Evaluation Manual for the Authorisation of plant protection products and biocides

EU part

Biocides

Chapter 4 Human toxicology; human toxicity dossier

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Chapter 4 Human toxicology; toxicological dossier
Category: biocides

1. GENERAL INTRODUCTION

This chapter describes the data requirements for estimation of the human toxicological effects of a biocide and the active substance, and how limit values are derived for the EU framework. In technical meetings agreements with general relevance focused on methodological decisions with respect to risk assessment and questions on the implementation and interpretations of the Biocides Directive 98/8/EC, are provided in the Manual of Technical Agreements of the Biocides Technical Meeting (MOTA) [1], an information document in a concise format (publicly available at the biocides web-site of JRC-IHCP). Relevant agreements are included in this chapter.
In the EU an Evaluation Manual for Product Authorisation (available at Circa Biocides Public (via the ECB website)) has been developed by The Netherlands and agreed (version 1.0) by all members states in the CA meeting in December 2012.

2. EU FRAMEWORK

The procedure for inclusion of active substances in Annex I of Biocides Directive 98/8/EC [2] is described under EU framework where only the procedure laid down in the EU is described. The NL procedure for evaluation of a substance, described in the NL part, is reverted to where no EU procedure has been laid down.

2.1 Introduction

The use of biocides may result in human exposure.
Such exposure may occur via different routes: oral, dermal and respiratory.
It is therefore important that the intrinsic human toxicological properties of each requested active substance and product can be evaluated and established.
The information about the toxic effects and kinetics of a substance is mainly based on the results of experimental toxicological research carried out with different test animal species.
Besides toxicity data on the active substance, study data on transformation products may also be required if human exposure to such transformation products occurs.

Each study is summarised separately in the toxicological summary and, if possible, the corresponding 'No Observed Adverse Effect Level' (NOAEL) is derived
This evaluation leads for each study and for each sub-aspect to a toxicologically based endpoint, and finally to the toxicological profile of a substance.

The toxicological endpoints derived from the submitted research, then form the basis of the risk evaluation for human exposure (see EU exposure part).

2.2 Data requirements

In order to qualify for inclusion in Annex I of 98/8/EC a dossier, which meets the provisions laid down in Annex IIA, IIB, IIIA and IIIB of 98/8/EC, must be submitted for the active substance as well as for the product. The data requirements have been elaborated in the TNsG (Technical Notes of Guidance) on data requirements [2]. For several product types addenda are available (see MOTA [1]).

* For PT 18, PT 19 (concerning extracts and oils of plant or animal origin)
a special document "How to deal with extracts and oils of plant or animal origin?" was endorsed at the 23rd CA meeting.

*For PT 19 (concerning naturally occurring substances) a special document "Guidance to Member States and industry on the data requirements for naturally occurring substances used as attractants / repellents" was endorsed at the 18th CA meeting

*For PT 19 (concerning pheromones) a special document “Guidance for Waiving of Data Requirements for Pheromones for Inclusion in Annex I/IA of Directive 98/8/EC” was endorsed at the 18th CA meeting. It is an addendum to, Chapter 1.4 (Guidance on non-submission of data).

The data requirements in EU framework have first been subdivided into data about the active substance and data about the product. These have then been subdivided into ‘common core data’ (data required for each product group) and ‘additional data’ (data to be submitted in certain situations (depending on factors such as use, expected exposure, toxicological properties and physical-chemical properties of the substance/product). All data requirements are elaborated in the sections below. The texts mainly originate from documents drawn up in the context of 98/8/EC.

The studies must be carried out in accordance with internationally recognised GLP (Good Laboratory Practice) principles and guidelines, as set out in the TGD (Technical Guidance Document) on risk assessment [3].

Appendix V of the TGD on risk assessment discusses the strategy that can be followed for selection of the most suitable exposure route for toxicity tests.

Where the applicant holds the view that a certain study is not meaningful, a relevant scientific justification can be submitted for the non-submission of the particular study. .For active substances that are normal components of foods and have been consumed in large quantities for centuries, waiving of studies which can normally not be waived is acceptable (see MOTA [1]; agreement TMIV 2011).

There should be no doubt about the identity of the tested substance, and the purity of the tested substance for each study.

Generally, open literature does not meet EU/OECD guidelines and is therefore usually considered as supplementary information. Although providing that the quality of public data fulfils the criteria below and the repetition of tests should be avoided to protect laboratory animals, it can be used as key studies (see MOTA [1]; agreement TMIII 2001).

1. The data comply with Article 8 of Directive 98/8/EC.
2. The identity, purity and the impurities of the substance have to be defined in the publication and to be comparable with the notified substance.
3. The test has to be conducted according to international guidelines (e.g. EU or OECD) and GLP is desirable. Deviations should be justified (Art. 8 of Directive 98/8/EC).
4. The reporting of the study allows evaluation of the quality of the study.

2.2.1 Data requirements active substance

Common core data
The text below in the grey frames is from the TNsG on data requirements. Numbering in these grey frames is the same as the section numbering in the TNsG on data requirements [2].

6.1 Acute Toxicity *[Ann IIA, VI. 6.1.]*

For studies 6.1.1 to 6.1.3, substances other than gases shall be administered via at least two routes, one of which should be the oral route. The choice of the second route will depend upon the nature of the substance and the likely route of human exposure.
Gases and volatile liquids should be administered by the inhalation route.

The acute toxicity tests provide an indication of possible adverse effects of the active substance. Administration via different routes makes possible an overall assessment of relatively acute hazard of exposure in different exposure routes. Furthermore, acute toxicity testing serves as an initial step in planning dosage levels for subsequent testing.
Acute toxicity testing may provide valuable information for accidental situations.
Any other acute toxicity studies conducted using other than oral, dermal or inhalation administration routes, must be referred to in accordance with Chapter 3, A.6.11.

6.1.1 Oral *[Ann IIA, VI. 6.1.1]*

For substances with low acute oral toxicity a limit test with 2000 mg/kg b.w. may be sufficient. However, need for testing of higher dose could be decided on a case-by-case basis. When planning new tests, the EC methods B.1.bis, B.1.tris (or the corresponding OECD guideline 420 and 423) and the OECD Guideline 425 are recommended.
EC method B.1 (or the corresponding OECD Guideline 401) should not be used.
Existing results based on EC method B.1 (or OECD method 401) are accepted.

6.1.2 Dermal *[Ann IIA, VI. 6.1.2.]*

Dermal toxicity must be reported in an active substance except for gases.
For substances with low acute dermal toxicity a limit test with 2000 mg/kg b.w. may be sufficient. EC method B.3 or the corresponding OECD guideline 402.

6.1.3 Inhalation *[Ann IIA, VI. 6.1.3.]*

Inhalation toxicity must be reported where the active substance is:

- a volatile substance (vapour pressure > 1 x 10-2 Pa at 20 oC),
- a powder containing a significant proportion (e.g. >1% on a weight basis) of particles with particle size MMAD <50 micrometers or to be included in preparations which are powders or are to be applied in a manner which generates aerosols, particles or droplets in the inhalable size range (MMAD < 50 micrometers).

Substances classified as corrosive in skin must not be studied.
The full study using three dose levels may not be necessary if a substance at an exposure concentration to the limit concentrations of the test guideline (limit test) or at the maximum attainable concentration produces no compound-related mortalities.
EC method B.2. or the corresponding OECD guideline 403.

6.1.4 Skin and eye irritation *[Ann IIA, VI. 6.1.3.]*

The tests will provide information on the degree and nature of skin, eye and associated mucous membrane irritation, especially with regard to the reversibility of responses.
These tests need not be carried out if the active substance is a strong acid or base (pH below 2 or above 11.5) and where the active substance has shown to have potential corrosive properties, or is a severe skin irritant, eye irritation test shall not be necessary.
It may be possible to accept positive findings from in vitro test methods which are close to validation by recognised organisations
EC methods B.4 (skin irritation) and B.5 (eye irritation) or the corresponding OECD guidelines 404 and 405.

6.1.5 Skin sensitisation *[Ann IIA, VI. 6.1.5.]*

The test will provide sufficient information to assess the potential of the active substance to cause skin sensitisation reactions.
While the guinea-pig Maximisation test is considered to be the preferred adjuvant technique in certain cases there may be good reasons for choosing the Buehler test or the Local Lymph Node Assay (LLNA). However, scientific justification may be given when either of the two latter mentioned is used.
The test is not needed if the active substance is classified as a sensitiser according to Directive 67/548/EEC or is otherwise known to be a sensitiser (e.g. see human data in paragraph A6.12.6).
EC method B.6 or the corresponding OECD guideline 406.

6.2 Metabolism studies in mammals. *[Ann IIA, VI. 6.2.]*

Basic toxicokinetics, including a dermal absorption study.
The test(s) should provide basic data about rate and extent of absorption, the tissue distribution and the relevant metabolic pathway including the degree of metabolism, the routes and rate of excretion and the relevant metabolites.
Usually a single application test with two different doses (low and high doses) and a repeated dose toxicokinetic study in one appropriate species, usually the rat, by the oral route is required. In some cases it may be necessary to perform additional tests on other species and using other exposure routes. However, these requirements depend on e.g. the results obtained in physico-chemical and toxicological studies of the test substance. An expert judgement is required for detailed additional data requirements (see Chapter 1.2, point 4).
An appropriate dermal absorption assessment is needed. A sequential approach should be applied for the decision if biological testing is needed (TNO 1999).
If testing is necessary to decide whether this test should be performed in vivo or in vitro, the present development of the OECD test Guidelines Programme for Guidelines on Percutaneous Absorption/Penetration has to be taken in account.
E.g. Method B.36. or the corresponding OECD guideline 417.

For the following studies, 6.3 (where necessary), 6.4, 6.5, 6.7 and 6.8, the required route of administration is the oral route unless it can be justified that an alternative route is more appropriate.
The primary required route is the oral route.
Justification to replace the oral route by another significant route, or to require testing in addition to the oral route includes: proposed or potential applications of the substance/products, route of exposure, the results of the acute toxicity tests and on physico-chemical properties of substance (for highly volatile (liquids) substances and gases an inhalation study could be appropriate; aerosols should be treated case by case).
The dermal route could be relevant if dermal penetration studies demonstrate significant dermal penetration.
Repeated dose toxicity testing provides information on adverse effects as a result of prolonged exposure. The repeated toxicity studies must be sufficient to establish or identify:

- the dose-response relationship
- the no-observed-adverse-effect-level (NOAEL)
- target organs and effects in target organs
- mode of toxic action, where possible
- the cumulative effects of the substance
- toxic effects after the different routes of exposure.

