-orientated bodies to these developments in order to achieve that purpose.

A database of characteristics for specific potential vulnerable groups could be a useful tool aiding the determination of relevant vulnerable groups, their specific hazard profile and risk for a specific compound and/or its use. This database can be filled with information from and experience gained within the various risk assessment regimes. Such a database might provide indicators both from substance characteristics as well as from subpopulation-specific information that might point at a potential higher vulnerability of an exposed population.

It is further recommended to initiate a human health monitoring program, comparable or analogous to the Post-Marketing Surveillance for human medicines, that can be applied to situations for which there are indications that exposed human (sub)populations might experience an increased risk. These indications might be based on both exposure and toxicity information.

A final development that has not further been discussed within the present project is the probabilistic risk assessment. These developments help to optimize the identification of dose-response relationships, and thereby identification of potential vulnerable groups. It is recommended to further explore the possibilities of these techniques within the present context.

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1. INTRODUCTION

The Commission's Action Plan on Environment and Health 2004-2010 states that the health effects of environmental contamination on vulnerable groups are of specific concern, and the treatment of vulnerable groups is also a central issue in the risk assessment procedures currently in place in the European Union. Clearly the aim of any policy to protect vulnerable groups is to identify the groups likely to be particularly vulnerable to a given stressor, to identify the extent of the vulnerability in question, as well as to identify and use of respective appropriate measures.

Within this project the treatment of vulnerable groups within current risk assessment procedures will be examined and ongoing discussions and new developments within the EU, relevant international bodies and major competing economies will be analysed and commented. Based on this, possibilities to improve the current risk assessment practice regarding the treatment of vulnerable groups will be identified. The following approach was chosen:

- a) to analyse and summarise current practice in the various existing risk assessment regimes with regard to the treatment of human vulnerable groups,
- b) to identify and analyse approaches to the treatment of vulnerable groups in the context of the EU scientific committees and agencies,
- c) to identify and analyse approaches to the treatment of vulnerable groups in major competing economies and in international bodies for the products covered by the various risk regimes,
- d) to identify and analyse the main recent developments regarding the treatment of vulnerable groups,
- e) to identify the best practice of the treatment of vulnerable groups, and identify further research needed,
- f) to make recommendations for improvements of the treatment of vulnerable groups in each of the regimes, and
- g) to describe recommendations for future research in the field of the treatment of vulnerable groups in risk assessment.

The outcome will be described in the following. First of all, the definition of the term “vulnerable groups” is further elaborated in Chapter 2. Based on this an inventory was performed regarding the current practice in the various existing risk assessment regimes and the approaches to the treatment of vulnerable groups in the context of the EU scientific committees and agencies – the outcome is described in Chapter 3 and Chapter 4, respectively. Furthermore, actions were taken to obtain information about the respective practice in major competing economies and international bodies, which are documented in Chapter 5, whereas in Chapter 6 the main recent developments are summarized. The best practise and further research on the subject of vulnerability and risk assessment as identified during a work shop with various TNO and RIVM experts is described in Chapter 7. Based on this, recommendations for an improvement of the current risk assessment practises are given in Chapter 8. The report will be concluded by recommendations for future research in Chapter 9; these include further development of possibilities for improvement that might become ready for implementation in the foreseeable future.

2. DEFINITION “VULNERABLE GROUPS” (working proposal)

2.1 Definition

The aim of any policy to protect vulnerable groups is to identify the groups likely to be particularly vulnerable to a given stressor, and to identify the extent of the vulnerability in question. In order to fulfil this goal the question arises how to define a “vulnerable group” in such a way that they can relatively easily be identified. The Technical Annex of the project “*Study on the treatment of vulnerable groups in EU risk assessment procedures*” provides the following definition:

“Vulnerable groups are those for which the dose-response curve varies from that for the population as a whole.”

It is clear from this definition that although a high-exposure population can be at extra risk, it is not ipso facto a vulnerable group. In *The Second Report on Harmonisation of Risk Assessment Procedures* adopted by the Scientific Steering Committee (SSC 2003a) the following factors which could affect the response towards exposure to a given chemical were addressed:

- Sex/gender
- Age
- Genetic traits
- Diseases/disorders
- Nutrition
- Life-style

It is noted that ethnic differences are not mentioned as a factor in itself but it can be assumed that these will mainly be determined by genetic differences, differences in nutrition and life style.

2.2 Elaboration on the definition

The main object of the present report is to answer the question how vulnerable groups are dealt with in the various risk assessment procedures currently in force in the European Union and to identify possibilities to improve these procedures. In order to answer these questions, the definition as given needs further exemplification, especially on what is meant by a “deviating dose-response curve”. It is beyond the scope of the present report to provide a comprehensive overview of all on-going discussions on this topic. Some basic considerations and perspectives will be briefly addressed to emphasize a few topics that are relevant for risk assessment and risk management.

Within the EU risk assessment frameworks a human dose-response curve is seldom known for the population as a whole, let alone for a particular vulnerable human subpopulation. Human data are required in only a few EU risk assessment frameworks (see Chapter 3), and for obvious reasons these rarely deal with the dose-response relationship. This makes the abovementioned definition difficult to apply in the present context. The general procedure includes derivation of a NOAEL (no observed adverse effect level) from animal data which is

further used as point estimate. Dose-response curves can be obtained from these animal data but are at best used qualitatively. Although dose-response modelling of such animal data gains increased interest, it is not common practice yet within EU risk assessment regimes. In cases where this methodology has been applied it has been used to estimate a Benchmark Dose or Critical Effect Dose to be used as a better estimate for a point of departure in risk assessment than a NOAEL. Methodologies for a full probabilistic risk assessment (based on both a probabilistic effect and probabilistic exposure assessment) are under development and these methodologies aim at providing quantitative risk estimates for humans (Pieters *et al.*, 2002; Slob and Pieters, 1998; SSC 2003a; SSC 2003b).

Within the context of the definition two kinds of susceptibility can be distinguished:

1. A higher susceptibility referring to a subpopulation for which the critical effect **differs** from that for the population as a whole and becomes manifest at lower doses or concentrations or at similar doses or concentrations but within a shorter period of exposure.
2. A higher susceptibility referring to a subpopulation for which the critical effect is **similar** as for the population as a whole but already becomes manifest at lower doses or concentrations or at similar doses or concentrations but within a shorter period of exposure.

Examples of the first situation are effects that are to be observed in women but not in men, or in the developing child or adolescent but not at older age, or effects that are due to some genetic predisposition. A subpopulation might be more susceptible for a toxic endpoint that was not identified as a critical effect in the toxicity tests. These situations are difficult to account for without the appropriate data in the population and/or on the (unknown) adverse effect. The available data might be restricted to “indications” or only of qualitative nature.

The second situation is less complicated in the sense that the critical effect is known and it can be considered whether it is likely that this effect might occur at lower doses in specific subpopulations. For instance, diabetics might be more susceptible towards nephrotoxicants. This situation can be dealt with by applying a larger or additional assessment factor although it might be difficult to quantify this factor.

It is recognized that within the context of the second situation a higher susceptibility might also reveal itself by effects becoming manifest after a shorter exposure period. Although this is an important topic, especially within the context of calculating Disability-Adjusted Life Years (DALYs), the present toxicity tests are not designed to provide relevant information. Most adverse effects are evaluated after the predetermined period of exposure as laid down in the OECD guidelines in which an interim evaluation is not a common procedure. However, risk assessment performed within the EU frameworks generally focuses on protection for lifelong exposures to chemical substances. It can then be argued that starting from an evaluation based on a relatively long exposure period will be a conservative approach with respect to this problem.

In both situations the basic question arises whether the more susceptible subpopulation falls within the variability that is covered by the generally applied intraspecies (or interindividual) assessment factor. Discussions are still ongoing whether this factor should be regarded as a safety factor, an uncertainty factor, or a mixture of both, but this discussion is beyond the

scope of the present report. Within the present context differences in “susceptibility” are considered to refer to the variability between humans in response to a chemical agent. It might be argued that application of additional factors are warranted if the database is very poor and does not provide any information whatsoever on potential vulnerable groups. Such factors are meant to cover the uncertainties due to lack of data and are not the subject of the present project. This project predominantly focuses on improvement of the identification of vulnerable groups and once identified how these groups can be dealt with in the risk assessment process. In this report the ‘neutral’ term *assessment factor* will be used.

2.3 Practical considerations

It is considered necessary for the present study to elaborate a little bit more on the given definition for vulnerable groups and its application in risk assessment procedures. As already stated, the discussions are still ongoing and it is not the aim of the present study to weigh all the pros and cons of the possibilities and assumptions or to provide a comprehensive overview of all viewpoints. The aim is on the present risk assessment procedures within the EU and for that purpose it suffices to make a few pragmatic choices in line with the methodologies as currently applied within these frameworks. A few additional remarks are made to further fill in the given definition for vulnerable groups. These are purely made for practical reasons for the present purpose and are not meant to provide the final answer on this subject. It is noted that some of these topics were also discussed at the workshop reported in Chapter 7.

- Although it is acknowledged that an increased vulnerability may not only become manifest at lower doses or concentrations but also within a shorter period of exposure, it is recognized that the present risk assessment methodologies and frameworks with their data requirements are not equipped for addressing the latter possibility.
- In the abovementioned definition the vulnerable group is compared with the population as a whole. However, the vulnerable group is basically part of the population as a whole. When the susceptible population encloses a large fraction of the population as a whole it will be more appropriate to compare this subpopulation with the remaining part of the population. An example is, for instance, when gender is the determinant for a higher susceptibility; men should be compared with women instead of the population as a whole of which they are part of.
- Vulnerable or susceptible groups should share a common factor by which they can clearly be discerned from the remaining population, although it is recognized that this will be difficult in practice for instance in case of genetic polymorphism. This means that, as a general rule, the most susceptible fraction of the population as a whole (e.g. the most susceptible 5%) will not be regarded as a vulnerable group in itself, unless they share a common distinguishable feature.
- Since the vulnerable group is part of the population as a whole, the performance of a separate risk assessment may be subject of discussion only when the higher susceptibility of the vulnerable group will not be protected by application of the default intraspecies assessment factor. It is a point of consideration whether it really is a matter of “higher

susceptibility” (i.e. outside the range of the “normal human variability”) or that it still should be regarded to be within the normal variation of the population as a whole. It is noted that it might be difficult to identify the shape of the dose-response curve for the human population. Most often the dose-response curve is assumed to be lognormal although sometimes it might be more appropriate to assume a dichotomous distribution (e.g. in case of genetic polymorphism).

- The default intraspecies assessment factor is meant to account for some (if not all) variability in the human population caused by at least some of the abovementioned factors addressed in a SSC report (SSC, 2003a) like gender, age and illness. Therefore it should be determined if it is likely that the default factor is not sufficient to protect the regarding subpopulation, i.e. that additional measures have to be taken. The risk assessor should then be aware of the following, second point of consideration: often the intraspecies factor is applied to account for the differences in susceptibility between the average and the susceptible human being. Assuming that human susceptibility follows a lognormal distribution the default factor is not meant to be equal to the total potential human variability, but to its square root. This means that a default intraspecies factor of 10 accounts for a (10x10=) 100-fold human variability, for the “distance” between the average and the most susceptible human being (which is meant to be covered by the default assessment factor) is similar to the “distance” between the average and the least susceptible human being (assuming a lognormal distribution). Some argue that the starting point for the application of the intraspecies assessment factor to derive for instance an acceptable daily intake (ADI) is in the lower end of the human dose response curve (Dourson *et al.*, 2002) in which case a 10-fold factor is considered even to cover between 100 and 1000-fold human variability.
For practical reasons, in the present project the intraspecies assessment factor is considered to account for the differences in susceptibility between the average and the most susceptible human being. This means that the point of departure is the average human being and assumes that the total variability in the human population will be the square of the default assessment factor (i.e. 100 in case of a default intraspecies assessment factor of 10).
- A special case occurs when the risk assessment can be based on appropriate (toxicological) data on the vulnerable subpopulation. The use of a default intraspecies assessment factor of 10 can then be considered as rather conservative for it can be argued that the inter-individual variability in the target subpopulation will be (considerably) smaller than that for the population as a whole (unless available data indicate otherwise) and thus a smaller than the default intraspecies assessment factor might be warranted. This may, for instance, be the case when risk assessment is based on relevant data on teratogenicity or developmental toxicity in case of the unborn or young infant as target population or when toxicity data obtained with female rats are used as point of departure when women are considered to be the more susceptible target population.

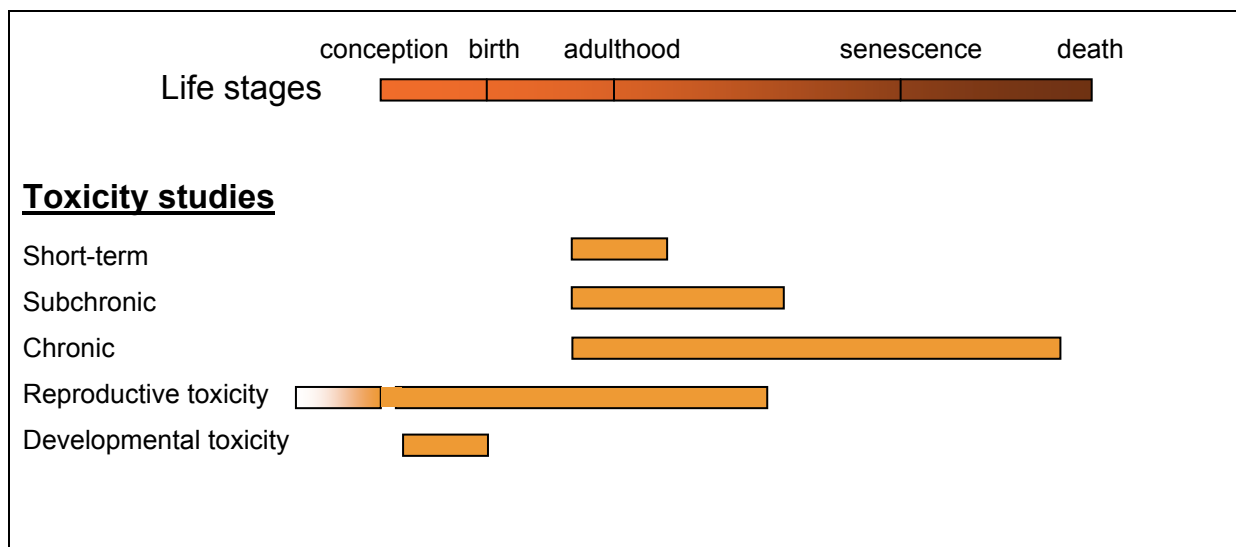
3. INVENTORY OF THE TREATMENT OF VULNERABLE GROUPS UNDER EXISTING RISK ASSESSMENT REGIMES

3.1 Preliminary remarks

Generally spoken, risk assessment is based on data regarding a variety of relevant physical, chemical and (eco-)toxicological properties of a compound.

A complete toxicological data set^A for the assessment of human health risks based on OECD (or similar) guidelines, includes among others, studies for reproductive toxicity, developmental toxicity and sensitization (see figure 1). Therefore, when risk assessment is performed on the basis of such a data set, it can be considered that groups that are vulnerable with respect to reproduction, development or to immunological sensitization are implicitly included in the risk assessment. A complete toxicological data set covers the total life span of an organism (figure 1). This means that for instance, the unborn and neonates are addressed by these studies. It is noted that sensitization is only assessed qualitatively.

Figure 1: Life-stages covered by specific toxicology studies



Therefore, it is often considered that a complete toxicological data set, and the use of intra- and interspecies assessment factor (usually for both: factor 10) is adequate to protect the human population, including subpopulations that potentially are vulnerable because of age (young, old) and sex (males/ females, women of child bearing age). In the present report the focus will be on the intraspecies factor.

In the following, the respective data requirements for each risk assessment regime are described. The respective guidelines and guidance documents on risk assessment and the aspects concerning vulnerable groups will be briefly outlined for the various regimes.

^A A complete toxicological data set consists of the type of studies as listed in figure 1 and acute toxicity studies including, among others, a sensitisation study.

3.2 Inventory of data requirements relevant for treatment of vulnerable groups in current EU risk assessment

3.2.1 Risk Assessment of Plant Protection Products

The risk assessment of pesticides is regulated by EU Directive 91/414/EEC concerning the placing of plant protection products on the market. All related activities are coordinated by the European Food Safety Agency (EFSA).

In Directive 91/414/EEC, the data requirements for both pesticides with a chemical compound as active substance, as well as pesticides which consists of micro-organisms, including viruses, are laid down. Then the Directives 2005/25/EC and 2001/36/EC were adopted as amendments to Directive 91/414/EEC.

For active substances (chemicals), a complete toxicological data package (as defined in chapter 3.1.) including skin sensitization, reproduction and developmental toxicity studies, is required.

In case the active substance is a micro-organism, the Directive describes a tiered approach: Tier 1 requests the available human data (medical data, reports of occupational health surveillance programmes, information on the sensitization and allergenic response of workers, including workers in manufacturing plants, agricultural and research workers and others exposed to the micro-organism, reports from public literature on the micro-organism or closely related members of the taxonomic group) as basic information. Sensitization studies^B are, next to studies on acute toxicity, pathogenicity and infectiveness, genotoxicity testing and short-term toxicity defined as basic studies of Tier I. In certain cases, it can be necessary to carry out supplementary studies to further clarify potential adverse effects on human (Tier II). For example, if results from earlier studies indicate that the microorganism may cause long-term health effects, studies on chronic toxicity, pathogenicity and infectiveness, carcinogenicity and reproductive toxicity must be carried out and in case a toxin is produced, kinetic studies must be performed. Furthermore, *in vivo* studies in somatic cells, possibly followed by *in vivo* studies in germ cells may be justified.