The results in short-term toxicity studies will help in selecting dose levels for long-term toxicity testing and to assess the need for further studies (e.g. mechanistic studies. See Chapter 3, A-6.10). Planning of the long-term studies should be made on the basis of the results in the short-term toxicity studies and studies on toxicokinetics.
Possible neurotoxic effects, immunological effects and endocrine disrupting effects should be taken into consideration. If some evidence of neurotoxicity or possible effects on immune or endocrine systems is provided, further in-depth investigation may be required. An expert judgement is required for deciding on supplementary studies Chapter 1.2, point 4).

6.3 Short term repeated dose toxicity (28 days) *[Ann IIA, VI. 6.3.]*
These tests are used as a range-finding test and are not required when an adequate sub chronic toxicity study is available in a rodent. These tests must be submitted if they have been conducted.
For substances with low toxicity, a limit test administered by oral routes with 1000 mg/kg b.w. may be sufficient.

6.3.1 Repeated dose toxicity (oral)
EC method B.7 or the corresponding OECD guideline 407.

6.3.2 Repeated dose toxicity (dermal)
A percutaneous study is required, where the potential dermal exposure is significant and route-to-route extrapolation is not possible.
However, a percutaneous study may be necessary where it is justified that dermal route is more appropriate or specific effects of concern are different from the effects seen in the studies in other routes. EC method B.9 or the corresponding OECD guideline 410.

6.3.3 Repeated dose toxicity (inhalation)
For volatile substances (vapour pressure >1x 10-2 Pa) or in cases where the potential inhalation exposure is significant, an inhalation study is required instead of the oral study. In some cases (e.g. aerosols and dusts/particulate matter) studies by the inhalation route should be required in addition to studies by the oral route.
EC method B.8 or the corresponding OECD guideline 412.

6.4 Subchronic toxicity *[Ann IIA, VI. 6.4.]*
Should usually be studied in two species, one rodent and one non-rodent.
For substances with low toxicity, a limit test administered by oral routes with 1000 mg/kg b.w. may be sufficient. Where testing in two species is required the testing may be waived only if it is scientifically justified; in case residues are found in the food chain waiving is not possible.

6.4.1 Subchronic oral toxicity test
Usually rat is the preferred rodent species and dog as the non-rodent species. If there is evidence from the 90-day studies that the dog is significantly more sensitive and where such data is likely to be useful in extrapolating results to man, in addition to the 90-day study a 12 month toxicity study in dogs may need to be conducted and reported. It is possible to replace a 90-day study in dog by a one-year study in a dog. An expert judgement is required to determine whether the one-year test is needed (see Chapter 1.2, point 4). EC methods B.26 (90-day repeated oral dose study using rodent species) and B.27 (90day repeated oral dose study using non-rodent species) or the corresponding OECD guidelines 408 or 409.

6.4.2 Subchronic dermal toxicity test
A percutaneous study in the rat is preferred, where the potential dermal exposure is significant and route to route extrapolation is not possible.
However a percutaneous study may be necessary where it is justified that dermal route is more appropriate or specific effects of concern are different from the effects seen in the studies in other routes.
The test should not be required for substances with low dermal toxicity, e.g. substances which have shown no toxic effects in the 28 day study at limit-dose.
EC method B.28 or the corresponding OECD guideline 411.

6.4.3 Subchronic inhalation toxicity test
For volatile substances and gases (vapour pressure > 1x 10-2 Pa)
In cases where inhalation exposure is significant, an inhalation study is required instead of the oral study. EC method B.29 or the corresponding OECD guideline 413.

6.5 Chronic toxicity *[Ann IIA, VI. 6.5.]*
The test is required for one rodent and one other mammalian species. It is recommended to study the rat first, and based on this result more testing in another mammalian species may be necessary.
A test should be performed in a rodent, the rat being the preferred species.
The long-term-toxicity of an active substance may not be required where a full justification demonstrates that these tests are not necessary based on the sub-chronic toxicity test (and demonstrated reversibility) in the same species.
Any new long-term toxicity study and the carcinogenicity study (A6.7) should be combined.
The recommended species is the rat.
EC methods B.30 or the corresponding OECD guidelines 451, 453.

6.6 Genotoxicity studies *[Ann IIA, VI. 6.6.]*
The testing of genotoxicity is a screening program to identify substances which might cause permanent transmissible changes in the amount or structure of a single gene or gene segments, a block of genes or chromosomes. Genotoxicity studies may provide pre screening information on the genotoxic carcinogenic potential of a substance.
At least one in vitro test for gene mutations, one test for clastogenicity in mammalian cells and one test for gene mutation in mammalian cells are required. Additional tests, which may become necessary upon positive results of the initial screening tests or for other reasons, should be selected on a case-by case basis taking into consideration genetic end-points, mechanistic aspects, cell-specific aspects, physico-chemical, toxicokinetic and toxicodynamic properties and relevant information on the chemical analogues of the substance. An expert judgement is required to decide on additional studies (see Chapter 1.2, point 4). EC methods B.10-B25 or the corresponding on OECD guidelines 471-485.

6.6.1 In vitro gene mutation study in bacteria *[Ann IIA, VI. 6.6.1.]*
E.g. EC method B.14 (Salmonella typhimurium-reverse mutation assay) or the corresponding OECD guideline 471.

6.6.2 In vitro cytogenicity study in mammalian cells *[Ann IIA, VI. 6.6.2.]*
E.g. EC method B.10 (In vitro mammalian cytogenetic test) or the corresponding OECD guideline 473.

6.6.3 In vitro gene mutation assay in mammalian cells *[Ann IIA, VI. 6.6.3.]*
E.g. EC method B.17 (In vitro mammalian cell gene mutation test) or the corresponding OECD guideline 476.

6.6.4 If positive in 6.6.1, 6.6.2 or 6.6.3, then an in vivo genotoxicity study will be required (bone marrow assay for chromosomal damage or a micronucleus test) *[Ann IIA, VI. 6.6.4.]*
EC methods B.11 (In vivo mammalian bone-marrow cytogenetic test, chromosomal analysis), B.12 (Micronucleus test) or the corresponding OECD guidelines 474, 475 are preferred testing methods. Tests performed accordingly EC methods B.24 (Mouse spot test) or the corresponding OECD guideline 484, B.39 (in vivo UDS assay) or the corresponding OECD guideline 486 and other tests may give supplementary information on genotoxicity.

6.6.5 If negative in 6.6.4 but positive in some of in vitro tests then undertake a second in vivo study to examine whether mutagenicity or evidence of DNA damage can be demonstrated intissue other than bone marrow. *[Ann IIA, VI. 6.6.5.]*
Methods: See point 6.6.4.

6.6.6 If positive in 6.6.4 then a test to assess possible germ cell effects may be required. *[Ann IIA, VI. 6.6.6.]*
EC method B 22 (Rodent dominant lethal test) and B23 (In vivo mammalian germ cell cytogenetics) or the corresponding OECD guidelines 478 and 483.

6.6.7 If the results are negative for the three tests 6.6.1, 6.6.2 and 6.6.3, then further testing is normally only required if metabolites of concern are formed in mammals, and in Chapter 1.4 further guidance is given on the non-submission of data. (See also the Technical Guidance Document for the Risk Assessment New and Existing Chemicals)

6.6 Carcinogenicity study *[Ann IIA, VI. 6.7]*
6.7 The carcinogenicity study identifies the carcinogenicity potential of the substance in laboratory animals in order to facilitate the extrapolation of potential risks to humans. The studies must be sufficient to establish the species specificity and organ specificity of tumours induced, to establish the dose-response relationship and for non-genotoxic carcinogens to identify doses eliciting no adverse effects (threshold dose).
One rodent and one other mammalian species should be tested. New studies should be combined with those in A6.5. The rat and the mouse are usually the species used for testing carcinogenic potential, while the rat is used for a combined chronic toxicity/ carcinogenicity testing.
The carcinogenicity of an active substance may not be required where a full justification demonstrates that these tests are not necessary.
On the basis of positive results in carcinogenicity studies, indicating non-genotoxicity effects additional mechanistic studies or considerations may be needed (especially if a non-genotoxic mechanism is indicated) (See Chapter 3, A6.10).
While the standard reference points for the treatment responses are concurrent control data, historical control data may be helpful in the interpretation of particular carcinogenicity studies. Where submitted, historical control data should be from the same species and strain, maintained under similar conditions and should be from contemporaneous studies.
The information on historical control data provided must include:

- identification of species and strain, name of supplier, and specific colony identification, if the supplier has more than one geographical location,
- name of the laboratory and the dates when the study was performed,
- description of the general conditions under which animals were maintained, including the type or brand of diet and, where possible, the amount consumed,

- approximate age, in days, of control animals at the beginning of the study and the time of killing or death,
- description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (e.g. diseases, infections),
- name of the laboratory and the examining scientists responsible for gathering and interpreting the pathological data from the study, and
- a statement of the nature of the tumours that may have been combined to produce any of the incidence data.

The doses tested, including the highest dose tested, must be selected on the basis of the results of short-term testing and where available at the time of planning the studies concerned, on the basis of metabolism and toxicokinetic data. The highest dose level in the carcinogenicity study should elicit signs of minimal toxicity such as slight depression in body-weight gain (less than 10%), without causing tissue necrosis or metabolic saturation and without substantially altering normal life-span due to effects other than tumours. If the long-term toxicity study is carried out separately, the highest dose level should elicit definite signs of toxicity without causing excessive lethality. Higher doses, causing excessive toxicity are not considered relevant to evaluations to be made.
In the collection of data and compilation of reports, incidence of benign and malignant tumours must not be combined, unless there is clear evidence of benign tumours becoming malignant with time. Similarly, dissimilar, unassociated tumours, whether benign or malignant, occurring in the same organ, must not be combined, for reporting purposes.
In the interest of avoiding confusion, harmonised terminology and diagnostic criteria such as that developed by the Hannover Tumour Registry (RENI) and published by WHO/IARC series should be used in the nomenclature and reporting of tumours.
If an alternative nomenclature is applied, the diagnostic criteria must be given in the report.
EC methods B.32 (Carcinogenicity test), B.33 (Combined chronic toxicity/carcinogenicity test) or the corresponding OECD guidelines 451, 453.