The plant protection product (formulation) which is intended to be authorized also has to be tested: in case that the active substance is a chemical substance, acute toxicity tests also have to be carried out, including skin sensitization tests. In case the active substance is a micro-organism, the test is not requested as a basic requirement, but only in case formulat(s) are suspected to have sensitizing properties.

The overall evaluation of the obtained toxicity data is only briefly described in Directive 91/414/EEC. The subject of identification, consideration and special treatment of vulnerable groups is not addressed.

For the performance of the risk assessment, guidance documents exists for both the worker (DG SANCO, 2001) and the general population (FAO, 1997). No remark is made whether data indicating a potential risk for vulnerable groups have to be considered especially and

^B Since available methods for testing dermal sensitisation are not suitable for testing micro-organisms, all micro-organisms should be regarded as potential sensitizers. This approach also takes into consideration immunocompromised or other sensitive individuals in the population (e.g. pregnant women, new-born children or elderly). As a consequence of the absence of proper test methods all micro-organisms will be labelled as potential sensitizers, unless the applicant wants to demonstrate the nonsensitizing potential by submitting data.

separately. The only step in this procedure considering differences within the general population is the application of an assessment factor for intraspecies differences^C. Within risk assessment on EU level, for both the consumer (general population) and the worker, a factor 10 is applied for the intraspecies differences due to the heterogeneous character of the population which is assumed to result in differences in sensitivity^D.

EC Regulation No. 396/2005 is amending Council Directive 91/414/EEC regarding maximum residue levels of pesticides in or on food and feed of plant and animal origin. The “maximum residue level” (MRL) is here defined as the upper legal level of a concentration for a pesticide residue in or on food or feed set in accordance with this Regulation, based on good agricultural practice and considering safe consumer intake with a view to protect vulnerable groups such as children and the unborn.

3.2.2 Risk Assessment of Biocidal Products

Biocidal products are any chemicals and/or micro-organisms intended to control unwanted organisms, such as animals, insects, bacteria, viruses and fungi. Medicines and products used to kill weeds or protect plants from pests are excluded categories and are regulated separately. The placing of biocidal products on the market is regulated by the Biocidal Products Directive 98/8/EC (BPD).

The European Chemical Bureau (ECB) is focal point for data and the assessment procedure on biocides and provides the related scientific and technical support for the conception, development, implementation and monitoring of EU policies..

The common core data set comprises the complete set of toxicity data (as defined in chapter 2.1.) For active organisms (fungi, micro-organisms, viruses) next to the complete data set as defined above, neurotoxicity^E and immunotoxicity (e.g. allergenicity) have to be addressed as well.

For the formulated biocidal product, data on acute toxicity, including skin sensitization, have to be submitted.

Vulnerable groups as such are not addressed in Directive 98/8/EC. However, supporting guidance documents are available, which elaborate more on various aspects of the risk assessment. The Technical Guidance Documents (EC, 2003) on Risk Assessment of biocides, new and existing industrial chemicals (TGDs) and the Guidance on Human Exposure Assessment are the basis for the human risk assessment. The latter does only comprise exposure-related items, (e.g. behaviour-related differences in exposure patterns for children), which are not relevant for vulnerable groups as defined here and have therefore not further been considered.

^C Various other assessment factors (also called uncertainty factors) might be applied as well (e.g. for both interspecies differences, for the duration of exposure etc.). However they are not further discussed here, since they are not of importance for the purpose of evaluation of treatment of vulnerable groups.

^D In the guidance document it is mentioned that the question of whether or not operators/workers, being a "selected" group, can be considered to be homogeneous and/or less susceptible in comparison to the general population. This is not resolved and the precautionary approach is followed unless a convincing scientific base allows a deviation from the default factor.

^E Additionally, neurotoxicity studies are requested in case the active substance is an organophosphorus compound or if there are any other indications that the active substance may have neurotoxic properties.

The Technical Guidance Document on Risk Assessment for biocides, new and existing industrial chemicals

In the TGD on Risk Assessment (part I) several aspects regarding vulnerable groups are addressed:

- For occupational exposure assessment, women (e.g. for some reprotoxic effects) or workers with specific vulnerability to certain types of effects (e.g. asthmatics) are mentioned as potentially (not-exposure related) vulnerable groups. The potential differences in risks for vulnerable groups or non-vulnerable groups should be discussed.
- For certain types of effects (developmental toxicity, respiratory sensitization) particular attention should be given to the magnitude of the “margin of safety” which may be necessary for the protection of sensitive sub-populations (pregnant women, individuals with high bronchial reactivity).
- For the consumer it is considered that some groups may be more vulnerable than the average population (here neonates, persons in poor health, the elderly, or consumers with specific vulnerability to certain types of effects, e.g. asthmatics are mentioned as example). The potential difference in risks between more vulnerable groups and the general population needs to be discussed.
- For effect assessment it is stated that data on toxicokinetics may also enable to evaluate inter-individual differences in order to take sensitive sub-populations into account in the risk assessment. It is mentioned that the application of enzyme inhibition in metabolism studies enables the identification of subpopulations which are susceptible due to the occurrence of functionally relevant genetic polymorphisms. Furthermore it is mentioned that the knowledge of the main route(s) of excretion will enable the identification of susceptible subpopulations such as subjects with impaired renal and/or liver function, e.g. the elderly.

Even though all these considerations were made in the TGD, neither conclusions were drawn nor recommendations were made how to identify and how to assess the risk for vulnerable groups; in this respect it is noted that also the item of assessment factors for interspecies differences is not elaborated in the current version of the TGD. Therefore this is still subject to a (national) case-by-case approach of the respective competent authorities.

3.2.3 Risk Assessment of Existing Industrial Chemicals

The risk assessment of chemical substances notified before September 18, 1981 (so-called “Existing Chemicals”) is based on data submitted by the respective notifier in accordance with Directive 67/548/EEC.

Risk assessment reports for existing industrial chemicals have to be carried out in accordance with Council Regulation (EEC) 793/93, which provides a systematic framework for the evaluation of the risks to human health and the environment of these substances.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94, which is supported by the Technical Guidance Document (TGD) published by the European Chemicals Bureau (ECB).

Since the relevant TGD on human risk assessment for existing substances is also used for the regulation for new chemicals and biocidal products, the respective remarks regarding the consideration of vulnerable groups in the TGD made under 3.2.2 apply also here.

3.2.4 Risk Assessment of New Industrial Chemicals

The risk assessment of chemical substances notified after September 18, 1981 (so called “New Chemicals”) is based on data submitted by the notifiers in accordance with Directive 67/548/EEC. This Directive lays down a scheme of data requirements, in which the extent of requested tests depend on the amount of production of the chemical in and/or import into the EU per year (tonnage per year, tpa).

All new chemical substances, manufactured in or imported into the EU at tonnage levels $\geq 10\text{kg}$, have to be notified. The notification has to allow the assessment of potential occupational/consumer risks and environmental impact.

For different human populations (e.g., workers, consumers and humans liable to exposure indirectly via the environment) a risk characterisation has to be performed. Dependent on substance-specific data it may be possible to take into consideration certain vulnerable sub-populations (e.g. children (the very young), pregnant women, the elderly, the sick, individuals with high bronchial reactivity).

Legal principles of risk assessment of new chemical substances are laid down in Directive 93/67/EEC. Detailed guidance, in relation to both human health and environment risk assessment is given in the Technical Guidance Documents (TGDs) published by the European Chemicals Bureau (ECB).

Since the relevant TGD on human risk assessment for new substances are also used for the Regulation for existing chemicals and biocidal products, the respective remarks regarding the consideration of vulnerable groups made under 3.2.2 apply also here.

3.2.5. REACH

The REACH^F approach for new and existing chemicals is intended to come into force in 2007/2008. The currently valid REACH Regulation has been agreed upon by the Competitiveness Council at its meeting on 13 December 2005 (doc.15921/05).

The Regulation is based on the principle that manufacturers, importers and downstream users have to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment.

Data requirements depend on the tonnage level at which the chemical is manufactured or exported per year within Europe. Data on sensitization have always to be submitted. Reprotoxicity and toxicokinetics have to be addressed at tonnage levels of $\geq 10\text{tpa}$.

Technical Guidance Documents are also under development. Based on the state of the decision process so far (March 2006) it seems most likely that the new version of the TGDs will not become available before the end of 2007 (see also 3.3 for an overview on the recent developments regarding REACH).

^F Registration (Schedule of substance priorities based on tonnage from 1t per year)
Evaluation (Technical Dossier from 10 tpa otherwise Chemical Safety Report
Authorisation (Persistence, Bioaccumulation & Toxicity - PBT(CMR) selection mechanism) of
Chemicals

3.2.6 Risk Assessment of Food Additives

Food additives, as regulated in Directive 89/107/EEC, are substances added intentionally to foodstuffs to perform certain technological functions, for example to colour, to sweeten or to preserve. Authorization of food additives is given by the European Commission in which the EFSA is responsible for the safety evaluation.

Directive 89/107/EEC is supported by a guidance document of the Scientific Committee on Food (SCF, 2001).

The required toxicological core data set comprises next to subchronic toxicity, genotoxicity, chronic toxicity and carcinogenicity also studies on reproduction and developmental toxicity. Acute toxicity and irritation/sensitization studies are not required but should be submitted when available. On a case-by-case basis immunotoxicity, allergenicity, intolerance reactions, neurotoxicity, human volunteer studies, and predictive mechanistic studies should be taken into account.

Furthermore, a remark is made in the guidance document with respect to additives used for infant formulae. Here it is stated that, since standard toxicity testing protocols do not adequately model artificial feeding in the neonatal phase, special strategies have been developed on the applicability of the ADI for food additives to infants. In order to adequately model the human exposure situation it may be necessary to perform a study in which the test substance is administered orally, directly to the offspring, from birth through to weaning. Postnatal survival, growth development, function and behaviour of the offspring should be examined.

3.2.7 Risk Assessment of Feed Additives

Feed additives, as regulated in Regulation (EC) 1831/2003, are products used in animal nutrition for purposes of improving the quality of feed and the quality of food from animal origin, or to improve the animals performance and health. Authorization of feed additives is given by the European Commission in which the EFSA is responsible for the safety evaluation. Although new guidelines are under development, the currently applicable guidelines for the assessment of additives in animal nutrition are given in Directive 2001/79/EC.

Beside a complete set of toxicological data for the target species, a safety evaluation for the human consumer (consumers who ingest food products obtained from animals having received the additive) and a worker safety assessment are required.

It is stated that the studies necessary for the evaluation of risks to human health will depend essentially on the nature of the additive and the circumstances of its use. However, acute toxicity studies, genotoxicity studies, subchronic (90-day) oral toxicity studies, and reproduction toxicity studies including teratogenicity studies are required. Metabolism and disposition studies should be conducted and the bioavailability of residues should be determined. Other specific toxicological and pharmacological studies should be conducted if there is any reason for concern. Furthermore, skin sensitization (allergenic potential) should be assessed for the worker safety assessment and inhalation studies should be performed if the product is likely to form a respirable dust or mist. When available, human data should be taken into account in the safety evaluation. With all the available information a NOEL should be identified for the calculation of the ADI. In the safety evaluation for human consumers it is

customary to employ a safety factor of at least 100 (10x10) to calculate the ADI, unless respective supporting data on the active substance are available for human. No attention is paid to vulnerable groups in the safety evaluation for human consumers.

3.2.8 Risk Assessment of Food Contact Materials

All food contact materials (FCM) are regulated by the framework Regulation (EC) No 1935/2004. In respect to food safety article 3 of that Regulation is relevant. This article requires that FCM shall not transfer their constituent to food in quantities that could endanger human health. Specific measures may be adopted for specific materials and articles. The EU has adopted specific measures for plastic materials (Directive 2002/72/EC), regenerated cellulose (Directive 93/10/EEC) and ceramics (Directive 84/500/EEC). The specific directives contain a positive list with substances that may be used for the manufacture of a food contact material. In addition restrictions on the migration of each of the substances are mentioned. The restrictions are established on the basis of toxicological data, while taking into account a number of conventional assumptions on the exposure of the consumer to those substances. For a conventional exposure it is assumed that a person with a body weight of 60 kg consumes every day during its lifetime 1 kg of packaged food that is contaminated at the maximum allowed level with the substance of concern. In addition it is assumed that that 1kg food is in contact with 6 dm² of packaging material. This convention means that the exposure to a specified substance is related to the level of migration into 1 kg of food. Based on the migration level toxicological data are required. In case the migration is <0.05 mg/kg then three different mutagenicity test are required. If migration is between 0.05 and 5 mg/kg, an additional 90 days feeding study is needed and a demonstration for the absence of potential bioaccumulation in man. In case the migration exceeds 5 mg/kg then a full core set of toxicity data should be provided which include, in addition to the tests for lower migration levels, an ADME study, a long term toxicity/carcinogenicity study and a study on reproduction and developmental toxicity. Pending the outcome of the toxicological data a restriction is established for the allowable migration of a substance in food. The evaluation of migration and toxicity data is performed by the European Food Safety Authority (EFSA).

In general there are no specific measures for vulnerable groups. However in a number of cases, it recently appeared that babies and small children, due to their high ratio of food consumption to body weight and their one sided diet, may be exposed to chemicals at a level exceeding e.g. a TDI. In those cases the special measures are taken to reduce the exposure to this group of consumers. In case of substances with specific properties, e.g. estrogenic substances, special attention is given to vulnerable groups which in general are babies and infants

3.2.9 Risk Assessment of Novel Foods

Novel foods as defined in Regulation No. 258/97/EC (supported by Commission Recommendation 97/618/EC) are foods and food ingredients that have not been used for human consumption to a significant degree within the Community before May 15, 1997 and which fall under certain specified categories. Authorization of Novel Foods is given by the European Commission in which the national Competent Authorities are responsible for the scientific evaluation.

In case the novel food or novel food ingredient may have implications for the health of certain sections of the population, specific labelling requirements are necessary.

Regulation No. 258/97/EC is supported by Commission Recommendation 97/618/EC, a guidance document concerning the data requirements needed for a Novel Food to support its safety and nutritional evaluation. It is noted that both nutritional and toxicological aspects of the novel food have to be considered in order to establish a toxicological testing program. The potential exposure of particularly vulnerable population groups must be taken into account: the greater the predicted dietary exposure the more extensive the required toxicological testing program will have to be. The safety assessment of the novel food requires an extensive toxicological data package, including reproduction and teratogenicity studies, and studies on potential allergenicity (skin sensitization studies).

In the Regulation a remark is made that the information provided in the application will need to be assessed in the light of its role in the diet of the population at large and particular sub-groups. Attention should be paid to the particular physiological characteristics and metabolic requirements of groups such as infants, children, pregnant and lactating women, the elderly, and those with chronic diseases (e.g. diabetes mellitus and mal-absorption).

3.2.10 Risk Assessment of Genetically Modified Food and Feed

Genetically modified (GM) food and feed are regulated in the European Community under Regulation (EC) No 1829/2003. Authorization of GM Feed and Food is given by the European Commission in which the EFSA is responsible for the scientific evaluation.

Commission Regulation (EC) 641/2004 describes detailed rules for the implementation of Regulation (EC) 1829/2003. Furthermore, a guidance document for the risk assessment of genetically modified plants and derived food and feed is available (SPGMO, 2004).

GM food or feed will be authorized only when the applicant has adequately demonstrated safe use based on a detailed assessment on potential allergenicity of the newly expressed protein and/or of the whole GM plant or crop as described in the guidance document. Toxicological testing in the safety assessment of food/feed derived from GM plants must be considered on a case-by-case basis and will be determined by the outcome of the assessment of the differences identified between the GM product and its conventional counterpart, including available information on intended changes. Thus, the toxicological testing would not only include studies on newly expressed proteins but also the consequences of any genetic modification. The core set of studies includes information on metabolism/toxicokinetics, sub-chronic toxicity, genotoxicity, chronic toxicity/carcinogenicity and reproduction and developmental toxicity.

With regard to vulnerable groups, only a remark is made in the labelling section of Regulation 1829/2003/EC. Respective labelling has to occur in case a food containing or consisting of Genetically Modified Organisms (GMO's) or food produced from or containing ingredients produced from GMO's is different from its conventional counterpart regarding implications for the health of certain sections of the population (these 'certain sections of the population' is not further specified in the regulation).

3.2.11 Risk Assessment of Human Medicines

Risk assessment of human medicines in the EU under Directive 2001/83/EEC occurs under the responsibility of the Committee for Medicinal Products for Human Use (CHMP, an EMEA committee).

The CHMP addresses specific groups by default; not in the toxicological phase, but in the clinical developmental phase. Determination of specific vulnerable groups to be addressed is based on the intended use and the target population for the drug in question.

A number of guidelines and notes for guidance addresses the evaluation of human medicines with respect to specific vulnerable groups, i.e. children (EC, 2004), patients with impaired hepatic function (CHMP, 2005a), patients with impaired renal function (CHMP, 2004), geriatric patients (CPMP, 1993a), patients of a reproductive age (CPMP, 1993b), males of a reproductive age (CPMP, 1995) and patients for which there is immunotoxic concern (CPMP, 2005). In addition there are guidelines for the clinical investigation of medicinal products in the paediatric population (CPMP, 2001) and on how to deal with cultural and ethnic factors in evaluating the acceptability of foreign clinical data (CPMP, 1998).

At present a juvenile animal toxicity study is not required by default, but the absence should be justified, e.g., by explaining that a medicine will not be used in children.

A guideline on testing in juvenile animals is in preparation (see 3.3).

3.2.12 Risk assessment of Veterinary Medicines

Risk assessment of veterinary medicines in the EU is regulated by Directive 2001/82/EEC and occurs under the responsibility of the Committee for Medicinal Products for Veterinary Use (CVMP, an EMEA committee).

The CVMP requires a complete toxicological data package for the evaluation of the health risk of a chemical for the user or consumer. If the risk evaluation is intended to set an ADI for a chemical, the complete toxicological data set, except for acute toxicity, irritation and sensitization studies, is required.

Besides the subpopulations addressed by the required toxicological data set, specific vulnerable groups are not addressed by default; the CVMP considers vulnerable groups on a case-by-case basis.

3.2.13 Risk Assessment of Consumer Products

The relevant legislation on consumer product safety is the General Product Safety Directive 2001/95/EC and the cosmetic products Directive 76/768/EEC. The General Product Safety Directive (GPSD) is aimed at ensuring that consumer products placed on the EU market are safe.

The Directive 2001/95/EC obliges producers to place only "safe" products on the market. Therefore, the responsibility of the risk assessment is implicitly in the hands of the producers. When the manufacturer is not based in the EU, this obligation applies to his representative in the EU or, in the absence of a representative, to the importer. The obligations on producers apply to manufacturers, but also to any professional in the supply chain who affect the safety characteristics of a product.

The Directive provides a generic definition of a safe product. In addition to the basic requirement to place only safe products on the market, producers must inform consumers of the risks associated with the products they supply. They must take measures to be informed of

risks posed by the products which they supply and take the appropriate measures to prevent such risks. Finally, they must be able to trace dangerous products.

In Annex 2 of the guidance document (EC, 2004b) two types of vulnerable groups are mentioned: Very vulnerable group (blind, severely disabled, very old, and very young (<3 years)) and vulnerable group (partially sighted, partially disabled, elderly, young (3-11 years)). This categorization is based on risks when using a product (due to behaviour), not on dose-response aspects.

The cosmetic products Directive 76/768/EEC obliges that a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking account, in particular, of the product's presentation, its labelling, any instructions for its use and disposal as well as any other indication or information provided by the manufacturer or his authorized agent or by any other person responsible for placing the product on the Community market.

Member States shall take all necessary measures to ensure that only cosmetic products which conform to the provisions of the Cosmetics Directive may be put on the market. This excludes a number of substances listed on Annexes, and excludes colouring agents, preservatives and UV filters that are not listed on separate Annexes (and are not assessed by SCCP or considered not safe by SCCP).

The use in cosmetic products of substances classified as carcinogenic, mutagenic or toxic for reproduction, of category 1, 2 and 3 are prohibited. A substance classified in category 3 may be used in cosmetics if the substance has been evaluated by the SCCP and found acceptable for use in cosmetic products.

The assessment of the safety for human health of the finished product has to take into account the specific exposure characteristics of the areas on which the product will be applied or of the population for which it is intended. There shall be a specific assessment for cosmetic products intended for use on children under the age of three and for cosmetic products intended exclusively for use in external intimate hygiene.

In table 1 the relevant information regarding the treatment of vulnerable groups in the different risk assessment regimes is summarized.

Table 1: Treatment of human vulnerable groups in the various EU risk assessment regimes - Summary

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
<p>Pesticides 91/414/EEC chemical active substance</p> <p>Regulation 396/2005 (MRL)</p> <p>Guidance documents on AOEL and ADI</p>	<p>Yes, for active substance data set as defined in figure 1, covering the total life span of an organism)</p> <p>For the plant protection product only acute toxicity testing, including skin sensitization, are required.</p> <p>Not addressed in this regulation refers to 91/414/EEC</p>	<p>No</p> <p>not addressed in this Regulation refers to 91/414/EEC</p>	<p>No</p> <p>No</p> <p>Yes: young, old, pregnant, ill and genetically susceptible people (YOGPI)</p>	<p>No</p> <p>No</p> <p>No</p>
<p>Pesticides Microorganism (including viruses) as active substance Directives 91/414/EEC and 2005/25/EC and 2001/36/EC</p>	<p>No - Tiered approach: Tier I a): basic information (available medical data, data from health surveillance programs, open literature etc.) Tier I b): basic studies, among other sensitization Tier II in case of indication of long-term effects, among others reprotoxicity studies</p> <p>For the plant protection product itself acute toxicity testing is requested, including skin sensitization testing in case the formulants are</p>	<p>defined as basic information of Tier I (have to be submitted in case they are available)</p>	<p>No</p>	<p>No</p>

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
	suspected, to have sensitizing properties.			
Biocidal products 98/8/EC	Yes (Data set as defined in figure 1, covering the total life span of an organism)	No	No	See also TGD
New industrial substances 67/548/EEC 93/67/EEC	Data requirement depends on the tonnage level per year <ul style="list-style-type: none"> ▪ ≥ 1 tpa: 'base set'^G is required ▪ $0.1 - \leq 1$ tpa: ▪ $0.01 - \leq 0.1$ tpa: only acute oral toxicity Dependent on specific reasons/indications (known toxicokinetic and toxicological properties, SAR, possibility of human exposure) additional information may be required.	No	No	See also TGD
Existing industrial substances 67/548/EEC Regulation (EEC) 793/93	'base set' ⁴ data must be submitted Dependent on specific	No	No	See also TGD

^G The 'base set' consists of:

- Acute toxicity: oral, inhalation and/or dermal (2 studies, depending on route of exposure)
- skin irritation
- eye irritation
- skin sensitization
- sub-acute toxicity: oral, inhalation and/or dermal
- mutagenicity: bacterial(Ames test) and non-bacterial (e.g. chromosome aberration study)

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
	reasons/indications (known toxicokinetic and toxicological properties, SAR, possibility of human exposure) additional information may be required.			
Technical Guidance Document (TGD) for biocidal products, new and existing Industrial Chemicals (ECB)	See respective entries of the directives on biocidal products, new and existing industrial chemicals	See respective entries of the directives on biocidal products, new and existing industrial chemicals	Yes (see remarks)	Within worker population: “women (e.g. for some reprotoxic effects) or workers with specific vulnerability to certain types of effects, e.g. asthmatics” consumer population: “e.g. neonates, persons in poor health, the elderly, or consumers with specific vulnerability to certain types of effects, e.g. asthmatics”
REACH Regulation document no 15921/05 (19-12-2005)	Data set required depends on the tonnage level per year: * 1 – <10 tpa (manufactured or exported): Skin irritation, skin corrosion, eye irritation, skin sensitization, mutagenicity, acute toxicity * 10 – <100 tpa additionally: short-term repeated dose, sub-chronic toxicity study, data on reproductive toxicity, toxicokinetics * ≥ 100 tpa additionally: Pre-natal developmental toxicity study, two-generation reproductive toxicity study	Before new tests are carried out to determine the properties listed in this Annex, including historical human data have to be assessed first.	Guidance document(s) under development, still under discussion	Guidance document(s) under development, still under discussion

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
<p>Feed additives 2001/79/EC and Regulation 1831/2003</p>	<p>Yes Required: -acute toxicity (including skin sensitization) -genotoxicity including mutagenicity -subchronic (90-day)oral toxicity -chronic oral toxicity including carcinogenicity -reproduction toxicity including teratogenicity - metabolism and disposition -bioavailability of residues (note: mutagenicity, carcinogenicity and reproduction toxicity studies may only be dispensed with when the effects can reasonably be excluded). On a case-by-case basis: -acute inhalation toxicity</p>	<p>No</p>	<p>No</p>	<p>No</p>
<p>Food additives 89/107/EEC and Guidance document: SCF/CS/ADD/GEN/26 final (12/07/2001)</p>	<p>Yes Required: -subchronic toxicity, -genotoxicity, -chronic toxicity/carcinogenicity, -reproduction and developmental toxicity Submitted when available: -acute toxicity -irritation/sensitization</p>	<p>on a case-by-case basis: human volunteer studies</p>	<p>Yes : Infants (infant formula) (specific test strategies)</p>	<p>No</p>

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
	<p>studies</p> <p>On a case-by-case basis:</p> <ul style="list-style-type: none"> -immunotoxicity -allergenicity -intolerance reactions -neurotoxicity -predictive mechanistic studies <p>Not required: skin – and eye irritation, skin sensitization</p>			
<p>Food contact materials</p> <p>Regulation (EC) no 1935/2004. Opinion of EFSA required. EFSA has established guidelines</p>	<p>Tiered approach depending on the migration level.</p> <p>Migration <math> < 0.05 \text{ mg/kg}</math>: 3 mutagenicity tests</p> <p>Migration 0.05 – 5 mg/kg: 3 mutagenicity tests, 90 days oral toxicity study, demonstration of the absence of potential accumulation in man</p> <p>Migration 5-60 mg/kg; 3 mutagenicity tests, 90 days oral toxicity study, study on adsorption, distribution, metabolism and excretion, Studie on reproduction and developmental toxicity, Study on long term toxicity/carcinogenicity</p>	No	<p>Yes :</p> <p>Case by case for babies and infants</p>	No
<p>Novel food</p> <p>Regulation 258/97/EC and</p>	<p>No</p> <p>(depending on substantial</p>	<p>nutritional assessment in human subjects - relevant to</p>	<p>-potential allergenicity should</p>	No

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
Commission Recommendation 97/618/EC	equivalence, on a case-by-case basis, tiered approach) (must consider toxicity studies in vitro and in vivo including mutagenicity studies, reproduction and teratogenicity studies as well as long term feeding studies, and studies on potential allergenicity)	the anticipated consumer groups.	always be considered -anticipated consumer groups (infants, children, pregnant and lactating women, the elderly, and those with chronic diseases)	
GMO in food and feed Regulations 1829/2003/EC and 641/2004/EC	No (on a case-by-case basis; different toxicological approaches for the assessment of newly expressed proteins, new constituents other than proteins, and possible changes in the level of natural constituents)	No	-potential allergenicity (see remarks)	GM food: Labeling 'implications for the health of certain sections of the population' should be mentioned ('certain sections of the population' is not further specified in the Regulation).
Human medicines Directive 2001/83/EEC	No	Yes (see remarks)	Yes (see remarks)	Specific groups are addressed by default; not in the toxicological phase, but in the clinical developmental phase. Determination of specific vulnerable groups to be addressed is based on the intended use and the target population for the drug in question. Identified vulnerable groups: <ul style="list-style-type: none"> • Children, • Patients with impaired hepatic function • Patients with impaired renal function

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
				<ul style="list-style-type: none"> • Geriatric patients • Patient of a reproductive age • Males of a reproductive age • Patients with immunotoxic concern • Ethnic factors
Veterinary medicines Directive 2001/82/EEC	Yes (see remarks)	No	No	If risk assessment is intended to set an ADI, studies on acute toxicity, irritation and sensitization are not required.
Consumer products General Product Safety Directive 2001/95/EC	No	No	Yes	<p>Vulnerability classification based on risks when using a product, due to behaviour (not in accordance with the current definition of “vulnerable groups” as described under 2.)</p> <ul style="list-style-type: none"> • Very vulnerable: blind, severely disabled, very old, very young (< 3years) • Vulnerable: partially sighted, partially disabled, elderly, young (3-11 years)

3.3 Developments in the recent 5 years

So far it can be stated that in most of the risk assessment regimes (e.g. biocides, pesticides, new and existing industrial chemicals) no proposals were made regarding the modification of the treatment of vulnerable groups.

However, within the ongoing activities regarding the implementation and elaboration of REACH, more detailed guidance on hazard identification and risk assessment is under discussion. A new guidance document is under development which will most likely become implemented under the REACH Regulation.

In this new TGD vulnerable groups are addressed in more detail than before. The following is stated: “It is recognised that in order to always cover the most sensitive person exposed to any chemical would require a very high default assessment factor. That is of course not workable and it is usually assumed that a default assessment factor of 10 is sufficient to protect the larger part of the population, including e.g. children and the elderly. This factor is also suggested in this guidance when assessing exposure to the general population. It is recognised that there are differences between children and adults in toxicokinetics (especially babies in their first months) and toxicodynamics (especially at different stages of development). These differences may render children more or less susceptible to the toxic effects of a substance. A higher intraspecies extrapolation factor for children from 10 to 100 should be considered when the following three criteria are fulfilled:

- One or more exposure scenarios point to specific exposure of very young children,
- There are indications or suspicions, obtained from, for example, experiments in adult animals, epidemiological studies, *in vitro* experiments and/or SARs (Structure Activity Relationships), of effects on organ systems and functions that are especially vulnerable under development and maturation in early life (in particular the nervous, reproductive, endocrine and immune systems and also the metabolic pathways), and
- Experimental data on such effects in young animals are not available.

Alternatively, further testing in young animals may be appropriate.

For workers, a default assessment factor of 5 is recommended. This is because it can be expected that the workforce does not include the more vulnerable humans (e.g. the very young, the sick, the elderly); workplace exposure levels and/or patterns of exposure can be controlled and populations or individuals potentially exposed in a workplace can be specifically protected and/or monitored. However, for certain types of effects (developmental toxicity, respiratory sensitization) particular attention should be given to the magnitude of the “margin of safety” which may be necessary for the protection of sensitive sub-populations (pregnant women, individuals with high bronchial reactivity). Relevant substance-specific information on intraspecies variations should always be used to adjust or substitute the default factors. Here it is referred to for instance the Guidance document for the use of data in development of chemical-specific adjustment factors (CSAFs) for interspecies differences and human variability in dose/concentration-response assessment (IPCS, 2001).

Further, a guideline on testing in juvenile animals is in the process of development within the framework of risk assessment of Human Medicines. Developmental neurotoxicity and immunotoxicity are specific paragraphs in this non-clinical guideline.

The discussion on juvenile toxicity is in the stage of implementation, as is the writing of regulations on pharmaceuticals for children. Implementation is expected in 2006.

The major gap that is identified is the lack of data on vulnerable groups. The EMEA/CHMP has noticed that the follow-up of the use of pharmaceuticals during pregnancy is lacking. In fact each treatment of a pregnant woman with a pharmaceutical drug is an N=1 clinical trial, which in most cases is neither followed by a report, nor even documented. It is very important to enhance the documentation of the use of pharmaceuticals during pregnancy and the effects on mother and child afterwards. An ICH guideline has recently been developed for the post-authorisation evaluation of compounds which are used during pregnancy (CHMP, 2005b). This guideline was adopted by CHMP in November 2005, and is set to come into effect in May 2006. However, the guideline has yet to be implemented by the pharmaceutical industry.

3.4 Summary

Since the treatment of vulnerable groups as lay down in the respective directives, regulations and guidance documents are interdependent related with the risk assessment in the context of Scientific Committees, which is the subject of the next chapter, they will be summarized and evaluated together (see Chapter 4, section 4.3).

4. INVENTORY OF THE TREATMENT OF VULNERABLE GROUPS IN THE CONTEXT OF THE EU SCIENTIFIC COMMITTEES

4.1 Risk assessment in the context of Scientific Committees

4.1.1 Scientific Committee on Consumer Products (SCCP)

The SCCP, for the risk assessment of a chemical, always requires acute toxicity, irritation, sensitization, short-term/semichronic and genotoxicity studies. When considerable oral intake is expected or when the data on percutaneous absorption indicate considerable penetration of the ingredients through the skin, in addition toxicokinetic, reproductive and developmental studies may be required. Specific studies on phototoxicity are requested when a cosmetic product is expected or intended to be used on sunlight-exposed skin. For risk assessment a MOS/MOE approach is used. In general, a $MOS \geq 100$ is considered acceptable.

Specific subpopulations that might be at extra risk are not considered by default.

4.1.2 Scientific Committee on Health and Environmental Risks (SCHER)

The SCHER panel always requires a full toxicological data base for its toxicological evaluation and risk assessment.

Besides the subpopulations already addressed by the required toxicological data set, the SCHER panel does not address specific vulnerable groups in the toxicological evaluation by default.

4.1.3 Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR)

The scientific area covered by SCENIHR is rather broad. For SCENIHR there are no specific relevant EU-directives that regulate the program and items discussed in the Committee. As also the area of medical devices is covered by SCENIHR the medical device directive may be applicable. In addition, ISO 10993 series describing safety evaluation of medical devices/biomaterials may be applicable. Most of these standards are derived from OECD guidelines and adapted for medical devices/biomaterials. For evaluation source materials the various OECD guidelines dealing with hazard identification and dose response effects may be used.

The SCENIHR does not address specific vulnerable groups in the safety evaluation.

4.2 Risk assessment in the context of EFSA panels

4.2.1 EFSA panel on additives and products or substances used in animal feed (FEEDAP)

The FEEDAP panel always requires a complete toxicological data base. Besides the subpopulations addressed by the required toxicological data set, the FEEDAP panel does not address specific vulnerable groups in the toxicological evaluation by default.

4.2.2 EFSA panel on Plant health, Plant protection products and their Residues (PPR)

The PPR comments on the monograph that has been drafted by the Rapporteur Member State. Therefore, in principle the PPR requires a complete toxicological data set, based on the requirements as defined in Directive 91/414/EEC. However, the applicant may submit a rationale for not providing certain data (a waiver). Specific vulnerable groups are not included in the risk assessment.