6.8 Reproductive toxicity *[Ann IIA, VI. 6.8.]*
These tests provide information on adverse effects on male and female fertility and embryonic and foetal development including possible adverse effects on the offspring during lactation and on the maternal animals. The tests will give additional information on any enhancement of general toxic effects on pregnant animals.

If, in exceptional circumstances, it is claimed that such testing is unnecessary, this claim must be fully justified.
A scientific expert judgement is required to decide on supplementary studies (see Chapter 1.2, point 4).

6.8.1 Teratogenicity test *[Ann IIA, VI. 6.8.1.]*
The tests should normally be performed in the rabbit and one rodent species.
In case that one study is performed the preferred species is the rabbit.
For substances with low toxicity a limit test with 1000 mg/kg b.w. may be sufficient
While the standard reference point for treatment responses are concurrent control data, historical control data may be helpful in the interpretation of the particular teratogenicity studies. The historical control data provided must include the same principles as reported (see Chapt.2, point 6.7). A computerised database as reference for these data may be useful. A glossary or detailed description of terminology and diagnostic principles for malformations and variations must be given in the report. EC method B.31 or the corresponding OECD guideline 414.

6.8.2 Two-generations reproduction study *[Ann IIA, VI. 6.8.2.]*
This should be conducted using two generations, in one species (the rat),
The investigation should carefully be performed both with male and female animals.
EC method B.35 or the corresponding OECD guideline 416.

(6.9 An additional data requirement. See Chapter 3, part A.)
(6.10 An additional data requirement. See Chapter 3, part A.)
(6.11 An additional data requirement. See Chapter 3, part A.)

6.12 Medical data in anonymous form *[Ann IIA, VI. 6.9.]*
Data and information on the effects of human exposure, if available, may provide valuable information for confirming the validity of extrapolations made and conclusions reached from animal data and for identifying unexpected adverse effects which are specific to humans. Data and information following accidental or occupational exposure have to be submitted where available and of adequate quality. Practical data and information relevant to the recognition of the symptoms of poisoning, on the effectiveness of first aid and therapeutic measures must be included. It is usually not possible to require this data for new active substances.

6.12.1 Medical surveillance data on manufacturing plant personnel if available *[Ann IIA, VI. 6.9.1.]*
The reports should include detailed information on the design of the programme and exposure to the active substance and to other chemicals. Data relevant to the mechanism of the action of substance should also be included where feasible. The data may consist of published articles or unpublished medical surveys.

6.12.2 Direct observation, e.g. clinical cases, poisoning incidents if available *[Ann IIA, VI. 6.9.2.]*
The reports should include a complete description of the exposure situation, clinical symptoms observed and therapeutic measures. Reports of any follow-up studies should be enclosed.

6.12.3 Health records, both from industry and any other available sources *[Ann IA, VI.6.9.3.]*

6.12.4 Epidemiological studies on the general population, if available *[Ann IIA, VI. 6.9.4.]*
Information related to occupational exposure or other exposure, consist of three main sources: case reports, descriptive epidemiological studies and analytical epidemiological studies, case-control or cohort studies. Where available, data should be supported with data on levels and duration of exposure.

6.12.5 Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available *[Ann IIA, VI. 6.9.5.]*
A detailed description of clinical signs and details of clinical tests useful for diagnostic purposes (bio-monitoring). Symptoms of poisoning including full details of the time courses involved to all exposure routes must be described.

6.12.6 Sensitisation/allergenicity observations, if available *[Ann IIA, VI. 6.9.6.]*
Information on the sensitisation/allergenicity of workers and others exposed must be provided and included, and where relevant, any incidence of hypersensitivity.
Reports should include details of frequency, level, duration, symptoms observed, and other relevant data.

Evidence that the substance can induce specific respiratory hypersensitivity will usually be based on human experience data. The clinical history data including both medical and occupational history, and reports from appropriate lung functions tests related to exposure to the substance should be submitted, if available. Reports of other supportive evidence must also be submitted, e.g.

- a chemical structure related to substances known to cause respiratory hypersensitivity
- in vivo immunological tests
- in vitro immunological tests
- studies indicating other specific but non-immunological mechanisms of action
- data from a positive bronchial challenge test.

6.12.7 Specific treatment in case of an accident or poisoning: first aid measures, antidotes and medical treatment, if known *[Ann IIA, VI. 6.9.7.]*
First aid measures in the event of poisoning and eye contamination must be provided. Therapeutic regimes and the use of antidotes must be described. Information based on practical experience, where it exists and is available, or in other cases information based on theoretical grounds, as to effectiveness of alternative treatment regimes, where relevant must be provided. Contraindications associated with particular regimes, particularly those relating to ”general medical problems” and conditions, must be described.

6.12.8 Prognosis following poisoning *[Ann IIA, VI. 6.9.8.]*
The expected effects and the duration of these effects following poisoning must be described.

(6.13 An additional data requirement. See Chapter 3, part A.)
(6.14 An additional data requirement. See Chapter 3, part A.)
(6.15 An additional data requirement. See Chapter 3, part, A.)
(6.16 An additional data requirement. See Chapter 3, part A.)

6.17 Summary of mammalian toxicology and conclusions
Each study submitted should be summarised and, for old studies, and the quality and relevance should be evaluated and the information should be stated at the relevant sub chapters. An overview of the results of the studies and any additional toxicological information should be given here. This is the initial mammalian hazard assessment.
A reporting format is under development.

Re. 6.2 For dermal absorption, the ‘EU guidance document ‘on dermal absorption’ [4] was. followed (see also Appendix IVB of the TGD on Risk Assessment). Starting point was a default value of 100% dermal absorption, unless a default value of 10% can be used on the basis of physical-chemical properties. Where required (if dermal exposure is an important exposure route and if the risk evaluation shows that the limit value based on health considerations is exceeded), an *in vitro* and/or *in vivo* dermal absorption study must be carried out as refinement of the risk assessment.
The studies must be carried out in accordance with OECD guidelines 427 and 428 and the corresponding ‘EU guidance document on dermal absorption’.
The used concentration(s) of the test substance must be of the same order of magnitude as the estimated human exposure. Dermal absorption studies are often carried out with the product and are therefore also included in §1.2.2 Data requirements product, Ann IIB, VI. 6.4 (see that paragraph for more information). Although the old EFSA guidance (Guidance Document on Dermal Absorption Sanco/222/2000 rev. 7) as described above is often used until the end of 2012 from now it is proposed to reference the updated EFSA guidance document on dermal absorption (EFSA Journal 2012;10(4):2665)

The applicability of the default values of the updated guidance was discussed in the TMs of 2012. Default values, i.e. of 25% for products containing >5% a.s or 75% for dilutions containing ≤5% a.s. or 10% dermal absorption in case MW>500 and log Pow < -1 or >4 or <75% for dilutions with an oral absorption <75% or <25% for concentrates and dilutions with an oral absorption <25%. The TM welcomed the use of the revised default values in general. The EFSA default values were endorsed by the TM; however, on a case-by-case basis divergence to higher or lower values may be possible when supported by robust evidence. The guidance should be used with flexibility and intended to be used with appropriate flexibility. The guidance is not a legally binding document; therefore deviation is possible if there is robust evidence supporting it.
Dermal absorption testing is only needed in cases where an unacceptable risk was identified in the first tier. In cases, where relevant dermal absorption studies are available, these data can be used in the first tier (The dermal absorption studies can be used in case they are acceptable for the product in question).

In the TM has been decided that more detailed information should be provided by the Rapporteur MS on the dermal absorption value(s) in the LOEP. This should indicate how the value(s) was derived (in vitro and/or in vivo studies) and what exactly was tested (concentration of the a.s. and type of formulation). The text should also indicate the basis of the applicability of such values to the representative product (both the concentrate and the in-use dilution). This information is crucial at the Product Authorisation stage when a decision is required whether the dermal absorption values established in the LOEP can be extrapolated to other products (see MOTA; agreement TMII2012).

Re. 6.6 For the mutagenicity assessment based on data requirements there is a TM agreement made at TMIII2012 (see MOTA version 5)..

Additional data
The text below in the grey frames is from the TNsG on data requirements. Numbering in these grey frames is the same as the section numbering in the TNsG on data requirements [2].

6.9 Neurotoxicity study *[Ann. IIIA, VI. 1.]*
This data may be relevant on the basis of the toxicological properties of a substance. Neurotoxicity studies detect functional changes and/or structural and biochemical changes in the central and peripheral nervous systems. These changes can be morphological, physiological (e.g. electroencephalographic changes), or behavioural nature, or can be changes in biochemical parameters (e.g. neurotransmitter levels).If there are any indications that the active substance may have neurotoxic properties then specific neurotoxicity studies are required. Indications of neurotoxicity can be acquired from the standard systemic toxicity studies. Further investigation is possible using standard repeated dose toxicity tests with incorporation of specific neurotoxicity measures, like sensory activity, grip strength, and motor activity assessment
(e.g. EC method B7 or the corresponding OECD guideline 407) and/or acute neurotoxicity testing using the OECD method 424. Expert judgement is required to decide whether a repeated dose neurotoxicity study is needed (see Chapter 1.2, point 4).

These studies have to be performed for substances of similar or related structures to those capable of inducing delayed neurotoxicity. If anticholinesterase activity is detected a test for response to reactivating agent may be required.

EC methods number B.37 (Delayed neurotoxicity of organophosphorus substances following acute exposure) and B.38 (Delayed neurotoxicity of organophosphorus substances, 28 repeated dose study) or the corresponding OECD guidelines 418 and 419.

6.10 Mechanistic study - any studies necessary to clarify effects reported in toxicity studies *[Ann.IIIA, VI. 7.]*
This data may be relevant on the basis of the toxicological properties of a substance.
Studies of the mechanisms of toxicity may be necessary when there are indications that active substance may have e.g. a non-genotoxic mechanism for carcinogenicity, species specific effects, adverse effects on reproduction, immunotoxicity or hormone related effects. Scientific judgement is required to decide whether any supplementary studies are needed (see Chapter 1.2, point 4).

6.11 Studies on other routes of administration (parenteral routes)
For existing substances, data (if already existing) by alternative routes should be submitted by the applicant.
New studies will be required only in exceptional cases.
Studies on parenteral routes may supplement the information received from toxicokinetic studies and give valuable information e.g. in cases when the gastrointestinal absorption of the chemical in question is poor.
E.g. acute toxicity studies on intraperitoneal, intravenous subcutaneous and intramuscular routes, where conducted, should be submitted.
A scientific judgement is required to decide whether any supplementary studies are needed (see Chapter 1.2, point 4).