The PPR does not address specific vulnerable groups in the toxicological evaluation by default. In the risk assessment for the consumer, children are addressed separately from the general population. A separate children's diet is used. Furthermore, separate ARfD's may be derived for general population (including children) and women of childbearing age. It is noticed that this is not common practice yet in the EU, but it is under discussion.

4.2.3 EFSA panel on food additives, flavourings, processing aids and materials in contact with food (AFC)

The AFC panel uses different data requirement for food additives, flavourings and food contact materials. For risk assessment of food additives, a complete toxicological data package, except for acute toxicity, irritation and sensitization studies, is always required. If applicable / possible, an ADI is set for a food additive, which is generally based on the overall NOAEL from the toxicity studies and a default assessment factor of 100. If there are indications that within the human population there are subpopulations with overly increased susceptibility, this is taken into account.

For food contact materials (FCM) the data requirement depends on the level of (allowed) migration of the substance into food (Barlow, 1994). If no data are available, no migration of the FCM is allowed. If the substance does migrate, data on genotoxicity are required. A non-genotoxic food contact material may migrate up to 0.05 mg/kg food. For substances migrating between 0.05 and 5 mg/kg food it must be shown that there is no accumulative potential, and a 90-days oral toxicity and three mutagenicity tests are required. For substance migrating in excess of 5 mg/kg, up to 60 mg/kg food, the required tests include among others a 90-day oral study, 3 mutagenicity tests, a toxicokinetics study, a long-term toxicity/carcinogenicity study and studies on reproduction and teratogenicity. The overall limit of migration of a FCM is 60 mg/kg food. The migration limits for food contact materials are sometimes linked to TDIs.

Flavourings (chemically defined flavouring substances; CDFS) are classified according to the Cramer / Ford and Hall system (Cramer *et al.*, 1978). For each class a Threshold Of Concern has been developed (Munro *et al.*, 1996). For the risk assessment the class thresholds or substance-specific toxicity data are compared to exposure estimates. Inter-individual differences in susceptibility are not taken into account.

4.2.4 EFSA Panel on genetically modified organisms (GMO)

The types of toxicity tests that have to be performed for a GMO can be chosen on a case-by-case basis, depending on the outcomes of the comparative safety assessment. In this assessment, the differences between a genetically modified product and an appropriate conventional counterpart with a history of safe use are established. Based upon the differences thus identified, further testing may be decided for. Given the wide possible variation of modifications as well as host organisms, these decisions are made on a case-by-case basis.

For risk assessment of GMOs, the GMO panel requires only a test on acute allergenicity. Additional data can be requested when considered necessary.

For risk assessment of a transgenic protein, the highest dose that showed no effects in toxicity testing may be compared with the expected intake of that protein, as present in the diet of consumers, including humans and animals that will consume the genetically modified product. Usually, these margins are so large that specific subgroups need not being considered.

Allergy patients are specifically mentioned by the guidance document as a target group that needs being considered in the assessment of potential allergenicity of a genetically modified product. As described by the Codex guidelines on the assessment of potential allergenicity of products derived from genetically modified plants and micro-organisms, there are various developments in the field of allergenicity testing, such as animal models, which, however, have not yet been validated.

4.2.5 EFSA panel on dietetic products, nutrition and allergies (NDA)

The NDA panel mostly deals with food allergens and novel foods, for which there are no specific EU Directives. Risk assessment is performed on an ad hoc basis, prompted by specific questions. The predominant sources of information are human data. Animal toxicity studies (mostly semi-chronic) are used when other data indicate their need. For food allergens, by definition the vulnerable (sensitized) groups are the subject of concern.

4.2.6 EFSA panel on contaminants in the food chain (CONTAM)

Toxicological data are not formally required for a risk assessment of contaminants by the CONTAM panel, however without toxicological information on the endpoints considered relevant a reliable hazard assessment is not possible. Furthermore, epidemiological could be a helpful tool in the health risk assessment of contaminants.

When sufficient data are available, and the panel is requested to derive a health based guideline value (e.g. TDI or TWI) the NOAEL/LOAEL and assessment factor approach will be applied. In that case the magnitude of the assessment factor relies on the availability of effect data for the most susceptible part of the population. When for instance there are indications that developmental effects might be the most crucial ones, but the available data are too limited to base an assessment on, an additional assessment factor (10?) could be applied. If reliable effect data for the susceptible population are available (e.g. in the case of dioxins) no additional assessment factor is deemed necessary, because the assessment is based on the most sensitive endpoint.

When the panel is not satisfied with the available data usually a MoE approach will be applied. This is often the case in “actual risk” scenarios, in contrast to evaluations aiming at preventive risk assessment. For that type of assessments there does not exist a set of fixed MoE to indicate the health concerns, but the final conclusion on the health impact is based on a “case by case” assessment. In practice: the more serious the potential health effect is (e.g. carcinogenicity, teratogenicity) the higher the MoE need to reach the conclusion “no health concern”.

In both cases (preventive or actual risk assessment) usually a body burden approach to cover huge differences in kinetics between humans and experimental animals will be applied for persistent contaminants like PCBs and dioxins.

The CONTAM panel does not address specific vulnerable groups in the toxicological evaluation by default.

In table 2 the relevant information regarding the treatment of vulnerable groups in the different scientific committees and EFSA panels as given in chapter 4 is summarized

Table 2: Treatment of human vulnerable groups in risk assessment by the relevant European scientific committees and EFSA panels

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
CVMP	Yes (see remarks)	No	No	If risk assessment is intended to set an ADI, studies on acute toxicity, irritation and sensitization are not required.
CHMP	No	Yes (see remarks)	Yes (see remarks)	Specific groups addressed by default; not in the toxicological phase, but in the clinical developmental phase. Determination of specific vulnerable groups to be addressed is based on the intended use and the target population for the drug in question. Identified vulnerable groups: <ul style="list-style-type: none"> • Children, • Patients with impaired hepatic function • Patients with impaired renal function • Geriatric patients • Patient of a reproductive age • Males of a reproductive age • Patients with immunotoxic concern • Ethnic factors
GPSD	No	No	Yes	Vulnerability classification based on risks when using a product, due to behaviour <ul style="list-style-type: none"> • Very vulnerable: blind, severely disabled, very old, very young (< 3years) • Vulnerable: partially sighted, partially disabled, elderly, young (3-11 years)
SCCP	No (see remarks)	No	No	Studies on acute toxicity, irritation, sensitization, short-term/semi-chronic toxicity and genotoxicity are always required. Additional data may be requested when considered necessary. Studies on phototoxicity are requested for substances intended to be used

Framework/Directive	Complete toxicological data set required	Human data required	Specific vulnerable groups addressed	Remarks on risk assessment for vulnerable groups
				on sunlight-exposed skin
SCHER	Yes	No	No	-
SCENIHR	No	No	No	-
FEEDAP	Yes	No	No	-
PPR	Yes	No	No	-
AFC	see remarks	No	No	<u>Additives</u> : Complete toxicological data required except for acute toxicity, irritation and sensitization studies. <u>Flavourings</u> : The required toxicological data set depends on the class threshold. <u>Food Contact Materials</u> : Data requirements depend on the level of migration of the substance into food.
GMO	No	No	No	Toxicological data requirement assessed on a case-by-case basis
NDA	No	Yes (see remarks)	Yes (see remarks)	The predominant source of information are human data. For food allergens, by definition the sensitized groups are of concern.
CONTAM	No	No	No	No toxicological data are required. However, a reliable hazard identification is only possible when relevant data are available.

4.3 Summary - Chapters 3 and 4

From the inventory of data requirements in the context of EU risk assessment regimes, scientific committees and EFSA panels, it is clear that a number of scientific committees and panels by default take into account groups that are vulnerable with respect to reproduction and the development and immunological sensitivity when toxicity data addressing these effects are requested.

Although in a number of frameworks it is mentioned that vulnerable groups should be addressed neither adequate data are requested nor practical guidance is provided. In a limited number of cases specific vulnerable groups are taken into account in the risk assessment procedure. However, in none of the different legislations (with exception of the CHMP) and publications of scientific bodies of the Commission and of major competing economies of EU and international bodies any rationale was given for the respective approaches of vulnerable groups.

It is noticed however that in general the toxicological data set does not provide information on subpopulations that are vulnerable on the basis of, for instance, certain genetic differences, illness, poor nutritional status or life style. Furthermore, it should be realized that the toxicological profile will never be fully investigated. For instance, the risk of early exposure to a chemical, i.e. during the first 6 weeks of life, on the development of cancer is not covered by the present data requirements.

As summarised in Chapter 3.3 some discussion within the framework of the development of new guidelines and guidance documents is ongoing, whereby especially the Committee for Medicinal Products for Human (CHMP) pays attention to the subject of the consideration and treatment of vulnerable groups.

The conclusions drawn regarding the consideration of the various vulnerable groups in the various regulatory frameworks are elaborated in Chapter 8.

5. APPROACH OF MAJOR COMPETING ECONOMIES AND IN INTERNATIONAL BODIES REGARDING THE TREATMENT OF VULNERABLE GROUPS IN THE VARIOUS RISK REGIMES

An inventory was made of the differences and similarities between the EU and regulatory bodies in major competing economies in the treatment of vulnerable groups. The inventory focused on national organizations in the USA, Canada and Japan and major international organizations.

5.1 Method of information collection

The following actions were undertaken in order to identify and analyse the approaches of the major competing economies and international bodies regarding the treatment of vulnerable groups in the various risk regimes.

In order to obtain the required information, existing contacts within the international bodies were directly approached or the institutions were contacted via an e-mail request.

The main questions posed were:

- Do present risk assessment procedures account for specific vulnerable groups by default, and if so how? (For instance, by always requesting information that is relevant for a specific subpopulation or by the application of additional assessment factors, i.e. additional to the intraspecies extrapolation factor).
- Are there any developments (e.g. of specific strategies or methodologies) in this field addressing the risk assessment of (potential) vulnerable subpopulations?

In addition to this direct approach, the websites of a number of national and international agencies and institutions were searched, in particular for guidelines and publications with respect to risk assessment and vulnerable groups. In addition, through their search engines the websites were scanned for information by using (combinations of) search terms such as vulnerable, susceptible, sensitive, (sub)population, age, sex, children, elderly, risk assessment were used. However, since these searches often resulted in a large number of (more or less relevant) hits, evaluation of this information was only limited and focused on the most relevant information for this project.

The websites of the following organizations were searched for information:

US-EPA	US-FDA	US-DPR
US-ATSDR	TERA	Health Canada
CEPA	Japan PMSB	ICH
IPCS	IARC	

In this chapter the outcome of the search is described and conclusions are drawn.

5.2 Treatment of vulnerable groups in major competing economies and international bodies

This paragraph deals with the treatment of vulnerable groups in major competing economies and international bodies. The inventory demonstrated that there are major similarities in the treatment of sensitive groups in risk assessment of products between the EU and regulatory bodies in the major competing economies. The similarities will not be discussed in this paragraph, but will be addressed at the end of the chapter.

In this paragraph the treatment of vulnerable groups in major competing economies and international bodies is described, in particular with respect to the differences as compared to the EU.

5.2.1 National bodies in major competing economies

▪ *US Food and Drug Administration (FDA).*

The FDA participates in the ICH (see below) and, together with the EU CMHP, the Japanese PMSB and industry is involved in the development of ICH guidelines on, among others, the treatment of sensitive subpopulations in risk assessment of medicinal products. In this respect the treatment of vulnerable subpopulations by the US-FDA is in line with that of the EU CMHP.

As compared to the EU, no additional guidelines on the approach of sensitive subpopulations in the risk assessment were found on the FDA website.

▪ *US-Environmental Protection Agency (EPA)*

FQPA factor.

In the context of pesticide regulation under the Food Quality Protection Act (FQPA), the EPA has introduced an additional factor for protection of children. The FQPA factor is often seen as an additional factor to the extrapolation factors for inter- and intraspecies variability (for both factors the value is usually 10). However, the FQPA factor is considered a safety factor and not to be confused with the standard uncertainty factors EPA uses to develop reference doses (RfDs). However, after much study it is now recognized that the toxicology issues considered by the FQPA safety factor completely overlap with EPA's database uncertainty factor, and when this latter uncertainty factor is used to address database deficiencies, the FQPA safety factor is not needed (Dourson *et al.*, 2002; EPA, 2002; Fenner-Crisp, 2001).

Guidelines for carcinogen risk assessment

The US-EPA has developed new guidelines for carcinogen risk assessment (EPA 2005a), which explicitly call for consideration of possible sensitive subpopulations and/or life stages (such as childhood). For childhood risk a supplemental guidance for assessing susceptibility from early-life exposure to carcinogens has been developed (EPA, 2005b). These guidelines are to be used for all carcinogenic risk assessments that are newly

initiated, on a case-by-case base for assessments that currently are being performed or when an updates carcinogenicity risk assessment is being performed^H.

▪ **Health Canada**

A detailed search of the website of Health Canada revealed no additional information in the approach of sensitive groups in the risk assessment of products. Although Canada does not participate in the ICH, it has adopted the ICH guidelines on vulnerable groups (see paragraph on ICH) and thus endorses the principles and practices described therein. Specific guidelines and policies have been developed for consumer and cosmetic products (e.g. on the flammability of children's sleepwear). However, these guidelines address risks when using a product and do not specifically consider the sensitivity of sub-populations.

▪ **Canadian Environmental Protection Agency (CEPA).**

The CEPA also recognizes the existence of sensitive subpopulations (in particular children) for adverse effects of chemicals. In a recent publication (Krewski *et al.*, 2006) the issue of children's environmental health is addressed in detail. However, no marked differences in the treatment of sensitive groups were found.

▪ **Japan**

The search for information, either through the existing contacts or through the internet, on the approach of vulnerable groups in the risk assessment of products in regulatory bodies in Japan yielded no relevant information, except for the field of human medicines, as described below.

▪ **Japanese Pharmaceutical and Medical Safety Bureau (PMSB)**

The PMSB participates in the ICH (see below) and, together with the EU CMHP, the US-FDA and industry, is involved in the development of ICH guidelines on, among others, the treatment of sensitive subpopulations in risk assessment of medicinal products. In this respect the treatment of vulnerable subpopulations by the PMSB is in line with that of the EU CMHP.

5.2.2 International organizations

▪ **International Conference on Harmonisation (ICH)**

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

^H <http://www.epa.gov/osa/spc/pdfs/canguid1.pdf>

The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The ICH guidelines are submitted to the EU Committee for Proprietary Medicinal Products (CPMP), the Japanese Pharmaceutical and Medical Safety Bureau (PMSB) and the US Food and Drug Administration for endorsement and implementation. The guidelines are published by the European Commission^I the Japanese National Institute of Health and Science^J and the US-FDA^K.

With respect to vulnerable groups the ICH has developed guidelines for clinical investigation of medicinal products in the pediatric population^L, geriatric populations^M, ethnic factors in the acceptability of foreign clinical data^N, and on the need of post-authorisation data in case of exposure to medicinal products during pregnancy^O.

▪ **IPCS**

The International Programme on Chemical Safety (IPCS) is a joint programme of the International Labour Organization, the United Nations Environmental Programme (UNEP) and the World Health Organization implementing activities related to chemical safety. IPCS briefly addresses vulnerable groups in risk assessment in the Environmental Health Criteria (EHC) publication nr. 70 (EHC, 1987). Here it is recognized that age, nutritional status, and health status may affect the sensitivity to the toxic effects of a substance, but that in general ‘animal toxicity studies are performed with healthy animal populations that is in a state of over-nutrition in a protected environment’. Furthermore it is noted that certain aspects of toxicity of chemicals e.g. carcinogenicity receive much attention whereas other manifestations of toxicity such as cardiovascular lesions receive little attention, although it is (one of) the most common cause of fatalities.

However, in the document it is not concluded that the respective data, which are presently lacking in the standard toxicity data package, are required for the derivation of an ADI for substances in food additional studies.

The evaluation of the toxicity of pesticides and the setting of an ADI for pesticide residues in food, as described in the IPCS publication EHC nr. 104 ‘Principles for the toxicological assessment of pesticide residues in food’ (EHC, 1990) is also based on the standard toxicological data set and the use of (default) assessment factors.

In a recent monograph, ‘Principles for evaluating health risks in children associated with exposure to chemicals’ (EHC 237, in press), the scientific principles to be considered in assessing health risks in children from exposures to environmental chemicals during distinct developmental stages are evaluated. Furthermore, information for public health

^I <http://www.emea.eu.int>

^J <http://www.nihs.go.jp/dig/ich/ichindexe.htm>

^K CDER: <http://www.fda.gov/cder/guidance/index.htm>, CBER: <http://www.fda.gov/cber/guidelines.htm>

^L <http://www.ich.org/LOB/media/MEDIA487.pdf>

^M <http://www.ich.org/LOB/media/MEDIA483.pdf>

^N <http://www.ich.org/LOB/media/MEDIA481.pdf>

^O <http://www.emea.eu.int/pdfs/human/phvwp/31366605en.pdf>

officials, research and regulatory agencies, and other experts responsible for protecting children's health is provided.

The IPCS is currently running a project to update the principles and methods for the assessment of chemicals in food^P. In this project attention is paid, among others, to sensitive or susceptible populations. The reports and other information on the project will be published on a website as they come available. The final monographs that are developed will serve as a guide for good risk assessment practices of chemicals in food.