6.13 Toxic effects on livestock and pets *[Ann. IIIA, VI. 2.]*
An estimation on toxic effects and exposure via different exposure routes (e.g. inhalation, licking, skin contact and ingestion of poisoned bait) and in relevant, but exceptional cases, toxicity testing in livestock and pets is required. Toxic effects for livestock and pets should to be estimated or studied if the substance is to be used in spaces in which animals are housed, kept or transported or exposure is possible via drinking water or feedingstuffs. Information on lethal doses for different species, symptoms of poisoning, details of the time courses in case of poisoning and antidotes should also be submitted, if available. This data may be relevant e.g. for product type 3 (substances used for veterinary hygiene purposes), product type 4 (disinfection of surfaces and equipment), product type 5 (drinking water) product types 8 and 10 (treated materials in areas in which animals are housed, kept or transported), product types 14, 15 and 23 (ingestion of baits), product types 16 and 17 (contaminated drinking water), product types 18 and 19 (repellents to be used for veterinary hygiene purposes). An expert judgement is required to decide whether any studies are needed (see Chapter 1.2, point 4).
This data is usually not required for the product types 1, 2, 6, 7, 9, 11, 12, 13, 20, 21 and 22.

6.14 Other test(s) related to the exposure of humans *[Ann. IIIA, XI.2]*
Toxicity of degradation products, by-products and reaction products related to human exposure. Information is required on the toxic effects of substances generated from an active substance, other than mammalian metabolites, in normal use of biocidal product.
The decision as to the need for this data should be made on case-by-case basis by expert judgement (see Chapter 1.2, point 4). Where human exposure is significant, toxicity testing may be needed. This data may be relevant for many product types.

As examples, product types 1 and 2 (reaction products with water when the substance is used for human hygiene purposes or reaction products with water or other materials released in water or air when the substance is used for the treatment of bathing waters), product type 5 (substances produced in a reaction with drinking water), product types 6, 7, 9 and 10 (residuals in treated materials), product type 8 (irritating and sensitising effects of chemical compounds, such as metal salts, developed on the surface of the treated wood) and product type 18 (products, which may produce harmful substances with water during gassing).

6.15 Food and feedingstuffs *[Ann. IIIA, VI. 4.]*
If the active substance is to be used in preparations for use where food for human consumption is prepared, consumed or stored, or where feedingstuff for livestock is prepared, consumed or stored, the tests and results in accordance with paragraphs A6.15.1-6.15.5. *shall be required.*
The list of the product types for which this data is required is not exhaustive. Decisions as to the need for the following data must be made on a case-by-case basis according to an expert judgement (see Chapter 1.2, point 4).
Any relevant regulations related to materials and articles indented to come into contact with food and feeding stuffs must be taken into consideration. Examples of such regulations are: Dir. 96/23/EC (residues in food of animal origin), and Dir. 89/109/EEC (on the approximation of the laws of the Member States relating to materials and articles intended to come into contact with foodstuffs) and 2377/90 (veterinary regulation). Applicable residue limits given in relevant legislation must be respected.
Examples of product types, for which all or some of these tests may be relevant, are product type 1 (products to be used by personnel in food production, the food processing industry or catering services), product type 3 (cleaning eggs), product type 4 (products used for surfaces with which food, feedingstuffs and drinking water may come into contact), product type 5 (drinking water disinfectants), product type 9 (polymerised materials or paper which may come into contact with food, feedingstuffs or drinking water), product type 12 (products used in the production process of materials, which may come into contact with food or feedingstuffs, e.g. paper used for packaging), product types 14 and 23 (products to be used in places where the contamination of food or feeding stuffs is possible, or near soils in agricultural or horticultural use), product types 16 and 17 (residues of the substance in fish or shellfish), product type 20 (food and feedstuff) and product type 21 (residues of products to be used for aqua-culture or fishing equipment, e.g. fish cages).

6.15.1 Identification of the residues (identity and concentrations), degradation and reaction products and of metabolites of the active substance in contaminated foods or feeding stuffs. *[Ann. IIIA, XI. 1.1. and XI. 1.3 , XI.1.5.and XI.I.6]*
Migration into foodstuffs and concentrations of the substances in contaminated food or feeding stuffs should be measured by exposing samples of representative food or feedingstuffs or their simulates for various periods of time to the substances in question. Any possible organoleptic changes in food, feeding stuffs and drinking water must be stated.

6.15. Behaviour of the residues of the active substance, its degradation and reaction products and, where relevant, its metabolites on the treated or contaminated food or feeding stuffs including the kinetics of disappearance *[Ann. IIIA, XI. 1.2 .and XI.1.3 , XI.1.5. and XI.I.6]*

6.15.3 Estimation of potential or actual exposure of the active substance to humans or animals through food and feeding stuffs and other means *[Ann. IIIA, XI. 1.4.]*
Expected exposure via diet taking into account consideration the average consumption of different food types and drinking water should be studied.
This data is usually not required for product types 11, 13, 14, 15, 16, 17, 18 and 23.

6.15.4 Proposed acceptable residues and the justification of their acceptability *[Ann. IIIA, XI. 1.7.]*
For product type 5 any relevant regulations relating to acceptable or unacceptable residues in drinking water must be taken into consideration in the justification.
For product type 21 any directions or restrictions at the Community or national level related to residues in fish and shellfish intended to be used as food or feeding stuffs must be taken into consideration in the justification.

6.15.5 Any other available information that is relevant *[Ann. IIIA, XI. 1.8.]*
E.g. information from other chemical programmes on ADI, MRL or relevant residues

6.15.6 Summary and evaluation of data submitted under point 6.15 *[Ann. IIIA, XI.1.9]*
This information is included in 6.18

6.16 Any other tests related to the exposure of the active substance to humans, in its proposed biocidal products, that are considered necessary may be required. *[Ann. IIIA, VI.3.5 and XI.2].*
An expert judgement for suitable tests and reasoned case is needed as to decision that such additional studies are required (see Chapter 1.2, point 4).

6.17 If the active substance is to be used in products for action against plants then tests to assess toxic effects of metabolites from treated plants, if any, where different from those identified in animals shall be required *[Ann. IIIA, VI.6].*
Ann. IIIA VI.6. is action against plants, and therefore seen as covered sufficiently by directive 91/414/EC.

Waiving, read-across and bridging
The basic principle is that the applicant submits all data or provides statements for the data requirements. In certain cases, data requirements may be waived by the non-submission of a study or by read-across or bridging. The applicant must in such cases explicitly give justification. More information about waiving is given in the TNsG on data requirements (§1.4 and corresponding addenda) and in the text below based on the MOTA [1].

Waiving of a 2-generation study can be accepted if justification is robust. The following points have to be considered (agreement TMI 2007):

- Is there a possibility for read-across?
- Are there other studies (especially chronic and developmental) with no effects on male or female reproductive organs? Is there histopathological evidence of lack of effect on these organs?
- Are there teratogenicity studies with no signs of developmental toxicity?
- Are there any CNS effects that might affect reproductive functions such as mating and lactation behaviour, milk production and hormonal balance?
- Are there related compounds with relevant effects?

- Are there any structural alerts?
- Is the substance bioaccumulative?

In a case where the 2-generation study is waived, an extra assessment factor (AF) of 3 should be used. A statement was agreed to be included in the CAR and Assessment Report that due to the waiving of the two generation study there is some uncertainty with regard to effects on fertility. However, it was concluded that any restrictions on women at child-bearing age should not be imposed.

Bridging of data between salt and ion/acid can be approved, but the acceptance needs to be considered for each case separately. Solid justifications should be given, and it needs to be clear whether the salt or the ion/acid is the active substance (agreement TM III 2001 and TM II 2007).

Several points need to be specifically addressed when considering read-across between salt and ion/acid:

- Different salts of the same substance can have different toxicological properties. Read-across should therefore be done with caution, and using reasonable worst-case assumptions.
- Special attention has to be given to the selection of test material for all physical-chemical end points, analytical methods and for dermal absorption.
- If the salt is (almost) completely dissociated in water, then an analytical method for the salt in aqueous solutions is not relevant. This is the case for organic acids.
- Toxicokinetic data may be required to elucidate the dissociation of the salt in physiological conditions.
- Physical-chemical studies have been required with the salt, except for obvious exceptions like the octanol-water partition coefficient that is not applicable for the salt.
- When the ion/acid is the notified active substance but testing is done with the salt, the bioavailability of different salts should be considered.

For more information, see the following links and embedded documents, noting that these are not directly relevant for biocides:

- OECD SERIES ON TESTING AND ASSESSMENT, Number 102: Guidance document for using the OECD (Q)SAR application toolbox to develop chemical categories according to the OECD guidance on grouping of chemicals.

  The Toolbox estimates missing values by: 1) Read-Across, that extrapolates for an untested chemical from tested chemicals within a category 2) Trend Analysis, that estimates for an untested chemical from a "trend" (increasing, decreasing or constant) in effect within a category and 3) (Q)SAR Models that estimate missing values from a statistical model for a category.

  This document is available at http://www.oecd.org/dataoecd/50/60/42294034.pdf.

- OECD SERIES ON TESTING AND ASSESSMENT, Number 80, Guidance on grouping of chemicals (see for PDF file appendix 3).

- Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals (Guidance for the implementation of REACH).

  This guidance is available at:
  http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08

For rodenticides there is a refined waiving concept endorsed at the 15th CA meeting. It is an addendum to the TNsG on Data Requirements, Chapter 1.4 (Guidance on non-submission of data) (see MOTA [1]).

2.2.2 Data requirements product

Common core data
The text below in the grey frames is from the TNsG on data requirements. Numbering in these grey frames is the same as the section numbering in the TNsG on data requirements [2].

Information may be derived from existing data where a justification acceptable to the competent authority is provided. In particular, the provisions of directive 88/379/EEC (amended as 1999/45/EC) should be used whenever possible to minimise animal testing.

6.1 Acute toxicity [Ann IIB, VI. 6.1.]
For studies 6.1.1. to 6.1.3. biocidal products other than gases shall be administered via at least two routes, one of which should be the oral route. The choice of the second route will depend upon the nature of the product and the likely route of human exposure. Gases and volatile liquids should be administered by the inhalation route.
In some cases it may be necessary to study acute toxicity in all three routes.
The acute toxicity tests are to provide an indication of possible adverse effects of the toxicity of the biocidal product. Administration via different routes makes possible an overall assessment of the relative hazard of different exposure pathways. Acute toxicity testing may provide valuable information for accidental situations.

6.1.1 Oral [Ann IIB, VI. 6.1.1.]
For preparations with low acute oral toxicity, a limit test at 2000 mg/kg b.w. may be sufficient.
When planning new tests, the EC methods B.1.bis, B.1.tris (or the corresponding OECD TGs 420 and 423) and the OECD TG 425 are recommended) EC method B.1 (or OECD TG 401) should not be used. Existing results based on EC method B.1 (or OECD TG 401) are accepted.

6.1.2 Dermal [Ann IIB, VI. 6.1.2]
Dermal toxicity must be reported except for gases.
For preparations with low acute dermal toxicity a limit test at 2000 mg/kg b.w. may be sufficient.
Preparations which are classified as corrosive must not be studied.
EC method B.3 or the corresponding OECD guideline 402.

6.1.3 Inhalation [Ann IIB, VI. 6.1.3.]
Inhalation toxicity must be reported, if the preparation is

- volatile (vapour pressure > 1 x 10-2 Pa at 20 oC) or
- a powder containing a significant portion (e.g. > 1% on a weight basis) of particles with particle size MMAD < 50 micrometers or
- to be applied in a manner which generates aerosols, particles, or droplets in an inhalable size range (MMAD < 50 micrometers).

Preparations classified as corrosive must not be studied.
A full study using three dose levels may not be necessary if a preparation at an exposure concentration to the limit concentrations of the test guideline (limit test) or at the maximum attainable concentration produces no compound related mortalities.
EC method B.2 or the corresponding OECD guideline 403.

6.1.4 For biocidal products that are intended to be authorised for use with other biocidal products, the mixture of products, where possible, shall be tested for acute dermal toxicity and skin and eye irritation, as appropriate [Ann IIB, VI. 6.1.4.]
These tests will be required where a product is used together with other product (e.g. to increase efficacy of certain product) and where exposure to the mixture can not be excluded.

6.2 Skin and eye irritation [Ann IIB, VI. 6.2.]
The tests will provide information on degree and nature of skin, eye and associated mucous membrane irritation, especially with regard to reversibility of responses.
If the active substance is a strong acid or base (pH value below 2 or above 11.5) the test does not need to be carried out.
It may be possible to accept positive findings from in vitro test methods which are close to validation by recognised organisations.
If the materials have been shown to have potential corrosive or severe irritant properties the test should not be carried out.
However, if the formulation of the product gives reasons to believe and accept that the product should be classified and labelled as an irritant then the tests not may be carried out.
EC methods B.4 (dermal irritation) and B.5 (eye irritation) or the corresponding OECD guidelines 404 and 405.

6.3 Skin sensitisation [Ann IIB, VI. 6.3.]
The test will provide information to assess the potential of the product to cause a skin sensitisation reaction.
This is not needed where the preparation contains a substance(s) which is/are classified as a sensitiser(s) according to Directive 67/548/EC or is otherwise known be a sensitiser(s), e.g. on the basis of epidemiological data.
While the guinea pig Maximisation test is considered to be the preferred adjuvant technique in certain cases there may be good reasons for choosing the Buehler test or the Local Lymph Node Assay (LLNA). However, scientific justification may be given when either of the two latter mentioned is used.
E.g. EC method B.6 or the corresponding OECD guideline 406.

6.4 Information on dermal absorption [Ann IIB, VI. 6.4.]
Estimation of effects of solvents and additives to the dermal absorption of active substance(s) should be given.
A dermal absorption test at an appropriate dose level could be performed if there is dermal exposure.

An appropriate dermal absorption assessment is needed. A sequential approach should be applied for the decision if biological testing is needed (TNO 1999). If testing is necessary to decide whether this test should be performed in vivo or in vitro, the present development of the OECD test Guidelines Programme for Guidelines on percutaneous Absorption/Penetration has to be taken in account.
EC method B.36 or OECD guideline 417

6.5 Available toxicological data relating to toxicologically relevant non-active substances (i.e. substances of concern) [Ann IIB, VI. 6.5.]
A short evaluation of the toxicological properties of the other substances in the preparation must be attached. The source(s) of information (scientific literature, regulatory reviews, etc.) must be stated and a summary must be given in the evaluation.
Copies of any literature cited must also be included in the data submission.
Detailed guidance on submitting this data is given in Chapter 4.

6.6 Information related to the exposure of the biocidal product [Ann IIB, VI. 6.6]
Sufficient information on exposure to the biocidal product likely to occur during the proposed conditions of use must be submitted.
The information should include all relevant stages of formulation and of use (Chapter 2 part A 2.10) and all possible exposure routes. Actual exposure data and/or calculations using validated models are
acceptable. Test reports of any studies conducted related to the exposure of the biocidal product on humans must be submitted. An expert judgement is needed to decide if any other studies are required (see Chapter 1.2, point 4). A starting point is the report 'Assessment of human exposures to biocides', see reference.
Where necessary, the test(s) described in Part A (core data set for the active substance), shall be required for the toxicologically relevant non-active substances of the preparation (see Chapter 4).

Re 6.4 Generally it is not possible to reliably estimate the dermal absorption from a formulation without specific studies using that formulation. A dermal absorption study of the representative product is not required for Annex I inclusion purposes. This assessment will be performed at the product authorisation stage, usually with studies on products rather than the active substance (agreement TMI 2007). Enhanced dermal absorption due to simultaneous application of a product other than the biocidal product in question should not be considered at Annex I inclusion stage. If information of such interactions is available, it should be included in the CAR under Elements to be taken into account by MSs when authorising products (agreement TMI 2009).
The 'EU guidance document on dermal absorption' [4] should be followed for dermal absorption (see also Appendix IVB of TGD on Risk Assessment). Starting point was a default value of 100% dermal absorption unless a default value of 10% can be used on the basis of physico-chemical properties. If necessary (if dermal exposure is an important exposure route and if the risk evaluation shows that the limit value set on the basis of health considerations is exceeded) an *in vitro* and/or *in vivo* dermal absorption study should be carried out to refine the risk evaluation.
The studies should be carried out in accordance with OECD guidelines 427 and 428 and the corresponding 'EU guidance document on dermal absorption'.
The test substance concentration(s) used should be of the order of magnitude of the estimated human exposure (see also §2.2.1 data requirements substance, Ann IIA, VI. 6.2.).

For an exposure estimate as starting point the 'guidance document ' on dermal absorption' [4](Sanco/222/2000 rev.7)) was used until the beginning of 2013. Default values, i.e. 100 % (diluted formulations) or 10 % (concentrate formulations) depending on physico-chemical properties, may be applied.. From now it is proposed to reference the updated EFSA guidance document on dermal absorption (EFSA Journal 2012;10(4):2665) The applicability of the default values of the updated guidance was discussed in the TM's of 2012. Default values, i.e. of 25% for products containing >5% a.s or 75% for dilutions containing ≤5% a.s. or 10% dermal absorption in case MW>500 and log Pow < -1 or >4 or <75% for dilutions with an oral absorption <75% or <25% for concentrates and dilutions with an oral absorption <25%. The TM welcomed the use of the revised default values in general. The EFSA default values were endorsed by the TM; however, on a case-by-case basis divergence to higher or lower values may be possible when supported by robust evidence. The guidance should be used with flexibility and intended to be used with appropriate flexibility. The guidance is not a legally binding document; therefore deviation is possible if there is robust evidence supporting it.
Dermal absorption testing is only needed in cases where an unacceptable risk was identified in the first tier. In cases, where relevant dermal absorption studies are available, these data can be used in the first tier (The dermal absorption studies can be used in case they are acceptable for the product in question).

In the TM has been decided that more detailed information should be provided by the Rapporteur MS on the dermal absorption value(s) in the LOEP. This should indicate how the value(s) was derived (in vitro and/or in vivo studies) and what exactly was tested (concentration of the a.s. and type of formulation). The text should also indicate the basis of the applicability of such values to the representative product (both the concentrate and the in-use dilution). This information is crucial at the Product Authorisation stage when a decision is required whether the dermal absorption values established in the LOEP can be extrapolated to other products (see MOTA; agreement TMII2012).

Re 6.5 Substance of Concern: A guidance/position on how to deal with substances of concern is in development (datarequirements and risk assessment).

Additional data
The text below in the grey frames is from the TNsG on preparation of dossiers and study evaluation (March 2002), Part I Dossier Guidance; Appendix 4.3 Check for completeness and quality of data compiled in Doc. IIIB [5].
Numbering in these grey frames is the same as the section numbering in the document mentioned above.

6.7	*Further human health-related studies*
6.7.1	*Food and feedingstuffs studies*
6.7.1.1	*If residues of the biocidal product remain on feedingstuffs for a significant period of time, then feeding and metabolism studies in livestock shall be required to permit evaluation of residues in food of animal origin*
6.7.1.2	*Effects of industrial processing and/or domestic preparation on the nature and magnitude of residues of the biocidal product*
6.7.2	*Other test(s) related to the exposure to humans Suitable test(s) and a reasoned case will be required for the biocidal product*

Re 6.7 There is a draft paper titled “stepwise approach on data requirements for the estimation of residues in food of animal origin and the need to perform food risk assessment” discussed in TM I09 (see TMI09Gen Item-8 revised framework paper). The purpose of the framework document is to define the general procedure for biocides DRA at Annex I inclusion stage, rather than provide detailed technical guidance.

Waiving, read-across and bridging
The basic principle is that the applicant submits all data or provides statements for the data requirements. In certain cases, data requirements may be waived by the non-submission of a study or by read-across or bridging. The applicant must in such cases explicitly give justification. More information about waiving is given in the TNsG on data requirements (§1.4 and corresponding addenda) and in 1.2.1 data requirements active substance.

2.3 Derivation endpoints and limit values

Instructions for the evaluation of toxicity studies are given in several EU documents. Studies are evaluated by using criteria. This evaluation leads for each study and for each sub-aspect to a toxicologically based endpoint, and finally to the toxicological profile of a substance. A brief indication of the chapters in various EU documents that are relevant for derivation of a toxicological profile of a substance is given below.

TGD on risk assessment [1]
PART I Chapter 2 Risk Assessment for Human Health (Ch 3 Effect Assessment and Ch 4 Risk Characterisation) contains useful information;
- Ch 3.1 - 3.4 explain the general principles of effect assessment.
- Ch 3.5 - 3.12 specifically deal with the principles of effect assessment per type of study.
- Ch 4 elaborates the factual assessment of studies.
- Appendix IVA-C describes various factual instructions as regards toxicokinetics (including dermal absorption) and several physiological factors.
- Appendix V describes the strategy that can be followed for selecting the most suitable exposure routes for toxicity tests.
- Appendix VI describes default reference values for several biological parameters of test animals (body weights, water and food consumption, body surfaces and respiration volumes).