▪ **IARC**

IARC coordinates and conducts research on the causes of human cancer, the mechanisms of carcinogenesis, and develops scientific strategies for cancer control. The objective of the IARC Monographs programme on the evaluation of carcinogenic risk to humans is to prepare and publish critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The evaluations of IARC working groups are scientific, qualitative judgements about the evidence for or against carcinogenicity provided by the available data. Quantitative extrapolation from experimental data to the human situation is not undertaken.^Q Depending on the chemical under review, the monograph may provide data on specific types of cancer, e.g. breast cancer or childhood cancer. The monographs also provide information on other toxic effects of the chemical. However no risk assessment is performed. In the overall evaluation, the chemical, mixture or exposure circumstance is categorized in to 1 of 4 groups. No recommendation is given with regard to regulation or legislation.

▪ **Toxicology Excellence for Risk Assessment (TERA)**

Although strictly speaking TERA is not an international agency, TERA is well informed about the current risk assessment approaches and developments in this field in North America, and is itself involved in the development and improvement of the underlying methods for risk assessment. Recent publications by TERA elaborated on the use of uncertainty factors (Dourson *et al.*, 2002; Scheuplein *et al.*, 2002). Among others the publication underscored the fact that the intraspecies uncertainty factor of 10 actually covers off between 100 and 1000-fold human variability (see also Chapter 2).

5.3 Discussion and conclusion

The inventory demonstrated that there are major similarities in the treatment of sensitive groups in risk assessment of products between the EU and regulatory bodies in the major competing economies. As in the EU, in general there is no specific approach to the treatment of vulnerable groups in risk assessment. As a rule, most organizations seek appropriate information for specific vulnerable populations, on a case-by-case basis, and use this information to establish safe doses for the general population such as MRLs,

^P <http://www.who.int/ipcs/food/principles/en/index.html>

^Q Preamble to the "IARC Monographs programme on the evaluation of carcinogenic risk to humans".

RfDs, ADIs, or TDIs. When information on vulnerable populations is not available, in general an intraspecies extrapolation factor, which is mostly based on a general default factor of 10, is used to account for sensitive groups within the population.

With respect to specific vulnerable populations in risk assessment of products there is an extensive literature on this subject (see chapter 6), including from regulatory bodies in the EU and the major competing economies, but little in the way of specific guidance. Most information focuses on the difference between children, as a potentially susceptible subpopulation, and adults. In particular toxicokinetic differences between adults and children have been a subject of research. Much less is known about toxicodynamic differences between adults and children, aside from some discussion in the context of cancer assessment; see the EPA supplemental cancer guidance for assessing susceptibility from early-life exposure to carcinogens.

With regard to other sensitive populations, the general approach both inside and outside the EU, is to consider the effects of the chemical or other exposure and the mode of action, and identify potential vulnerable populations based on those considerations. However, it is rarely possible to quantify differences in susceptibility.

As was observed in chapter 3 for the European situation, most activities regarding vulnerable subpopulations occur in the field of medicinal products.

In conclusion, the present inventory demonstrates that there are major similarities in the treatment of vulnerable subpopulations between the various regimes within the EU and their counterparts in other countries and international organizations. In view of the various international collaborations, the exchange of information on risk assessment methods and the tendency to strive for international harmonization this may come as no surprise.

6. MAIN RECENT DEVELOPMENTS REGARDING THE TREATMENT OF VULNERABLE GROUPS

In order to elucidate the main recent developments regarding the treatment of vulnerable groups in risk assessment a search was performed in databases of public literature as well as of reports and publications of international organizations (e.g. the Dutch Health Council, RIVM, TNO, the German Federal Ministry of Health and Social Security, UK PSD, US EPA, TERA, Health Canada, ILSI etc.) on risk assessment and exposure assessment in relation to sensitive groups.

In this chapter the set-up and outcome of the search are described and conclusions are drawn.

6.1 Method of information collection

6.1.1 Information from public literature

A literature search was performed in PubMed including Toxline and Medline. The search covered the years 2001-2005 assuming that then the references on ongoing discussions are will be identified and relevant developments before this date will also be described and/or referred to. The (combinations of) the following search terms were used:

age	genetic	sex
children	gender	(sub)population
disease	polymorphism	susceptible
disorder	risk assessment	traits
dose-response-curve	risk factor	uncertainty
elderly	sensitive	vulnerable

The references found were first screened based on their abstracts. All references expected to be relevant were then evaluated in detail, starting from recent review articles and documents published by relevant research groups or by international organizations in order to identify the main developments followed by the more specialised publications on certain focal points.

6.1.2. Information of international bodies, institutes, organization not covered by the search in public literature

To obtain relevant documents published by international institutes, they were approached directly via already existing contacts or via the respective websites to obtain an overview on the activities and publications of the respective organizations/institutes in the field of risk assessment and exposure assessment in relation to vulnerable groups. In case the site-linked search engines were not advanced enough to perform the specific search on the described topic, the respective institutions were contacted via an e-mail request.

The following organizations/institutions were approached:

- World Health Organisation
- Food and Agricultural Organisation

-
- European Food Safety Authority
 - DG SANCO
 - TERA
 - UK PSD
 - German Federal Ministry of Health and Social Security
 - Umweltbundesamt (Germany)
 - BfR Federal institute for risk assessment (Germany)
 - BAuA Bundesanstalt fuer Arbeitsschutz und Arbeitsmedizin (Germany)
 - FoBiG Research and advisory institute for hazardous substances (Germany)
 - Dutch Health Council.

6.2 Results

Based on the selected references, the following main items related to the different parts of risk assessment of vulnerable groups can be identified:

Age-related vulnerability

- children as vulnerable group
- elderly as vulnerable group

Testing and related issues

- modification/adoption of testing strategies in order to include the special properties of vulnerable groups
- the possibilities of *in silico* methods
- perspective regarding the application of new technologies (genomic data/toxicogenomics)

Risk characterisation assessment in relation to vulnerability

- early life time exposure and cancer risk assessment

In the following it will be elaborated on the different subjects in more detail.

6.2.1. Vulnerable groups

Vulnerability can be affected by various factors, e.g. as mentioned in the SSC-report: age, gender, genetic traits, diseases/disorders, nutritional status, life style factors (SSC, 2003a). However, the ongoing discussions and current publications focus on age related items and here especially the subject of children as well as on elderly as vulnerable groups.

6.2.1.1. Children

Clearly the most attention is given to children as a vulnerable group. Various workshops were held and (review-)articles were published on this topic by relevant organizations

(e.g. RIVM/ATSDR, German and Danish governmental organizations/institutions, ILSI, EPA). The main catchphrase here is “children are no little adults”.

Due to the intense work in the last years (BgVV, 2001; Ginsberg *et al.*, 2004a; Ginsberg *et al.*, 2004b; Landrigan *et al.*, 2004a; Scheuplein *et al.*, 2002; UBA, 2004; Wolterink *et al.*, 2002) the special features of children as distinct subpopulation are quite elaborated. Briefly, they can be summarized as being related to:

- Differences in toxicokinetics:

These include for instance: higher inhalation rate, high body surface/bodyweight-ratio, different gastric pH, gastric emptying rate, concentration of digestive enzymes and gut flora, high body water content, low plasma protein binding capacity and the permeability of the blood brain barrier, immaturity of the metabolic enzymes, low renal blood flow and glomerular filtration rate.

- Differences in toxicodynamics:

This is mainly attributed to the sensitivity of developing tissues: disruption or proliferation, differentiation, migration and maturation of cells may have severe and irreversible consequences. Sensitivity of developing system: the respiratory tract, the immune and endocrine systems and the brain, continues long after birth.

Furthermore, also the group “children” as such is not homogenous, but so far there is no consensus and clear definition about the sub-categorization of this age group.

Various criteria can be the base for the distinction like the general terms of:

- preconception, embryo/foetal and newborn/pre-weaning life stages and on adults of all ages, including the young and aged (ILSI/HESI, 2005) as well as toxicokinetic parameters, resulting in the categories:

- 0-1 week premature; 0-1 week full term; 1 week to 2 months; 2-6 months; 6 months to 2 years; 2-12 years; and 12-18 years (Hattiet *al.*, 2003).

Based on these data and information available discussions are ongoing regarding the consequences of these differences for the practice of risk assessment. Three main areas can be identified for which possibilities are seen to take the vulnerability of children into account: the modification of current testing strategies, the application of *in silico* methods and the modification of the risk assessment procedure. They will be described in more detail in the respective chapters below.

6.2.1.2. Elderly

Elderly are another potential vulnerable age group with specific toxicokinetic and toxicodynamic properties. This group of the population is also of increasing social relevance due to the proportional increase of the ageing population (Geller and Zenick, 2005).

The respective items of ongoing discussions and current publications relate mainly to age-related kinetic differences in kinetics.

Vulnerability of elderly is mainly based on decelerated metabolism and renal excretion. But also other ADME-related properties can differ as well as exposure (sources and pathways), dose (Geller and Zenick, 2005).

-
- Absorption: Marked age-related changes in gut absorption after oral exposure, except decreased acid production in the stomach, which reduces the dissolution of basic compounds. The inhalation pathway may show changes in absorption or deposition due to age- or disease-related changes in lung volume, ventilation rate, and alveolar elasticity. For example, changes due to airway obstruction that accompany chronic obstructive pulmonary disease result in deeper penetration of PM and a higher rate of particle deposition (Brown *et al.*, 2002; Kim and Kang, 1997). Changes in dermal structure and function with aging may alter dermal absorption such that the ability of the skin to exclude certain compounds may be reduced with aging.
 - Distribution: Changes in body composition can result in reduced volume of distribution or increased half-lives for xenobiotic compounds, depending on whether compounds are soluble in lipids or water. Changes in plasma protein binding may also be critical because the main factor determining the effect of a compound in the body is the free, unbound fraction of that compound (Birnbaum, 1991; O'Mahoney, 2000; Moltke *et al.*, 1995). The increased permeability of the cerebral microvasculature to toxicants could result in neurodegenerative disease. Most data currently indicate that there are no significant changes in permeability with normal aging (Shah and Mooradian, 1997). However, diseases often associated with aging, such as diabetes, hypertension, and cerebral ischemic events, may compromise this barrier function.
 - Metabolism: Liver activity drops with aging (Youssef and Badr, 1999). This decreased activity could result in slowed detoxification of some compounds and reduced excretion rates. Although it was initially thought that the age-related decrease in metabolism was due to changes in the activity of liver enzymes, current data indicate that most age-related changes in hepatic activity are due to declines in liver volume and blood flow with age. But many gaps still remain in the understanding of aging-related metabolic changes. The role of the liver enzymes is critical to another aspect of the issue of age-related changes in metabolism is polypharmacy, the administration of numerous drugs to a single patient, is very common in elderly individuals and increases the risks for drug interaction and side effects (Ginsberg, 2005). Either induction or inhibition of metabolic enzymes by environmental chemicals could alter the body's critical processing of pharmacologic agents. Conversely, metabolic processes can make some environmental chemicals more biologically active, as in the case of some carcinogens or pesticides. Polypharmacy may also affect plasma protein binding if competitive displacements occur.
 - Elimination: The elimination of toxicants and their metabolites is affected by age-related changes in hepatic function, and by decreased kidney function. In addition, the alterations in pulmonary function that affect absorption of gases and volatile compounds also will affect their excretion through the pulmonary route. There is also evidence that bile flow and biliary transport is reduced with aging, thus reducing excretion through that route (Birnbaum, 1991).

Also for elderly kinetic data lack and a similar approach as described above for children using therapeutic drug studies could be a solution. A geriatric pharmacokinetic database was developed to analyze changes in drug clearance with advancing age. This analysis shows that the half-life of drugs processed by hepatic cytochrome P450 enzymes or via

renal elimination is typically 50-75% longer in those older than 65 than in young adults. Liver and kidney diseases are more common in elderly individuals and can further decrease the clearance function of these organs.

With increasing age the nervous system undergoes a variety of changes, including neuronal loss, altered neurotransmitter and receptor levels and decreased adaptability to changes induced by xenobiotics. These changes in the central nervous system can make elderly individuals more susceptible to neurological dysfunction when confronted with single pharmacologic agents, polypharmacy, or environmental toxicants.

6.2.2 Modification of testing strategies

6.2.2.1 Identification of age-related vulnerability

The drawbacks of the current testing procedures regarding the identification and inclusion of age-related vulnerability, especially for the young, are quite clearly pinpointed in the literature:

Currently applied testing strategies are not designed to detect e.g. effects of a chemical on lung development or on the developing immune system (BgVV, 2001) as well as the nervous system (DHC, 2004) since in most studies animals are not exposed to the test compound until they have been weaned. Therefore, if a substance is capable of interfering with development processes before birth and when suckling, a study designed along standard lines will not reveal the potential impact.

Only in multi-generation reproductive toxicity studies are F1 animals that have been exposed in the womb allowed to reach adulthood and produce a second generation (F2). Even in studies of this type, however, insufficient importance is attached to the information that could be gleaned from F1 animals exposed in the womb. Neither immune system functionality (resistance) nor central nervous system functionality (behaviour, learning ability, memory, motor skills) are thoroughly investigated, if they are investigated at all. Similarly, no routine attention is given to parameters that could indicate subtle disruptions of the hormone balance. Furthermore, F1 animals are studied only in small numbers, so low-incidence hormone-related effects can remain undetected (DHC, 2004). Furthermore, the consequences of an *in utero* exposure on the leukaemia risk are not evaluated.

The Dutch Health Council (DHC, 2004) did stress the advantage of determination of immune parameters (structural parameters like histopathology of lymphoid organs, numbers and types of lymphocytes in the blood as well as functional parameters (such as DTH response) incorporated into the multi-generation reproductive toxicity study in order to identify substances that interfere with the development of the immune system.

In an earlier workshop organized by the German Federal Institute of Risk Assessment, proposals were already made to include the determination of parameters relevant for the validation of developmental immunotoxicity in the current testing package (BgVV, 2001). However, it was emphasized that there are a variety of techniques available for assessing immunosuppression in adult animal models it is uncertain how to apply these approaches to a developing animal, especially if the goal is to have some standard

procedure(s) that could be applied for regulatory risk assessment. Ultimately, the primary conclusion from this workshop was that developmental immunotoxicology, as a science, is not ready to be applied in a risk assessment strategy.

Attempts are already made in order to include developmental neurotoxicity testing in the risk assessment. The OECD draft guideline 426 (4th version from 15 April 2006) is under development, however there are also discussions ongoing regarding the question if animal data can adequately model the development of the human nervous system, especially its higher functions (COT, 2006).

It is also stated that the critical windows of effects have to be identified and be correlated to the development of the test animal species used. Within this context the use of young animals is discussed (COT, 2006).

The Dutch Health Council (DHC, 2004) further recommends the incorporation in this study of functional, neurological parameters, in order to provide an initial indication as to whether the substance might be harmful to development of the nervous system.

A recent update of the OECD guidelines 416 on two-generation reproductive toxicity studies already includes a recommendation that parameters such as motor activity, sensory functions and reflexes should be investigated in F1 animals. Other relevant parameters that might be examined include those listed in the guidelines for developmental neurotoxicity studies. The OECD is currently working on revisions of its guidelines for developmental toxicity studies and multi-generation reproductive toxicity studies, with a view to enhancing detection of the more subtle consequences of hormone. In this context, it has been recommended that greater numbers of first-generation offspring should be allowed to reach adulthood and reproduce, in order to increase the likelihood of low-incidence abnormalities being detected.

6.2.2.2 Application of *in silico*-methods

In the recent years there has been an increasing use of pharmacokinetic data for the risk assessment. This was possible due to the development of computerized toxicokinetic (PBTK) and physiologically-based pharmacokinetic (PBPK-)models (Clewell et al., 2002).

The health effects of a chemical depend on its kinetics and its dynamics. With respect to kinetics, PBPK-modelling has proven to be a powerful tool to overcome uncertainties related to physiological, biological and kinetic differences for individual chemicals. An additional advantage is that insight is obtained in tissue concentrations through which a more accurate assessment can be made than when only based on external doses.

However, up to now PBPK-modelling is considered to be data-demanding and has therefore only been applied for individual substances. Several initiatives have been taken to obtain more insight in interindividual differences in toxicokinetics by pharmacokinetic modelling. An example of such an initiative are the efforts of Clewell *et al.* (2002) who conducted a comprehensive review to identify quantitative information related to age- or gender-specific physiological and biochemical factors that could influence susceptibility to exposure to chemical substances (Clewell et al., 2002). The final goal is to develop a methodology that will incorporate PBPK-modelling to assess the likelihood that a (class of) substance(s) may present an age- or gender-specific risk. EPA recently published a report in which human variability resulting from interindividual variability in activities of

biotransformation enzymes (EPA, 2006). Data on biochemical and physiological variability were incorporated into PBPK-models for adults and children which were designed to assess interindividual differences. The possibilities were illustrated with cytochrome P450 2E1-mediated biotransformation of chloroform and trichloroethylene. A further excellent example of how PBPK-modelling can help to estimate for instance the child and adult intraspecies assessment factors has been provided by Pelekis and co-workers (Pelekis et al., 2001; Pelekis et al., 2003). They estimated the kinetic-driven part of the intraspecies assessment factor for adults and children. They simulated venous blood concentrations of dichloromethane (methylene chloride) from lifelong exposure to dichloromethane. Their model showed for instance that the ratio of the P₉₅ (i.e. 95th percentile) and the median for the concentration of dichloromethane in venous blood was about 2 at all ages. This shows that PBPK-modelling can provide insight in the variability of internal (tissue) concentrations and thus in the interindividual variation. Price *et al.*, (2003) developed an interesting model to estimate the interindividual variability in internal exposure dosemetrics. The tool is based on the natural interindividual variability of a number of physiological parameters; the basis is the NHANES database which contains physiological data for about 30,000 individual of varying age, sex and ethnicity. In this way the influence of e.g. age, sex and body weight (obesity) on target tissue concentrations can be estimated (Price et al., 2003).

▪ PBPK-modelling and life stages

The use of (PBPK-)modeling is considered as promising tool in order to include the special features of children in the risk assessment. Possibilities for the use of such models are

- extrapolation from adults to children
- the determination of the biologically effective dose
- the identification of the group of children most at risk
- the identification of the effects in children not observed in adults, the group of children most at risk
- the development of child-specific TK adjustment factors

In the recent years progress was made in the refinement of PBPK-models and their specific application: first, databases were constructed based on pharmacokinetic data in children from the therapeutic drug literature (Ginsberg et al., 2002a; Ginsberg et al., 2002b; Ginsberg et al., 2004a; Ginsberg et al., 2004b). Combined with adult PK studies of the same drugs, comparisons can be made between adult and child PK-parameters (Ginsberg et al., 2002a) which results in constructing a qualitative assessment of whether child/adult differences are possible for given chemical and what direction such differences may take. In the future possibly also quantitative inferences (e.g., child-specific toxicokinetic adjustment factors) will be possible (Ginsberg et al., 2004a; Ginsberg et al., 2004b). PBPK-models were also used to define age groups based on PK-parameters. This resulted in the already mentioned arrangement: 0-1 week premature; 0-1 week full term; 1 week to 2 months; 2-6 months; 6 months to 2 years; 2-12 years; and 12-18 years, reasonable for depicting child-adult pharmacokinetic differences, even though the data for some of the earliest age groups were highly variable (Hattis et al., 2003).

The available pharmacokinetic data were used for the development of PBPK-models, like the model described by Ginsberg *et al.* (2004a) for substrates of one P-450 isoenzyme

(CYP1A2) for neonates and adults. Model development involved scale-up of in vitro metabolic parameters to whole liver and adjusting metabolic function for the ontological pattern of CYP1A2 and other CYPs. Model runs were able to simulate the large differences in half-life and clearance between neonates and adults. Neonatal PBPK-models developed for these drugs may be adapted to other CYP1A2 substrates (e.g., arylamine toxicants). A stepwise approach for modelling environmental toxicants in children is proposed (Ginsberg et al., 2002a; Ginsberg et al., 2002b).

▪ **PBPK-modelling and genetic polymorphism**

Not only the impact of different life stages can be addressed by PBPK-models, but also ADME- related genetic polymorphisms can be taken into account. Data on human variability in phase I metabolism (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, hydrolysis, alcohol dehydrogenase), phase II metabolism (N-acetyltransferases, glucuronidation, glycine conjugation, sulphation) and renal excretion are available and were analysed and applied in PBPK-models (Dorne, 2004a; Dorne et al., 2004b; Ginsberg, 2004a). The data finally could be used in risk assessment - also the EPA did address the incorporation of human interindividual biotransformation variance in health risk assessment (Ginsberg et al. 2004; EPA, 2002, EPA, 2006).

6.2.3 New technologies

The last years fast developments regarding various “omics” technologies are subject of growing interest: genomics, proteomics, metabolomics, metabonomics allowing to monitor the expression (concentration) and abundance of genes, proteins, metabolites, biomarkers, respectively. These developments are likely to have also influence on the identification and treatment of vulnerable groups in the risk assessment. Most advanced are the DNA –base techniques, which are among others be used to decode the human genome.

Within the Human Genome Project (HGP) the subject of human vulnerability is taken into consideration. One of the defined tasks within the HGP is to identify and characterize common sequence polymorphisms since certain genes have a greater than average influence over human. Therefore a central database of polymorphisms for these genes will be developed. Moreover a proposal is made how to incorporate information on genetic polymorphism into risk assessment (Waters et al., 2003).

So far, the respective progress is still mainly technology-driven. However they seem to be a promising tool to be used in the near future for risk assessment purposes.

The expectation is stated (Dorne et al., 2005a, Dorne et al, 2005b) that these techniques offer opportunities to refine uncertainty factors (see chapter 2.3.) based on a deeper mechanistic understanding on different levels (molecular level, cells, individuals, (sub)populations.

6.2.4 Modification of risk assessment-procedure

Attempts are made to adapt the current risk assessment procedures on the special requirements for vulnerable groups for instance by application of special/additional uncertainty factors for children. The Committee on Toxicity of Chemicals in Food,

Consumer Products and the Environment (COT, UK Department of Health) states that use of an additional assessment factor in order to protect the sensitive groups in the human population, among others children, should always be considered, on a case-by-case basis (COT, 2006).

On the other hand the discussion is also ongoing whether or not there is evidence that the currently applied uncertainty factors (factor 10 for interspecies differences x factor 10 for intraspecies differences) were not sufficient to protect all part of the population, including all susceptible groups. The ILSI-Life stage Task Force does conclude in their White paper on life stages that the 10-fold uncertainty factor for susceptible populations would adequately protect the elderly (ILSI/HESI, 2005).

In this context a general decision has to be made about the proportion of the total population (or of the subgroup) that should be protected. This decision has to be based on political and ethical, rather than scientific considerations. It is a very complex question involving cost-benefit analysis and issues of acceptance of risks in the society (Mielke et al., 2005).

The application of a factor for human variability assumes that there is variability in response to chemical toxicity from one human to the next and that this variability may not have been detected in the epidemiology study, usually due to factors such as small sample size. Use of this factor may also assume that groups of humans exist, such as children, the elderly, or those with genetic polymorphisms that predispose them to unique sensitivity when compared with the average population (e.g., a bimodal distribution of sensitivity; see below for further discussion). A review of this default factor indicates that it is relatively robust, with greater than 99% of the population, including sensitive subgroups, being protected.

The same counts for polymorphism: the literature justifies the factor of 10 when considering single polymorphism. However, the authors state that risk may increase far above a safety of 10 for individuals with several susceptible metabolism genotypes as well as other determinants of susceptibility, e.g. defective DNA repair, poor nutritional state, etc. (Knudsen et al., 2001). So far this has never been proven in practice. It is once again remarked that an intraspecies assessment factor of 10 is considered to account for a 100-fold variability between humans (see Chapter 2).

However, approaches are made to refine the current practice by introduction of (chemical specific) assessment factors which are based on toxicokinetic and toxicodynamic properties of compounds and therefore also taken vulnerability into account. It is recognised that variations in the toxicokinetics and/or toxicodynamics of a compound may be the result of differences in the age, diet, physical well-being and genetic make up of individuals (COT, 2006).

The default intraspecies assessment factor is considered to protect sensitive groups most of the time. Virtually all of the studies available suggest that a high percentage of the population, including children, is protected by using a 10-fold uncertainty factor for human variability or by using a 3.16-fold factor for either toxicokinetic or toxicodynamic variability. Based on specific comparisons for newborns, infants, children, and adults, the percentage of the population protected is between 67 and 100, with the studies in larger

populations that include sensitive individuals suggesting that the value is closer to 100%. Where available, quantitative analysis of the extent of toxicodynamic and toxicokinetic variability among humans indicates that relying on a default value of 10 to compensate for variability among humans, including that due to age, and on a default value of 10 to compensate for a limited toxicity database, when necessary, is adequate to protect most of the people—including children—most of the time. Taken together, information on the relative sensitivities of children and adults, on the sensitivity and specificity of toxicity testing protocols, and on the extent to which current uncertainty factors compensate for increased sensitivities and limited data suggests that the use of additional uncertainty factors to limit environmental chemical exposures is unlikely to provide significantly greater protection to children over 6 months of age. The same conclusion might not always hold true for children younger than 6 months of age in the absence of adequate developmental or systemic toxicity testing.

However, while younger children are often more sensitive to toxicity than older children or adults, so are younger laboratory animals. Thus, appropriate *in utero* and early neonatal toxicity testing will compensate for any additional early sensitivity.

Developmental and reproductive toxicity testing protocols such as those recommended by the EPA, FDA, and OECD are useful for characterizing toxicity in developing animals and for assessing risks to children that might arise from *in utero* and postnatal exposures (Dourson et al., 2002).

Certain risk assessment frameworks are considering sensitive subpopulations.

The operating procedure developed by the US Acute Exposure Guideline Level (AEGL) was extended by Mielke et al. (2005) in order to cover sensitive subpopulations. This includes the:

- identification of sensitive subpopulations for the chemical of interest (no subpopulation is particularly sensitive towards exposure to every chemical).
- quantification of the higher risks of these subpopulations have to be quantified. This can be done by deriving an intraspecies factor for the particular subpopulation which has to be applied additionally to the intraspecies factor considering the ‘normal’ variability in healthy young adults. In order to derive a reasonable factor, the quantitative distribution of the response in terms of mean and variability has to be known for the specific subgroup and for the ‘normal’ population. A serious problem is often the lack of data for exact quantification of the variability of responses in humans. Therefore, in many cases only an informed guess is possible (Mielek et al., 2005).

In the current EPA guideline on cancer risk assessment includes some aspects (early life time exposure: i.e. *in utero*, early postnatal, during lactation) is so far not yet being considered for review in Europe (DHC, 2004). In this guideline the incorporation of sensitive subpopulations in cancer risk assessment is addressed by stating that use of mode of action information can be used to identify susceptible populations and identifying risk factors, such as differences due to genetic polymorphisms, disease, altered organ function, life style, and life stage). In the accompanying guidance document for assessing susceptibility from early-life exposure to carcinogens a chemical-specific adjustment of risk estimates that pertain to childhood is proposed.

Furthermore, the general discussion of improvement of the risk assessment by applicability of methods like benchmark-dose approach is also ongoing with respect to the determination of risk for vulnerable groups.

6.3 Summary and conclusion

Currently there is still relevant discussion, investigation and method development ongoing on the field of vulnerable groups. This is reflected by the amount of scientific publications, discussion papers and other documents on various aspects of these subjects as well as the amount of workshops organised.

Based on the public literature, the following items are identified as main recent developments and are considered especially promising for improvement of the risk assessment of vulnerable groups in the (near) future (see Chapters 7-9)

- data regarding children and elderly as age-related vulnerable groups
- modification/adoption of testing strategies in order to include the special properties of vulnerable groups
- the possibilities of *in silico* methods
- perspectives regarding the application of new technologies (“-omics” techniques).

7. IDENTIFICATION OF THE BEST PRACTICE ON THE TREATMENT OF VULNERABLE GROUPS AND THE FURTHER RESEARCH NEEDED

The work presented in the preceding chapters was used to give the initial impetus for a broad discussion on risk assessment of vulnerable groups and whether possibilities for improvement could be identified. For this purpose a workshop was organized in July 2006. It was ascertained that a broad number of relevant disciplines were represented by TNO and RIVM experts, including risk assessors for most of the EU frameworks addressed in chapter 3 as well as experts on the fields of toxicokinetics and physiological modelling.

The workshop addressed three main topics:

1. The definition of vulnerable groups and the adequacy of the default intraspecies assessment factors;
2. Relevant current developments;
3. Recommendations for improvement.

Each topic was briefly introduced and subsequently plenary discussed. The outcomes of the discussions are summarized below per topic.

7.1 Definition of vulnerable groups and the adequacy of assessment factors

It was stressed that a distinction should be made between people at a higher risk due to an increased sensitivity to the adverse effects of a chemical and human beings that are at higher risk due to a high exposure. The latter are e.g. factory workers that are at extra risk but are in the present context not considered as “vulnerable group” as defined in chapter 2.

At present, within most frameworks safe levels for human exposure are usually determined on the basis of animal toxicity studies. In case a complete toxicological data set is available, the acceptable exposure level(s) (e.g. ADI, TDI, AOEL, ARfD) are general determined on the basis of the overall NOAEL from the animal toxicity studies divided by a total assessment factor of 100. The factor of 100 is considered to consist of a factor of 10 for extrapolation from the animal to the human situation and a factor of 10 to cover the interindividual variability. As already discussed in Chapter 2, it should be realised that when starting from the philosophy that the intraspecies factor should account for the difference between the average and the most susceptible human being, a default factor of 10 is meant to account for a 100-fold human variability (Dourson et al., 2002; Scheuplein, 2002). This is even larger when the point of departure for the intraspecies factor is considered to be at the lower end of the human dose-response curve, i.e. the more than average susceptible part of the population. There appear to be different philosophies about the shape of the human dose-response distribution and about the starting point for the intraspecies assessment factor but none of these are scientifically well-founded and there is no consensus yet. Most often it is assumed that human susceptibility follows a lognormal distribution but in specific situations other

distributions might be more applicable (e.g. dichotomous distributions in case of genetic polymorphisms). However, in general no human data on the shape of the dose-response curve are available and one has to rely on animal information. It was therefore felt not appropriate to discuss this into more detail at the workshop.

In the USA the FQPA urged an extra safety factor of 10 for the protection of children. However, it is now recognized that the toxicology issues considered by the FQPA safety factor completely overlap with EPA's database uncertainty factor, and when this latter uncertainty factor is used to address database deficiencies, the FQPA safety factor is not needed (Dourson et al., 2002; EPA, 2002, Fenner-Crisp, 2001). In line with this proposal it was argued during the workshop that there are no indications that the current risk assessment procedures provide insufficient protection for children. No examples could be brought up indicating that a well-defined exposed subpopulation did run an unacceptable high risk that was not anticipated beforehand. Therefore, it was stated that the often used total assessment factor of 100 has proven its merits in practice. This factor was therefore believed, in general, to adequately protect the human population, including vulnerable subpopulations. It was noted, however, that it is rather the overall factor of 100 that provides a "feeling of safety" and confidence in the human limit values rather than the factor of 10 for intraspecies variability. Hence, if for any reason the default of 10 for the intraspecies assessment factor would be lowered (e.g. because of chemical specific data) the need for insight into possible vulnerable subpopulations will increase.

It was further remarked that if adequate data on a potential vulnerable subpopulation are available (i.e. for the unborn or the young infant (developmental toxicity data)) there is no need for additional assessment factors. In contrast it can be reasoned that the variability within such a subpopulation will be smaller than in the population as a whole, so that a default factor of 10 for intraspecies variability can already be interpreted as conservative.

A number of remarks on the adequacy of the safety factor of 100 were/should be made. First of all it will be difficult, if not impossible, to detect, for instance through epidemiological studies, small or rare health effects in a human (sub-)population and relate these to exposure to a specific chemical. This could explain the absence of reports on inadequate protection of vulnerable groups by the present risk assessment procedures. Moreover, if subpopulations are not suspected to be more vulnerable beforehand they will hardly be identified during the test phase of a chemical because the study designs are not aimed at the detection of all possible susceptible subpopulations.

Summarising, based on the experience so far, the general notion was that the current risk assessment procedures (i.e. applying an overall factor of 100 for inter- and intraspecies variability) is sufficient to protect potential vulnerable populations. Therefore, applying an additional assessment factor *by default* in order to protect vulnerable subpopulations is not necessary. Especially when data on potential vulnerable subpopulations is available the default factors might already be considered as conservative. Obviously, additional assessment factors can be applied in case of incomplete or unreliable data sets.

7.2 Relevant current developments

The results of the literature search (see Chapter 6) were presented followed by a plenary discussion that focussed on two questions:

- Are there any developments that were not covered by the literature search?
- Which of the developments are most promising within the framework of this project?

Additional options which came up as not presented but possibly of interest for the current project were:

- the development of a quantitative risk assessment for skin sensitization and
- the pharmacosurveillance-approach, i.e. post-marketing-identification of potential vulnerable subpopulations due to the use of drugs.

The first option was not further discussed since no initiatives on this subject were known. The latter was discussed into more detail. It was mentioned that the raw data, gathered by the responsible pharmaceutical industries, will most likely not be publicly available for further analysis. It was also proposed that clinical trial data of individual subjects as well as preliminary R&D data of not further developed compounds could be a valuable data source to investigate human variability. But again, the use of them will be hampered by the confidentiality of the data.

However, it was recommended by the participants of the workshop to consider the possibilities on how to improve the public nature and accessibility of this information for obtaining more insight in interindividual variability.

The second part of the session was dedicated to the identification of promising current developments. The following subjects were brought up:

▪ *In silico* methods (e.g. PBPK modelling): In general a lot is known about computerised modelling of toxicokinetic data, but much less for toxicodynamic data. Part of the human variability is related to differences in toxicokinetics. Due to these differences people who are exposed to the same external exposure will show a variation in internal tissue concentrations. Therefore, PBPK-modelling is useful to identify human subjects or groups that show relatively high internal exposures at the level of the target organ based on physical and physiological characteristics. The relation between kinetics and dynamics (dose-effect) must be established in order to be able to ultimately link tissue concentrations with effects.

It was stated that PBPK-modelling has the potential to support the choice of and confidence in assessment factors in case the relevant physiological and physico-chemical parameters important for the identification of vulnerable groups can be thoroughly investigated (identified and quantified). PBPK-modelling can be a useful and powerful tool for identification and consideration of critical factors relevant for groups that might be extra vulnerable due to e.g. age, gender, obesity and genetic polymorphism.