TNsG annex I inclusion [6] and the chapter 4.1 Quantitative Risk Characterisation [7]
- Ch 2 Hazard and Effects assessment of an active substance very briefly describes how to determine whether a substance meets the criteria for Annex I inclusion.
- Ch 3 Exposure Assessment briefly describes how exposure estimation and cumulative exposure should be dealt with.
- Ch 4 Risk Characterisation briefly discusses how a NOAEL must be determined, and which safety factors can be used. The concepts AEL (Acceptable Operator Exposure Level), MOE (Margin Of Exposure) and ADI (Acceptable Daily Intake) are explained as well.
- Chapter 4.1 Quantitative Risk characterisation describes the tiered approach for human health risk characterisation of biocides for threshold-based effects based on the derivation of systemic acute, medium-term, and/or long-term AELs and MOEs.
- Ch 5 Criteria for Annex I, IA and IB inclusion presents the criteria for Annex I inclusion.
-

TNsG on product evaluation [8].
- Ch 4 Risk assessment for human health briefly describes the risk assessment process.
- The Appendices of Ch 4 mainly describe procedural instructions for assessment per type of study.

TNsG on preparation of dossiers and study evaluation [5].
Describes the format in which the studies must be summarised.

2.3.1 Derivation endpoints list for the human toxicological profile

The toxicological endpoints derived from the submitted studies form the basis of the risk assessment. Ch 4.3 of the TNsG on Annex I inclusion [6] briefly discusses the use of data from studies when deriving endpoints per type of study.

The text below in the grey frames is from the TNsG on Annex I inclusion, chapter 4.1 [7]. The numbering in these grey frames is the same as the section numbering in the TNsG on Annex I inclusion.

4.3 Evaluation of each human health endpoint

Toxicokinetics and dermal absorption
Data on toxicokinetics will provide information on the possible fate of the active substance in the human body. Sufficient information on absorption should be available to support route-to-route extrapolation in the risk characterisation for product types where it is needed or to address species-specific mechanisms if relevant.
Studies on, for example dermal absorption may contribute indirectly to risk characterisation. They may also provide information on the possible toxic behaviour of the active substance for example it may indicate a potential for dermal toxicity or a dermal deposit leading to the possibility of skin sensitisation or carcinogenic effects. Dermal absorption must also be taken into account, since dermal exposure may be higher and prolonged if a product is not washed off the skin.

Acute toxicity
Acute toxicity will not often feature as a critical endpoint in risk assessments for professional use. Most exposure will probably be via the dermal route and also by inhalation.
Risk characterisation will be quantitative since acute effects usually have a threshold, and thus can be based on a $LD(C)_0$ or $LD(C)_{50}$ value.

While acute toxicity is usually not characterised by a NOAEL(C) (or LOAEL(C)), these can be used if available from sub-acute toxicity studies. $LD(C)_{50}$ values are the most frequently available data but are not so suitable for risk characterisation since they are based on the endpoint of lethality. Additional assessment factors are needed as described in 4.1.3.
Occasionally information from human case reports of poisoning may be available. The use of this for risk characterisation will depend upon expert judgement on the reliability of the reported information. Problems include the availability of an effect level but no information on a no-effect level or a dose-response relationship. Oral toxicity will have an impact upon risk assessment where ingestion may occur for example through poor occupational hygiene. A substance would normally have to be very toxic or toxic for this to be an issue of concern.
Non-professional users may use large quantities of some active substances on an occasional basis and with less control over exposure than professional users (for example, in wood preservative products and antifouling products). Non-professionals will not usually use protective equipment and, in fact, cannot depend on it to reduce risk to an acceptable level, (Annex VI para. 73 and 74) so, in practice, dermal and inhalation exposure may be considerably greater than for professional users for the same pattern of use.
For the general public the most relevant acute toxicological endpoint is oral for exposure following accidental/intentional ingestion of an active substance. Risks based on oral toxicity of active substances shall be considered for all product types due to the risk of accidental ingestion by young children. Dermal exposure to for example treated fabrics or soft furnishings would usually be low level and would be compared to data from a repeated dose study.
Inhalation exposure is especially relevant where volatile active substances have been applied recently indoors.

Irritation and corrosivity
The risk to professionals from irritation and corrosivity should be considered in the first place without taking into account the risk reduction provided by personal protective equipment and respiratory protective equipment. The risk for dermal and inhalation exposure and contact with the eyes should be considered.
These toxicity endpoints are more significant for products for non-professional use since one must assume that no PPE is worn during application of products.
Dermal contact could be significant depending on the formulation type and method of application for the product. Formal quantitative risk characterisation is not usually possible but comparison of information on the maximum non-irritating dose and the proposed product concentration (and in-use concentration, where relevant) may be possible if sufficient information is available. The severity of the irritant effect of the product and the predicted frequency of use should also be taken into account. A measure of that severity is provided by the classification criteria for which the active substance qualifies under directive 67/548/EC.
Particular attention should be given to an active substance which is classified as corrosive or severely irritant to the skin or eyes when it is likely to trigger the classification of biocidal products under 99/45/EC as severely irritant or corrosive or as irritant to the respiratory tract. Exposure during all stages of use of typical products should be described for prescribed conditions of use taking into account the presentation and/or delivery of the product, and also realistic worst case conditions. Data from Poison Control Centers could also be used in the assessment process.

The full range of risk management procedures should be used to reduce the possible risk arising from the use of biocidal products classified as severely irritant or corrosive to an acceptable level, bearing in mind for non-professional use paragraph 73 of Annex VI of the Biocidal Products Directive[1]. Risk management could play a key role for the final acceptability of the use of products and would, therefore, be influential in the decision as to whether the risk from use of the active substance is acceptable. Consequently, the risk from these effects of particular concern will have to be considered on a case-by-case basis for both active substances and products.
In some cases, use of biocidal products will leave residues that cannot be removed, or are not intended to be, removed. It is, therefore, important to consider the potential for irritation effects, especially when exposure is frequent. For example, dermal exposure might occur for those handling treated wood, or working in areas that are frequently cleaned with biocidal products (for example furniture polish).
Important for the risk characterisation of these effects could also be that an active substance, as it dries may increase in concentration within the residue to a level that causes irritation.
Irritation can also be an important endpoint for the assessment of risks to children. These may spend a larger proportion of their time in contact with treated surfaces, for example carpets and textiles. This applies also to companion animals (pets).

Sensitisation
Risk characterisation for skin sensitisation is more difficult to formalise than for many other toxic endpoints. Test methods to detect the potential sensitising effects, and classification and labelling guidelines are well-established.
However, the potency with which sensitising substances cause skin sensitisation appears to vary widely, depending on chemical class and structure. Less well developed is a method to either quantify the risk of sensitisation following exposure, or compare the potency between substances. Data from the Local Lymph Node Assay will provide useful information on these points when they are available for an active substance and, in the longer term, its use may develop to form the basis of a formalised method of comparing potency within groups of substances.
In the meantime, the risk assessment of sensitising active substances will often have to be conducted on a more semi-quantitative basis.
Actual or estimated exposure can be compared with either the NOAEL in the LLNA or the potency (expressed as the amount of the chemical per unit area of skin required to cause a defined response) when reliable data is available. When such data are not available, judgements will have to be made on a case-by-case basis as to whether the potential for skin sensitisation described in an animal study report constitutes a cause for concern. Such judgements will take into account all available data from animal studies, evidence from human case reports (including concentrations/formulations resulting in effects and frequency of exposure required to elicit an effect) and estimates of likely exposure. Information from closely related formulations may also be useful in the risk assessment. Structural alerts and signs of ability of the substance to cause respiratory sensitisation or hypersensitivity must also be taken into account. The irreversibility of sensitisation and the apparent variation of sensitivity amongst the human population will influence the caution with which the acceptability of the risk is interpreted.
It is recognised that the role of the whole range of available risk management procedures will be extremely influential on the risk assessment for sensitisation.

[1] This remark relates to biocidal products whose evaluation should be carried out in accordance with the guidelines prepared on Annex VI of the BPD. Therefore if the risk is decreased in a subsequent biocidal product, this submission should be evaluated on its own merits/on a case-by-case basis.

The reliability of the control of exposure will be of paramount importance for the acceptability of risk from the use of products by both professionals and non-professionals. In some cases the use of biocidal products will leave residues. It is, therefore, important to consider the potential for sensitisation, especially when exposure is frequent. For example, dermal exposure might occur for those handling treated wood, or working in areas that are frequently cleaned with biocidal products (for example, furniture polish). It should also be taken into account that, as it dries, an active substance may increase in concentration within the residue to a level that causes sensitisation or elicit an allergic reaction.
Sensitisation can also be an important endpoint for the assessment of risks to children. They may spend a larger proportion of their time in contact with treated surfaces such as carpets and textiles. This applies also to companion animals (pets).
The potential of active substances to cause respiratory sensitisation appears to vary widely. Where criteria (Dir. 67/548/EEC) for classification as a respiratory sensitiser are met, a case-by-case evaluation has to be performed to determine if the risk from exposure to the substance is acceptable or not.

Repeated dose effects
Repeated dose effects (as interpreted from the 28 day study, the 90-day study and the long term toxicity study, for observations of genotoxicity or carcinogenicity see following sections) will be of concern whenever exposure is on a regular and/or frequent basis and especially if the effects have been observed to be irreversible or only partially reversible. Most effects can be assessed using quantitative risk characterisation and therefore depend upon the difference in dose levels at which adverse effects are seen in animals (or humans) and the estimated exposure for the accompanying product. The key factors are the most sensitive, relevant NOAEL, the effects it is based upon and the dose response that occurs at higher doses. If the effects are irreversible a greater assessment factor will be required between the NOAEL and the exposure for humans.
Effects noted in repeated dose studies are critical endpoints for secondary exposure (man via the environment and via occupational settings) because exposure can be repeated for various reasons. It might be that the same individuals enter treated areas immediately following regular treatments (including staff in hospitals, offices, shipyards) or that they frequently handle treated goods (such as carpenters). Long-term, low level inhalation exposure is also possible from indoor use of treated material. Exposure in the diet via residues should normally be compared to chronic NOAELs.

Genotoxicity
When a positive result has been obtained in genotoxicity studies the strategy to be followed for further testing is detailed in Annex IIA and is amplified in the TNsG on data requirements.
Since it is usually assumed that a threshold does not exist for genotoxicity (with the possible exception of aneuploidy) these studies cannot provide any quantitative input to the risk characterisation. However, a conclusion that potential for genotoxic activity exists is a fundamental qualitative input to risk characterisation.
Genotoxicity will be a critical endpoint for all active substances, but especially those used in non-professional products. The BPD (Art.5 (2)) states that “A biocidal product classified according to “ Council Directive 1999/45/EC “as….a category 1 or 2 mutagen….shall not be authorised for marketing to, or use by the general public.” The risk to the general public from secondary exposure to these substances would also usually be unacceptable.
Genotoxicity will be a critical endpoint for most active substances where positive results are obtained in appropriate studies. In general the risk from these substances will be unacceptable if exposure is likely to occur but will depend upon the available measures to control and limit exposure.

Furthermore, if genotoxic substances are listed on Annex I, they should be considered as strong candidates for comparative assessment, see chapter 8.
It is essential that such active substances be subject to strict risk management.
The criterion in 67/548/EEC for category 3 mutagens states that indications of possible genotoxic effects in somatic cells cause concern for humans but there is insufficient evidence to place the substance in category 2. The risk from a category 3 mutagenic substance in a biocidal product for non-professional users only, who are assumed to be unprotected from exposure, may be considered acceptable on a case-by-case basis, for example, where exposure via a route of concern is not likely to occur. The significance of adverse effects in genotoxicity studies for those exposed via the environment would be the same as for non-professionals in the sense that one must assume that they are not protected from exposure. However, whereas non-professionals cannot use products containing category 1 or 2 mutagens, they may be exposed to these substances from the environment following use of products by professionals. A thorough assessment of possible groups entering treated areas or handling treated goods is essential. The possibility of exposure and the available measures to control and limit exposure would also influence whether the risk was so low as to be acceptable.
The developments in the field of carcinogenicity testing strategies should be followed and applied to biocides where relevant. Sometimes a substance can be classified as a Cat 3 Mutagen. The supplier will then handle the substance with caution and may consider that further testing, for carcinogenic potential is unnecessary as the results of the testing will not affect how the substance is handled. In this case the substance is never formally classified into Cat 2 for carcinogenicity. However, it should be considered that, if it should be possible to waive studies in these circumstances, then the restrictions under BPD that are placed on substances classified in Cat 2 should apply.

Carcinogenicity
The acceptability of the risk from active substances for which carcinogenic potential exists will depend upon the appropriate category of carcinogenic classification, the likely mechanism of carcinogenicity and the extent of exposure.
The BPD (Art.5 (2)) states that “A biocidal product classified according to “Council Directive 1999/45/EC “as….a category 1 or 2 carcinogen….shall not be authorised for marketing to, or use by the general public.” The risk to the general public from secondary exposure to these substances would also usually be unacceptable. The risk from active substances that meet criteria for categories 1 or 2 carcinogenicity under 67/548/EEC will not be acceptable where exposure is likely to occur.
Furthermore, if they are listed on Annex I, they should be considered as strong candidates for comparative assessment, see chapter 8. It is essential that such active substances be subject to strict risk management (see Annex VI para.75).
The inclusion of active substances meeting the criteria for category 3 classification under 67/548/EEC will be strongly dependent upon the mechanism and levels of exposure.
If the most likely mechanism has a threshold then a normal risk assessment approach can be taken. However an assessment factor of 1000 might be used to the critical carcinogenic effect (such as increased incidence of tumours). If more data on the mechanism is awaited (one of the criteria for category 3) or if it is believed that a genotoxic (non-threshold) effect may be responsible for the carcinogenic potential then a threshold approach to risk assessment is not possible and the acceptability of the risk must be carefully considered qualitatively.

Toxicity to reproduction and development

The BPD (Art.5 (2)) states that “A biocidal product classified according to “Council Directive 1999/45/EC “as….classified as toxic for reproduction category 1 or 2….shall not be authorised for marketing to, or use by the general public.” The risk to the general public from secondary exposure to these substances would also usually be unacceptable

Active substances that meet criteria for categories 1 and 2 as toxic to reproduction under 67/548/EEC and cause effects on reproduction at dose levels which do not produce other signs of toxicity in animals should, in general, be considered as strong candidates for comparative assessment (see Chapter 8). It is essential that such active substances be subject to strict risk management (see Annex VI para. 75).

Effects on the reproductive system are often threshold-based allowing a quantitative risk characterisation to be carried out. However, effects on the development of offspring can be due to a genotoxic mechanism and the potential for this needs to be considered since a qualitative risk characterisation would then be appropriate.

If an active substance is classified as category 1 or 2 toxic to reproduction and is subject to quantitative risk characterisation, then an assessment factor of 1000 applied to the critical reproductive toxicity effect (such as increased incidence of malformations) might normally be used. The assessment factor for category 3 substances will depend upon the severity of effects, their relationship to toxicity observed in the mothers and the exposure level at which they occurred compared with effects seen in other animals. It should also be remembered that the general public is unprotected from exposure and that the people concerned may not be aware of their exposure, which implies the use of a very stringent assessment factor.

Fertility and developmental effects are relevant endpoints for exposure scenarios involving repeated exposure. However, developmental effects can occur following short-term exposure if this happens to coincide with the critical formative stages of embryonic and foetal development. Furthermore, effects on fertility have been reported already following short-term exposure so this risk should also be characterised where indicated.

Other Toxicity End-points

In addition to the above-mentioned effects, other effects such as endocrine disruption, immunotoxicity and neurotoxicity must be risk assessed.

The toxicity endpoints neurotoxicity, immunotoxicity, behavioural toxicity and endocrine effects may be as significant for professional as for non-professional users. They may also be significant for secondary exposed persons, among them children, especially if the use of the biocidal product leaves residues that cannot, or are not intended to be, removed.

For these effects there are no specific criteria for classification according to 67/548/EC. Consequently, judgement as to the entry onto Annex I must be made on a case-by-case basis, taking into account the use pattern and consequent potential primary and secondary exposures.

The effects may be of concern after any type of exposure (ranging from acute to chronic); they may be reversible or irreversible. In any case, the acceptability of the effects will be reflected by the relevant NOAEL and the assessed exposure.

Re. toxicokinetics and dermal absorption:

1) Dermal absorption

Primary and secondary exposure may occur via the dermal route.

The expected external dermal exposure is calculated by means of models. For calculation of the systemic exposure it is important to know the extent to which the skin absorbs a substance and/or formulation after exposure to a relevant level. These dermal absorption data are used to convert the external exposure to systemic exposure and this is then in the risk evaluation compared with the systemic AEL.

Where no data are available, the percentage dermal absorption for man can be estimated. In case dermal absorption data are available, these are used for derivation of the dermal absorption percentage.
The situations with and without available data are elucidated below. The 'EU guidance document ' on dermal absorption' is used [4]. For an exposure estimate as starting point the 'guidance document ' on dermal absorption' [4](Sanco/222/2000 rev.7)) was used until the beginning of 2013. Default values, i.e. 100 % (diluted formulations) or 10 % (concentrate formulations) depending on physico-chemical properties, may be applied. From 2013 it is proposed to reference the updated EFSA guidance document on dermal absorption (EFSA Journal 2012;10(4):2665) The applicability of the default values of the updated guidance was discussed in the TMs of 2012.

No dermal absorption data available
If no suitable (animal) experimental data are available, physico-chemical data can give an indication of the extent of skin penetration.
The choice of the default value should be justified in the decision making. If suitable toxicokinetic data via the oral route are available, it can also be assumed that the dermal absorption, in the absence of animal experimental data with the relevant route, will be <75% for dilutions with an oral absorption <75% or <25% for concentrates and dilutions with an oral absorption <25%..

Dermal absorption data available
In vitro and/or *in vivo* research with the formulation is required if it is expected that the systemic AEL will be exceeded under application of default values for dermal absorption, and dermal exposure is an important exposure route [4, 9, 10,11].

In vivo research (usually carried out with the rat) and/or *in vitro* research (rat versus man), both carried out with a relevant dose, are used for derivation of the dermal absorption for man. *In vitro* research is carried out with the formulation to study the differences between species (rat/man). The triple pack (combination of *in vitro* and *in vivo* rat studies and an *in vitro* study on viable human skin according to OECD 427 and 428) is often considered the "gold standard". If no comparison can be made between species because the required research is lacking, the percentage dermal absorption is derived from the *in vivo* study with the rat. This is in many cases a worst case assumption because the human skin generally forms a better barrier than the shaven rat skin. For the interpretation of the animal experimental data and the subsequent derivation of dermal absorption we refer to the guidance document [4]. However, in vitro studies on viable human skin according to OECD 428 will also be accepted as stand alone.

The dermal absorption studies described above must be carried out with dose levels that correspond with the exposure expected for applicator and re-entrant. The toxicological dossier may also contain dermal toxicity studies, such as, e.g., a 28-day study with dermal administration.
Such studies are usually carried out with dose levels that are (much) higher than the expected exposure and they are not suitable for derivation of dermal absorption values for man. These dermal toxicity studies, however, may -if relevant- form the basis for derivation of a systemic AEL (see NL tox part 'Calculation of the systemic AEL on the basis of dermal studies').

In TMIII2006 there was agreement that a general approach for inclusion or exclusion of the amount retained in the stratum corneum cannot be followed.
Including all skin levels is the worst-case approach that can be used in the absence of tape stripping data. Expert judgment will be needed, taking into account the overall data set, the exposure time, the tape stripping data if available and the kinetics of the substance in the receptor fluid. The number of tape strips needed to remove a given fraction of the stratum corneum varies due to a number of variables, and therefore the decision should be made case by case. It has been suggested that the two first strips would be excluded, and considered as the upper layer of the stratum corneum. The total number of strips varies greatly, and with a larger total numbers of strips, more strips can generally be excluded.
In addition to the methodology specifically agreed to by the TM, newer guidance like the Dermal Absorption document of the WHO (Environmental Health Criteria 235, 2006, see the link below) and REACH guidance should be taken into account.
WHO guidance on Dermal Absorption (Environmental Health Criteria 235, 2006) is available at: http://www.who.int/ipcs/publications/ehc/ehc235.pdf

More detailed information should be provided by the Rapporteur MS on the dermal absorption value(s) in the LOEP. This should indicate how the value(s) was derived (in vitro and/or in vivo studies) and what exactly was tested (concentration of the a.s. and type of formulation). The text should also indicate the basis of the applicability of such values to the representative product (both the concentrate and the in-use dilution). This information is crucial at the Product Authorisation stage when a decision is required whether the dermal absorption values established in the LOEP can be extrapolated to other products (see MOTA; agreement TMII2012).