▪ The “-omics” (e.g. genomics, proteomics, metabolomics) technologies are currently still under development but definitely considered as promising tools in the future. However, the workshop members stated that the current developments are still too much

technology-driven, i.e. more driven by what is technically feasible than by possible applications like improvement of risk assessment methodologies. It was therefore recommended that these developments should be more guided by risk assessment-orientated instances as well.

7.3 Recommendations for improvement

The last part of the workshop focused on the possibilities for improvement in the present risk assessment procedures.

A major opportunity for improvement is considered to be the development of guidance for a more coherent testing strategy. The participants expressed their concern that toxicity dossiers admitted within EU frameworks often implied that tests were performed independent from each other. It was felt that if the tests are more tuned to one another additional useful information on potential vulnerable groups might become available. At present, the underlying data base is mostly driven by the data requirements and guidelines. More flexibility on the part of the notifier/producer and on the part of the evaluating bodies could improve the data base, by for instance making optimal use of the possibilities of a test set-up, making intelligent use of the available knowledge in the set-up of new studies (e.g. adding test parameters to a study, or waving the need for a particular study on the basis of previous knowledge).

Adaptation of the present guidelines could yield more information on the toxicological profile of a substance. For instance, in multi-generation reproductive toxicity studies treatment of the animals covers a large part of the life-span of the animal, from the development of the germ cells well into adulthood. However, these studies are mainly focused on the effect of a substance on the reproductive potency and, at a histological level, on the reproductive organs. Incorporation of additional parameters may provide valuable information on the (lack of) effects of the substance on other parameters. The additional parameters could be made part of the standard data requirements of this test procedure (e.g. immunological parameters) or could be added on the basis of findings from other toxicity studies.

For instance, should a short-term study indicate that the critical effects of a substance are haematological changes; these parameters could also be investigated in the multi-generation reproductive toxicity test, in order to investigate whether the (pregnant) mother or pup is more sensitive to these effects. As another example, specific studies in juvenile animals could be used to obtain information on possible effects of a chemical in children.

It is stressed that such studies need not to be included in the set of standard toxicity tests, but should be performed only when data indicate the need for such a test. Continuing research will aid the development of appropriate guidelines. It is recommended that guidance on the use of specific studies in risk characterisation and risk assessment should be developed.

A number of recommendations for the general approach of vulnerable subpopulations in risk assessment were put forward. It was noted that in general, although kinetic data often are presented, these often provide only limited information. Kinetic data can easily be reported into more detail and made more easily accessible (at present valuable information is often available but “hidden” in the documentation). A more detailed report of such data can provide more information on potential vulnerable groups.

The current treatment of vulnerable groups in the risk assessment varies depending on the framework. In the risk assessment of human medicines potential vulnerable groups already play a prominent role. This can be explained by the fact that for human medicines the exposure is well known, the toxicological data base of the drugs in question is extensive, and the health status of the target groups (the patients) is rather well known and changes in the health status can be (should be) monitored during treatment. Moreover, by definition human drugs are expected to exert an effect.

In conclusion, it was noted that adaptation of the current practice (testing strategies) depends for a large extent on the respective frameworks. A more detailed inventory of the recommendations and data gaps for the respective frameworks is presented in Chapter 8.

7.4 Summary and conclusion

Summarizing the main outcome of the workshop the following conclusions and recommendations were supported:

- The application of a default overall factor of 100 for inter- and intraspecies variability is considered sufficient to protect potential vulnerable populations. Therefore, applying an additional assessment factor *by default* in order to protect vulnerable subpopulations is not necessary.
- It is recommended to consider the possibilities on how to improve the public nature and accessibility of confidential information (especially from pharmaceutical companies) for obtaining more insight in interindividual variability. This concerns both the data from the drug development phase as from post marketing surveillance.
- PBPK-modelling is a useful tool to identify human subjects or groups that show relatively high internal exposures at the level of the target organ, especially with respect to the factors age, obesity and genetic polymorphism.
- The “-omics” (e.g. genomics, proteomics, metabolomics) technologies are considered as promising tools on the long-term. More input and guidance from risk assessors will be helpful to develop the appropriate tools for identification of potential vulnerable groups.
- The development of guidance for a more coherent testing strategy was put forward as a major opportunity for improvement that could be implemented within the foreseeable future. If the required tests are more tuned to one another additional useful information on potential vulnerable groups might become available. This also includes the toxicokinetic testing data.

8. RECOMMENDATIONS FOR IMPROVEMENT OF THE TREATMENT OF VULNERABLE GROUPS IN THE VARIOUS RISK ASSESSMENT REGIMES

8.1 Introduction

8.1.1 Considerations and starting point for recommendations

The evaluation of current approaches in the risk assessment of potential vulnerable groups did show that although most frameworks state that vulnerable groups are dealt with, this is in practice only done on a case-by-case basis if appropriate data happen to be available. With the exception of the framework for human medicines there is no structured protocol to address potential vulnerable groups. The possibilities are predominantly restricted by the data requirements.

Furthermore, regarding the risk assessment procedure, the default assessment factor for interindividual variability applied during the various risk assessment procedures is meant to cover the general variability due to e.g. a poorer health status and age (the old and the very young). No hard data are available to support the assumption that a default factor of 10 (covering a 100-fold human variability) is sufficient or whether it is not. It is generally assumed that most of the potential vulnerable subpopulations are already accounted for and protected by this approach. However, as already noted in Chapter 7, it will be difficult, if not impossible, to detect small or rare health effects in a human (sub-)population and relate these to exposure to a specific chemical. This could explain the absence of reports on inadequate protection of vulnerable groups by the present risk assessment procedures. Thus, for practical reasons it can be considered that at present there is only a need for additional concern with respect to vulnerable subpopulations if the available data do indicate so. However, there still is a need to verify the sufficiency of these default factors.

The main issue then is not so much how to deal with vulnerable groups but how to identify them. For each risk assessment framework it depends on the data requirements which potential vulnerable groups can be addressed. Data requirements differ between the various frameworks. If one wants to address potential vulnerable groups without knowing beforehand which subpopulation might be more vulnerable, the only way is to ask for a large (full) toxicological data set. However, it appears to be premature and not feasible to recommend extensions of dossier requirements by default without knowing what one should look for. Therefore, it is recommended on the one hand to make a more optimal use of the already available data set and on the other hand to initiate further developments to obtain more insight in factors relevant for the human variability. The latter suggestion will help to identify potential vulnerable subpopulations and thus to define better tailor-made data requirements.

Thus the present chapter will primarily focus on recommendations for optimization of the use of the data already required and on some possibilities to obtain more insight in the human variability in the near future. The main purpose of these recommendations is to gain more insight in human variability for two reasons. The first is to evaluate the

appropriateness of the default factor of 10 for interindividual variability, since, as previously mentioned, there are neither data to confirm nor to disprove its appropriateness. The second is to study the possibilities for improvement of the current risk assessment procedures of vulnerable groups by derivation and application of more refined assessment factors for human variability. A strictly legally fixed harmonized approach seems not feasible and/or desirable, due to the varying scopes, aims and type of compounds covered in the various regulatory frameworks.

8.1.2 Approach and set-up of this chapter

Based on the considerations, discussions and findings as mainly described in Chapter 6 (literature search for recent developments in risk assessment of vulnerable groups) and Chapter 7 (workshop discussions), the various risk assessment regimes are re-analysed in order to identify possible improvements regarding risk assessment of vulnerable groups within the EU frameworks.

As described in Chapters 3 and 4, no special attention is paid to vulnerable groups in most of the frameworks - except for children in several regulations. Within most of these regulations only general remarks are made on this subject^R. A clear guidance on how to identify vulnerable groups and the consequences for the hazard identification and assessment is however lacking.

As remarked in Chapter 7.1, the overall default factor of 100 that is often used to account for inter- and intraspecies variability, provides a “feeling of safety” since no examples could be brought up indicating that application of this overall factor induced unforeseen risks in a defined human (sub)population. However, although this will be true for major risks relatively small or rare health effects are difficult to detect and/or linked to exposure to a specific chemical. It is therefore advisable to improve the identification and protection of potential vulnerable groups.

In Chapter 8.2 recommendations for improvement of the treatment of vulnerable groups will be presented. It will be indicated whether they can be implemented with relatively little efforts or that further development is necessary. In Chapter 8.3 it will be described whether and how each of the recommendations can be applied to each of the vulnerable groups as identified in the SSC-report (SCC, 2003a) and to which frameworks they are applicable. Finally, in Chapter 8.4 some remarks regarding the application of the recommendations in the risk assessment procedure will be made.

8.2 General recommendations for improvement

8.2.1 Need for urgent actions

As already stated in chapter 7, at present no urgent actions seem to be required from a risk assessment point of view. Current practice indicates that the applied assessment

^R such as: “MRLs should be set ... with a view to protecting vulnerable groups such as children and the unborn.” in EG Regulation 396/2005.

factors for human variability sufficiently cover the differences in susceptibility, although it has to be mentioned that no appropriate data are available to verify this consideration. For practical reasons, the general notion is therefore that the current risk assessment procedures are sufficient to protect potential vulnerable groups. However, on a long-term perspective it is recommended to improve and refine the risk assessment procedures, by increasing the insight in and identification of human variability. The respective recommendations are described into more detail in the following section.

8.2.2 Recommendations for long-term improvement

The recommendations for improvements are aiming on a refinement of the current practice due to an improvement of identification and quantification of relevant differences in susceptibility toward exposure to chemicals (vulnerability) within a population. They have a general character and apply to all frameworks in a similar way. Their intention is to make a more optimal use of the available data set and to initiate further developments to obtain more insight in factors relevant for the human variability. The recommendations cover four different aspects. The first recommendation deals with possibilities at the level of testing requirements and the second recommendation focuses on the use of human data. The third recommendation concerns the development of a database of characteristics that are specific for individual vulnerable groups. Finally, recommendations regarding recent promising developments can be made.

1) Coherent testing strategies

As pointed out in Chapter 7.3, the current practice can be improved by the application of more coherent testing strategies.

The applicability of this recommendation depends on the data requirements within each framework. As described in Chapter 3, data requirements vary considerably between the frameworks; from a few basic tests to a complete toxicological data set (Figure 1, Chapter 3). It is believed that through a better tuning of results of individual toxicity tests (e.g. considering the effects found in one test for the experimental set-up of related/follow-up tests) more information relevant for vulnerable groups can be obtained. Sometimes this can be realised by changing the order in which the tests are carried out; in other situations it might be recommendable to study additional toxicity endpoints. Although it is beyond the scope of the present report to develop guidance for all possibilities a few brief examples are given (see also Chapter 8.3):

- Toxicokinetic data might provide insight in the relation between external exposure and internal tissue dose metrics. For instance, distribution data might provide data on tissues concentrations and thereby on potential target organs. Further, if the delivered doses are tuned to those in the toxicity studies the results might help to explain and interpret the dose-response curve. The obtained data might also provide information that can be useful for PBPK-modelling.
- Relevant information on a potential increased vulnerability during pregnancy and/or lactation might be obtained by studying the most relevant endpoint(s) derived from a (sub)chronic toxicity study in female animals also in pregnant animals in a developmental toxicity study or a multi-generation reproduction toxicity study.
- Relevant information on a potential increased vulnerability at different ages might be obtained by studying critical endpoints derived from a (sub)chronic toxicity study also in offspring in a multi-generation reproduction toxicity study.

Therefore it is recommended to further explore the possibilities of a more coherent testing procedure and to provide appropriate guidance where possible.

II) The use of human data

Available human data are always to be preferred above animal data. Therefore it is recommended to include data on epidemiology and human exposure in the risk assessment procedure, wherever available. However, within most frameworks human data are generally absent and when available, they often are of poor quality. Human data especially will be absent for those frameworks where the assessment is predominantly aimed at registration or admittance to the market of a newly developed substance.

It is recommended to initiate a human health monitoring program that can be applied to situations for which there are clear indications that exposed human (sub)populations might experience an increased risk. These indications might be based on both exposure and toxicity information. If for instance the toxicity data point out that children might be a vulnerable group then a representative subgroup of exposed children might be monitored. Also a subpopulation that might be at increased risk via a relatively high exposure might be subject of a monitoring program. Such a program will provide relevant additional information on the substance in question.

For an adequate health monitoring program it is necessary to develop practical guidance on how to identify the relevant exposure situations for health monitoring and on how to select the appropriate parameters for monitoring. The principle for this recommendation is comparable to the Post-Marketing Surveillance for human medicines.

It should be stressed that this recommendation is not intended to initiate toxicological studies in humans.

III) Database development

A database of characteristics for specific potential vulnerable groups could be a useful tool aiding the determination of relevant vulnerable groups, their specific hazard profile and risk for a specific compound and/or its use.

Data to be incorporated include substance-specific characteristics (including physicochemical properties; toxicokinetic and –dynamic data) on the one hand and (vulnerable) group specific characteristics on the other hand (as e.g. pointed out for children and elderly in paragraph 6.1.). Such a database might provide indicators both from substance characteristics as well as from subpopulation-specific information that might point at a potential higher vulnerability of an exposed population.

This harmonised strategy would then allow the identification of sensitive groups and the related hazard profile and/or the relevant additional information necessary to identify their special risk compared to the mean population. Filling such a database will be an ongoing process based on the experience within the various risk assessment frameworks. Further, such a database will have a two-way interaction with the two other recommended activities, PBPK-modelling and the use of human data. The database can provide relevant input for both areas (e.g. provide guidance to the monitoring program),

but also can the output of these two areas be used to improve and fine-tune the database.

A tiered approach could be applied to identify data gaps for sensitive groups and give guidance on how to fill them case-by-case. The latter should be based on smart information linking, e.g. by considering data of *in silico* models and *in vitro* models, and/or “-omics”-based technologies, to determine the relevance of e.g. metabolic deficiencies. Further *in vivo* testing is not intended without sufficient justification.

IV) The applicability of recent developments

There are currently certain developments ongoing (see also Chapters 6 and 7) which potentially can contribute to the improvement of treatment of vulnerable groups in the risk assessment:

- Data on structure activity relationships (SARs) can indicate whether a substance belonging to a certain class of chemicals may particularly exert toxic effects in a certain sub-population. It is recommended that such data, when available, are included in the risk assessment procedure. Specific software programs have been developed that make use of (Q)SARs, e.g. DEREK and TOPCAT. However, prudence is called for since the currently available models do not provide definitive answers and are seriously criticised. Generally, from a regulatory point of view positive indications for specific toxic effects are endorsed but supportive additional (testing) data are considered necessary in case of negative results. Developments within the REACH Implementation Projects on this subject will be worthwhile to keep up with.
- PBPK-models are promising tools to obtain more insight on interindividual variability in physiological and toxicokinetic parameters (see Chapter 6). These models have proven their value in the risk assessment of individual substances. Recent developments show that these models might have interesting possibilities to be used in a more generic way.
PBPK modelling can be a useful tool for identification and consideration of critical factors relevant for groups vulnerable due to e.g. age, obesity and genetic polymorphism. In this way they have the potential to support the choice of and increase the confidence in assessment factors, or might be of help to explain differences observed between specific groups. Especially the influences of age and gender on the internal tissue concentrations have been addressed (Clewell *et al.*, 2002; Pelekis *et al.*, 2003; Price *et al.*, 2003). Other possibilities for application are e.g. studying the effect of obesity on the distribution of a chemical substance, or the effects of genetic polymorphism in biotransformation enzymes on the biotransformation of a substance.
- Even though still not directly applicable for risk characterization and assessment, the ongoing development of various “-omics” technologies have to be followed and considered as promising tool e.g. for the identification and elucidation of certain vulnerabilities. These technologies might be able to provide important tools for the identification of potential vulnerable groups. In order to achieve that purpose it is recommended that these developments will be more guided by risk assessment-orientated instances.

8.3 Recommendations for improvement: Coherent Testing Strategies

Some vulnerable groups as identified by the SSC can easily be dealt with, since relevant data can already be obtained from the required data set. The potential vulnerability of other subpopulations might be more difficult to deal with and more detailed data or even specific human data might be necessary, e.g. factors like diseases, nutrition and lifestyle are typical for humans and will not or very limitedly be addressed in animal toxicity studies.^S

In the following this is elaborated into more detail for all vulnerable groups mentioned by the SSC.

8.3.1 Age

This factor is covered depending on the available dataset. If the full toxicological dataset (Figure 1, Chapter 3) is required, all life-stages will be covered.

- Prenatal stage (*in utero*); covered by developmental toxicity study or multi-generation toxicity study. It is noted however that in these studies generally only reproduction-related toxicity endpoints are studied. It can be considered to also study relevant toxicity endpoints identified in (sub)chronic toxicity testing in these studies when possible.
- Lactating stage, childhood; covered by developmental neurotoxicity study or multi-generation toxicity study. It is noted that relevant toxicity endpoints derived from (sub)chronic toxicity tests are not standard addressed.
- Adolescents and adulthood; covered by repeated dose (subchronic) toxicity and multi-generation toxicity studies.
- Elderly; covered by chronic toxicity study. It is noted that studies addressing exposure only during the senescence stage are not performed for logical reasons. A chronic toxicity study can be considered as a worst case point of departure for this life-stage.

8.3.2 Gender

Since it is generally required to expose both male and female animals gender issues will almost always be covered in the repeated dose toxicity tests. Pregnant and/or lactating women are not standard subject of study but could be covered when a developmental toxicity study or multi-generation toxicity study is required. However, it is necessary to also include the relevant toxicity endpoints as identified in the (sub)chronic toxicity study in these two studies.

8.3.3 Genetic trait

Increased vulnerability due to genetic predisposition is not covered by the present required toxicity tests.

^S Only in specific cases specially developed animal strains are used to obtain relevant information, but this is not standard procedure within the EU risk assessment frameworks.

8.3.4 Diseases/nutrition/lifestyle

These factors are not subject of standard toxicity testing as required within the various EU risk assessment frameworks. Therefore, the datasets will not provide information on potential increased vulnerability induced by one of these factors. It is acknowledged however that experience on some of these topics is available within the research on topics related to e.g. human nutrition. For instance, specific animal strains have been developed to study the health implications of specific diseases like obesity. Although these studies are not focused on a potential increased susceptibility for exposure to chemical substances these studies might provide relevant data to provide more insight in physiological and kinetic differences between “normal” and “modified” animals and extrapolate these data to humans. These data might be useful for the PBPK-modelling and the database described in section 8.2.

Table 8.1. summarizes those studies that will provide relevant information for the respective factors of vulnerability. It shows which studies may provide useful information if one wants to address a specific potential vulnerable population in the risk assessment of a chemical substance. The factors and their subgroups are coded for easy reference in table 8.2.

Table 8.1: Summary of studies covering relevant factors of vulnerability

Factor	subgroups	Code	Covered by studies (OECD guideline)
Sex	general	A1	- repeated dose toxicity studies (407-413, 424, 451-453)
	pregnant/ lactating female	A2	- one-/multi-generation reproductive toxicity (415, 416, 421, 422) - developmental toxicity (414) - developmental neurotoxicity (draft 426)
Age	prenatal	B1	- one-/multi-generation reproductive toxicity (415, 416, 421, 422) - developmental toxicity (414) - neurodevelopmental toxicity (draft 426)
	lactation	B2	- one-/multi-generation reproductive toxicity (415, 416, 421, 422) - neurodevelopmental toxicity (draft 426)
	child (up to puberty)	B3	- one-/multi-generation reproductive toxicity (415, 416, 421, 422) - developmental neurotoxicity study (draft 426)
	adolescent	B4	- one-/multi-generation reproductive toxicity (415, 416, 421, 422) - developmental neurotoxicity (draft 426)
	adult	B5	- repeated dose toxicity studies (407-413, 424, 451-453) - one-/multi-generation reproductive toxicity (415, 416, 421, 422) - developmental toxicity - developmental neurotoxicity
	aged	B6	- chronic toxicity (451- 453)
Genetic traits		C	-
Disease		D	-
Nutrition		E	-
Life- style		F	-

Table 8.2 indicates per EU framework which vulnerable groups are covered or not by the present data requirements. Combination of this table with Table 8.1 also provides suggestions which additional studies could improve the treatment of vulnerable groups. A “best practice” as such is not assignable, since the frameworks differ too much (regarding e.g. scope, aim and type of compounds covered) to allow a direct straight comparison. However, as stated and reasoned in more detail in chapter 7, for practical reasons the current risk assessment procedures are considered to be sufficient to protect vulnerable groups from a risk assessment point of view. Current practice indicates that the applied assessment factors for human variability may sufficiently cover the differences in

susceptibility, although it has to be mentioned that no appropriate data are available to verify this consideration.

Table 8.2: Overview of the treatment of vulnerable groups in the various EU risk assessment regimes

Framework/Directive	Vulnerable groups addressed	Vulnerable groups NOT addressed
Pesticides 91/414/EEC chemical active substance	A1, A2, B1-B6	C, D, E, F
Pesticides Micro-organism (including viruses) as active substance Directives 91/414/EEC and 2005/25/EC and 2001/36/EC	None by default. Under certain conditions A1, A2, B1-B6 (Tier 2 studies)	C, D, E, F
Biocidal products 98/8/EC	A1, A2, B1-B6	C, D, E, F
New industrial substances 67/548/EEC 93/67/EEC	Base set covers vulnerable groups A1, B4, B5	A2, B1-B3, B6, C, D, E, F
Existing industrial substances 67/548/EEC Regulation (EEC) 793/93	Base set covers vulnerable groups A1, B4, B5	A2, B1-B3, B6, C, D, E, F
REACH Regulation document no 15921/05 (19-12-2005)	Data set required depends on the tonnage level per year: * 1 – <10 tpa: None * 10 – <100 tpa: A1, A2, B2-B5 * ≥ 100 tpa additionally: B1	B6, C, D, E, F
Feed additives 2001/79/EC and Regulation 1831/2003	A1, A2, B1-B6	C, D, E, F
Food additives 89/107/EEC and Guidance document: SCF/CS/ADD/GEN/26 final (12/07/2001)	A1, A2, B1-B6	C, D, E, F
Food contact materials Regulation (EC) no 1935/2004. Opinion of EFSA required. EFSA has established guidelines	Depending on the migration level Migration <0.05 mg/kg: None Migration 0.05 – 5 mg/kg: A1, B4, B5 Migration 5-60 mg/kg: A1, A2, B1-B6	C, D, E, F
Novel food Regulation 258/97/EC and Commission Recommendation 97/618/EC	on a case-by-case basis, (tiered approach) A1, A2, B1-B6	C, D, E, F
GMO in food and feed Regulations 1829/2003/EC and 641/2004/EC	A1, A2, B1-B6	C, D, E, F
Human medicines Directive 2001/83/EEC	Depending on target population	

Framework/Directive	Vulnerable groups addressed	Vulnerable groups NOT addressed
Veterinary medicines Directive 2001/82/EEC	A1, A2, B1-B6	C, D, E, F
Consumer products General Product Safety Directive 2001/195/EC and the Cosmetic Products Directive 76/768/EEC	None	A1, A2, B1-B6, C, D, E, F

8.4 Application of the recommendations in risk assessment procedures

The recommendations made are generally applicable; therefore the individual regulatory frameworks will not be separately addressed. It is noted that the recommendations are already carried out to some extent in the risk assessment of chemicals. However, at the moment this is not structurally carried out but done on a case-by-case basis, and possibly even depending on the insight and expert judgment of the individual risk assessor. Formalising the recommendations will improve the (treatment of vulnerable groups in the) risk assessment of chemicals and enhance their uniformity and consistency. Evaluation of the possibility of the existence of a vulnerable group at higher risk might be regarded as a three-step process, i.e. answering the following three questions:

1. Can a vulnerable group be identified from the available data?
2. Are appropriate and adequate toxicity data available for that subpopulation?
3. a) Does the exposure assessment indicate that this group is really at extra risk?
b) Is this group protected by the default intraspecies assessment factor or is an additional factor warranted?

The present report predominantly addresses the first two questions, which are closely related. It should be noted that vulnerable groups will not be identified if the right endpoints are not addressed, no matter how many studies are performed. Since it is practically impossible to study every possible endpoint one will seldom be sure that all relevant effects are covered. It is this point that makes it difficult to identify the first type of higher susceptibility as defined in Chapter 2 (i.e. the critical effect in a subpopulation differs from that of the general population). Recommendations for improvement of answering these questions have been provided, including a listing of the kind of data needed and that might be relatively easy obtained within the present guidelines. However question 3 a) is not less relevant: if a potential vulnerable group will not be exposed they will not be at extra risk, and no additional measures have to be taken. Sometimes, this question might be the first one that needs to be considered. It is however noted that a re-evaluation might then be necessary in case of new uses or the use of higher amounts of the substance. An appropriate monitoring program might be of help to control changes in use and in thus human exposure.

Question 3 b) has already been dealt with in Chapter 2. It was reasoned that the generally applied intraspecies assessment factor is meant to at least partially account for the interindividual variability due to defined factors like age, gender, well-being and life-style. It is very difficult to quantitatively assess to what extent the default intraspecies assessment factor already accounts for an identified increased vulnerability. It should further be realized that the use of a default intraspecies assessment factor of 10 can be considered as rather conservative if the point of departure is already in the lower end of the human dose response curve^T.

^T For instance, when the risk assessment is based on relevant data on a developmental toxicity study and the target subpopulation consists of the unborn or young infant it can then be argued that the interindividual variability in the target subpopulation will be (considerably) smaller than that for the population as a whole. Thus in such a case a smaller factor than the default intraspecies assessment factor might be warranted.

9. RECOMMENDATIONS FOR FUTURE RESEARCH IN THE FIELD OF VULNERABLE GROUPS AND RISK ASSESSMENT

Summarising the considerations, discussions and findings described so far, recommendations can be made about focal points for future research. They enclose ongoing discussions and activities as well as methods and techniques which are currently still in an early stage of development but are promising and/or necessary for a better identification and treatment of vulnerable groups in the risk assessment. These recommendations are only briefly addressed; more details on some of the recommendations have already been given in the previous chapters.

9.1 Further development of PBPK modelling

PBPK models have to be considered as a relevant *in silico* tool to predict the behaviour and effects of chemicals in human. More recently, initiatives have been taken to obtain more insight in the interindividual variability as a result of physiological and kinetic differences. Promising examples have been published with respect to for instance age and gender. These studies can be used to underpin the intraspecies assessment factor as well as for providing valuable information on (sub)populations that might be more vulnerable due to physiological and/or kinetic factors. PBPK-models have been successfully used for specific substances. It is recommended to explore the possibilities to build more generic applicable models for risk assessment purposes.

9.2 Preparation of a data base on characteristics of vulnerable groups

It would be very useful to set-up and maintain a data base with human data on vulnerability, originating from all different kinds of regulatory frameworks and other related fields. Developing and filling the database would be an on-going process, the database would be continuously enlarged with data and experience obtained within the various risk assessment frameworks.

This database might serve multiple purposes. In the present context the most important one is that such a database can provide alerts for potential vulnerable groups based on e.g. substance-specific data, structural alerts and experience obtained within other frameworks.

Another purpose might be that the database can be used to control consistent evaluations between the risk assessment frameworks and be helpful to indicate whether substances have already been evaluated within other frameworks.

All kind of related data (e.g. chemical- and group-specific data on critical effects and their concentration), gathered in a structured, logical manner could then also be supportive for e.g. the development of coherent testing strategies (see Chapter 8) due to the possibility of anticipation and prognosis of a certain chemical-specific behaviour identification of possible vulnerable groups. The collected data can then also be used for the development of appropriate PBPK-models as recommended under 9.1.

They could also be useful in order to identify other vulnerable groups which are so far not

considered but arise and become relevant under certain circumstances.

9.3 Further improvement of (Q)SAR

The currently available models on (qualitative) structure activity relationships ((Q)SARs) should be further developed and validated. By integration of parameters related to certain vulnerabilities they could become a useful tool for the prediction of effects that are specific for individual subpopulations.

9.4 Investigating the possibilities of the various “-omics” technologies

The various “-omics” technologies – like genomics, proteomics, metabolomics- are quickly developing and considered promising for a variety of purposes and applications. These techniques should also get attention from the regulatory authorities and related decisions makers. Among others, these techniques could be used to improve the understanding of vulnerability and the identification of vulnerable groups (e.g. identification of genetic polymorphisms) by elucidating underlying mechanisms as well as resulting effects and/or target organs, resulting in the identification of relevant markers and parameters. In order to achieve that purpose it is recommended that these developments will be more guided by risk assessment-orientated instances.

9.5 Further elaboration of probabilistic tools

Tools for probabilistic risk assessment are under development. Probabilistic exposure assessment have been accepted and used in risk assessments within several frameworks, e.g. the admittance of pesticides. Probabilistic effect assessment, based on dose-response modelling, is for the moment not as much common practice as the probabilistic exposure assessment. However, as described in Appendix 4 of the SSC-report (SSC, 2003) interesting and promising tools have already been developed and are ready to be used in quantitative risk assessments. At present, further valuable tools are under development, for instance in the EU 6th framework Integrated Project SAFE FOODS. These developments help to optimize the identification of dose-response relationships. Their integration in the risk assessment procedure would therefore be especially useful for the identification of vulnerable groups as well as the provision of quantitative risk estimations for humans. These possibilities should be further explored.

9.6 Improvement of risk assessment procedures for certain vulnerable groups

Further guidance for the identification of vulnerable groups has to be developed. Some causes of vulnerability are more investigated and integrated in the human risk assessment than others; especially children are often addressed. A lot of research has

been performed on for instance topics as genetic traits, disease, nutrition and life style. However, the research projects often are rather fundamental and very detailed and provide information that has a rather qualitative character. It is recommended to explore whether these developments could contribute to or could be implemented in a more quantitative way.

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Annex I

OVERVIEW OF LEGISLATIONS, SCIENTIFIC AND INTERNATIONAL BODIES EVALUATED IN THIS REPORT

Legislation

Pesticides:	91/414/EEC 396/2005 (MRL) Guidance documents on AOEL and ADI 2005/25/EC and 2001/36/EC
Biocidal products	98/8/EC Technical Guidance Document (TGD) for biocidal products, new and existing Industrial Chemicals (ECB)
New and existing industrial substances	67/548/EEC 93/67/EEC Regulation (EEC) 793/93 Technical Guidance Document (TGD) for biocidal products, new and existing Industrial Chemicals (ECB)
REACH	Regulation document no 15921/05 (19-12-2005)
Feed additives	2001/79/EC and Regulation 1831/2003
Food additives	89/107/EEC SCF/CS/ADD/GEN/26 final (12/07/2001)
Food contact materials	Regulation (EC) 1935/2004
Novel food	258/97/EC 97/618/EC
GMO in food and feed	1829/2003/EC and 641/2004/EC
Human medicines	2001/83/EEC
Veterinary medicines	2001/82/EEC
Consumer products	2001/95/EC

Scientific Bodies

European Food Safety Agency

EFSA panel on additives and products or substances used in animal feed (FEEDAP)

EFSA panel on Plant health, Plant protection products and their Residues (PPR)

EFSA panel on food additives, flavourings, processing aids and materials in contact with food (AFC)

EFSA Panel on genetically modified organisms (GMO)

EFSA panel on dietetic products, nutrition and allergies (NDA)

EFSA panel on contaminants in the food chain (CONTAM)

European Chemicals Bureau

Committee for Medicinal Products for Human Use

Committee for Medicinal Products for Veterinary Use

Scientific Committee on Consumer Products

Scientific Committee on Emerging and Newly-Identified Health Risks

Scientific Committee on Food

Scientific Committee on Health and Environmental Risks

Scientific Steering Committee (European Commission Health and Consumer Protection Directorate-General)

International Bodies

US-EPA

US-FDA

US-DPR

US-ATSDR

TERA

Health Canada

CEPA

PMSB

ICH

IPCS

IARC

WHO

FAO

DG SANCO

TERA

UK PSD

German Federal Ministry of Health and Social Security

Umweltbundesamt (Germany)

BfR (Germany)

BAuA (Germany)

FoBiG (Germany)

Health Council of the Netherlands

Annex II GLOSSARY

ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
AEGL	Acute Exposure Guideline Level (USA)
AFC	Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
ATSDR	Agency for Toxic Substances and Disease Registry
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (Germany)
BfR	Bundesinstitut für Risikobewertung (Germany)
BPD	Biocidal Products Directive
CDFS	Chemically Defined Flavouring Substances
CEPA	Canadian Environmental Protection Agency
CHMP	Committee for Medicinal Products for Human
CONTAM	EFSA panel on Contaminants in the food chain
COT	Committee on Toxicity of Chemicals in Food (UK)
CSAF	Chemical Safety Assessment Factor
CVMP	Committee for Medicinal Products for Veterinary Use
CYP	Cytochrome P450
DALYs	Disability-Adjusted Life Years
DTH	Delayed-type hypersensitivity
DHC	Health Council of the Netherlands
EC	European Commission
ECB	European Chemicals Bureau
EFSA	European Food Safety Authority
EPCO	EFSA Peer Review Co-ordination
EHC	Environmental Health Criteria
EMEA	European Medicines Agency
EPA	Environmental Protection Agency (USA)
EU	European Union
FCM	Food Contact Materials
FDA	Food and Drug Administration (USA)
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FoBiG	Research and advisory institute for hazardous substances (Germany)
FAO	Food and Agricultural Organisation
FQPA	Food Quality Protection Act
GMO	EFSA Panel on genetically modified organisms
HESI	Health and Environmental Sciences Institute
ICH	International Conference on Harmonisation
ILSI	International Life Sciences Institute
IPCS	International Programme on Chemical Safety
PMSB	Pharmaceutical and Medical Safety Bureau (Japan)

MOE	Margin of Exposure
MOS	Margin of Safety
MRL	Maximum Residue Levels
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NOAEL	No Observed Adverse Effect Level
LOAEL	Low Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PBPK	Physiologically Based Pharmacokinetic Modelling
PPR	EFSA panel on Plant health, Plant protection products and their Residues
(Q)SAR	(Quantitative) Structure Activity Relationships
RfDs	Reference Doses
RIVM	National Institute for Public Health and the Environment
SCCP	Scientific Committee on Consumer Products
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks
SCF	Scientific Committee on Food
SCHER	Scientific Committee on Health and Environmental Risks
SSC	Scientific Steering Committee (European Commission Health and Consumer Protection Directorate-General)
TDI	Tolerable Daily Intake
TGDs	Technical Guidance Documents
TK	Toxicokinetic
TWI	Tolerable Weekly Intake
PSD	Pesticides Safety Directorate (UK)
UNEP	United Nations Environmental Programme
DPR	Department of Pesticide Regulation
WHO	World Health Organisation

Annex III

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