Enhanced dermal absorption due to simultaneous application of a product other than the biocidal product in question should not be considered at Annex I inclusion stage. If information of such interactions is available, it should be included in the CAR under *Elements to be taken into account by MSs when authorising products* (agreement TMI2009 see MOTA).

2) Absorption after oral exposure

Determination of the level of the systemic AEL after oral exposure requires insight into the extent to which a substance is absorbed by the body after oral administration.
The value for absorption after oral exposure to a relevant amount of substance is the sum of the amounts of substance and metabolites that are subsequently excreted in the urine and that remain in tissues and carcass. If the absorbed dose is significantly lower (<80%) than the administered dose, this is adjusted by a correction factor equal to the percentage absorption. According to experimental data when the oral absorption rate exceeds 80% the default value of 100% should be applied for the derivation of AELs and internal exposure levels *via* the oral route See MOTA; agreement TMII2011).
Because absorption may be dose-dependent, absorption data are required of a dose in the range of the NOAEL.
Recent research has shown that inclusion of bile excretion in the amount of absorbed substance may result in overestimation of the systemic availability of substances and their metabolites as result of a first pass effect [12].
In the first pass effect, a substance is in the liver totally or largely removed from the blood after absorption from the intestines, either before or after being metabolised, and is excreted via the bile without getting into the total circulation. In case the critical effect does not occur in liver or gall ducts but more peripherally, there is a chance that the established AEL is too high when the total fraction excreted with the bile is considered as systemically available.

If liver or gall bladder toxicity is the critical effect on the basis of which the AEL is established, bile excretion studies are, however, useful for establishing the “organ availability” of the administered dose.
Biliar excretion is therefore no longer taken into account for determination of the systemic availability of a substance if the critical effect has not been found in liver or gall ducts. In that case the sum of the amount of substance and metabolites that are excreted in the urine and that remain present in tissues and carcass are used as value for absorption after oral exposure.
This means that the risk will be overestimated in some cases.
This can be overcome by a comparison of “Areas Under the Curve” after administration via the oral and intravenous routes which gives a much more reliable picture of the systemic availability.

Re. acute toxicity:

For harmonisation with other substances, the rat data would be preferred. On the other hand, if the mouse LD_{50} is lower, it would be the precautionary approach to select this value. Since this decision would in most cases only affect classification and labelling which is decided in the RAC of ECHA, it was agreed that both values can be included in the LOEP (agreement TMII2009 see MOTA).

Re. carcinogenicity:
In the EU the lifetime cancer risk methodology is mentioned in the in Ch 4.1.TNsG on Annex I inclusion, chapter 4.1 The text in the grey frames below is from the TNsG on Annex I inclusion chapter 4.1 [7]. Numbering in these grey frames follows the section.

For carcinogenic substances with a non-threshold mode of action a risk characterisation should be conducted following both a qualitative and/or semi-quantitative approach for cancer effects as well as the quantitative approach for non-cancer effects (threshold-based), as described above where relevant. The relevance of the mode of action for humans should also be considered. The DMEL methodology in the context of REACH provides guidance for semi-quantitative risk assessment of carcinogenic substances with a non-threshold mode of action, incorporating two specific methodologies, the ‘linearised’ approach referring to the lifetime cancer risk and the ‘Large Assessment Factor’ approach as proposed by EFSA. Guidance for the evaluation of carcinogenic substances with a genotoxic mode of action is also available from U.S EPA.

Re. toxicity to reproduction and development:
The use of developmental studies in risk characterisation are discussed in the TM based on 4 questions and answers:

Should developmental studies be used for AEL derivation if their NOAEL is the lowest available?

A1: When valid developmental studies are available, all relevant critical effects should be evaluated together with other observations from other studies. If the NOAEL derived from relevant effects in a valid developmental toxicity study is lower than those from short-term RDT studies, and this cannot be explained by dose spacing, the NOAEL from the developmental toxicity study should be used for the derivation of the AEL value. This will apply to the global population (thus protecting both pregnant and non-pregnant women).

Developmental studies are often the only studies to use gavage dosing with the aim of determining a NOAEL. This can give rise to Cmax related effects, such as certain clinical signs, that might not be relevant to dermal exposures where a spike of absorption is not normally seen.

It should be noted that due to their inherent limitations, developmental studies cannot be considered as surrogates for other repeated-dose toxicity studies when these are missing or invalid.

Q2: Can maternal effects be regarded as critical effects for characterising medium- and long-term risks? If so, is it necessary to apply duration extrapolation factor?

A2: Maternal effects can be regarded as critical effects for deriving medium- and long-term AELs if they are deemed relevant in comparison with other critical effects observed in other valid repeated dose toxicity studies.

Usual assessment factors and duration extrapolation factors (as recommended in the chapter 4.1 of the TNsG on annex I inclusion) should then be applied, unless scientific rationale is presented for adapting them to the specific situation. Deviating from the default factors will need to be justified e.g. by explaining why an effect is specific to the pregnancy period.

Q3: Can developmental effects (i.e. embryotoxic or foetotoxic effects) be regarded as critical effects for characterising medium- and long-term risks?

A3: When the lowest relevant NOAEL is based on developmental effects, this may be used for deriving medium- and long-term AELs on a case-by-case basis. This will depend on the type of effect and its relevance for humans. Duration extrapolation factor might not be needed if the effect is specific to the developmental-time window investigated.

Q4: In case where a RC is based on a maternal effect, should the intra-species factor remain at 10 or should it be reduced for taking into account the higher sensitivity of the pregnant subpopulation?

A4: There is no evidence that pregnant women are always more sensitive than the rest of the population. The AEL derived from maternal effects will cover the whole population, and the intra-species factor is 10 unless there are specific reasons to deviate from this.

Re. other toxicological endpoints:

The use of Developments NeuroToxicity (DNT)studies are discussed in the TM to assess the effects of pyrethoids (agreement TMII2010 see MOTA).

Possible DNT effects induced by pyrethroids are covered by the AELs set on neurotoxicity in the acute neurotoxicity and medium-term studies, since DNT effects from acceptable OECD TG 426 performed studies are taking place at higher LOAELs than other neurotoxicological effects. The DNT effects are also covered by the AELs set for long-term exposure (based on neurotoxic or other critical endpoints. The data available also indicate that an additional assessment factor for species sensitivity is not required.

It has been agreed that the basis for the assessment of this category of substances will be the following paper available in Circa:

http://circa.europa.eu/Members/irc/env/ber/library?l=/meeting_documents/technical_meetings/2010_-_tm_ii&vm=detailed&sb=Title

2.3.2 Relevant NOAELs for AEL and MOE derivation

The text in the grey frames below is from the TNsG on Annex I inclusion chapter 4.1 [7]. Numbering in these grey frames follows the section.

4.1.2 Relevant NOAELs for AEL and MOE derivation

The quantitative extrapolation of hazard from the animal experiment to exposed humans is based on the most relevant endpoints. In most cases, these endpoints should correspond to relevant NOAELs, but LOAELs or benchmark dose levels are also used. Generally, a whole set of relevant NOAELs is established with respect to different exposure time-frames and exposure routes. Relevant NOAELs for AEL and MOE derivation should be identified for all relevant exposure scenarios characterised by duration, frequency as well as route of exposure, and by the exposure profile for the target (sub-) population exposed. It should not be concluded from the absence of a particular exposure scenario for a given product that a relevant NOAEL is not needed, because different exposure scenarios might become relevant with subsequent product authorisations on Member State level. As specified in Article 14 of the Directive 98/8/EC the holder of an authorisation for a biocidal product shall notify the Competent Authority of information concerning an active substance or a biocidal product containing it, which may affect continuing authorisation. If new or additional data on the active substance (a.s) are submitted for the national product authorisation, a re-evaluation of toxicological data already submitted for Annex I Inclusion might be necessary at Member State level.

- Identification of Critical Effects

In the first step of hazard assessment, the whole data package should be evaluated for assessment of the most relevant critical effects considering the biological plausibility of the dose-effect relationship, its consistency over the whole data package, its severity and reversibility as well as the mode of action if known and its relevance for humans. For the latter IPCS/WHO has developed a framework for analysing the relevance of a non-cancer [13] or cancer mode of action for humans [14]. Likewise, appropriate studies should then be identified from which the relevant NOAELs for each of the relevant exposure time frames can be used to establish AEL and MOE values.

Furthermore, the data package should be evaluated with respect to local effects at the port of entry, e.g. lesions in the airways in inhalation studies or on the skin in dermal studies for which the derivation of a local threshold needs to be considered. Also indications for route-specific sensitivity and dose-response relationship shall be taken into account when considering the relevant NOAELs, if the data package allows and external values can be derived.

- General Approach

The study in the most sensitive and relevant species resulting in the most relevant lowest LOAELs will be selected for establishing the relevant NOAELs for AEL and MOE derivation. Often, several studies addressing a certain endpoint are available for one species. Different dose spacing in these studies results in different NOAELs and LOAELs. If study design and endpoints addressed are comparable, it might be appropriate to consider these studies together.

When they are comparable studies regarding study design (endpoints investigated, duration of exposure, route of exposure) and species/strain of animal, the 'overall NOAEL' should be the highest value identified in the available studies that provides a reasonable margin (≥ 2) over the lowest LOAEL, provided that due consideration is given to the shape of the dose–response curve [15].

As a general rule, if several relevant NOAELs are available the one that would result in the lowest Acceptable Exposure Level (AEL) for a given time-frame should be chosen.

- Relevant Time-Frames

A comparison of relevant NOAELs for AEL derivation for different time-frames provides useful information on the influence of exposure duration on the severity and spectrum of toxicity. Therefore, an assessment of the entire data package is of high scientific value, as it helps elucidate time-dependency of toxicity. This information is helpful to adjust human health risk assessment to varying time-frames for professional as well as consumer exposure.

The ILSI Health and Environmental Sciences Institute Task Force for Systemic Toxicity Assessment has also proposed the use of different time-frames for human exposure for which risk assessment might be required for PPPs (Table 1) [16].

The proposed time-frames are considered useful for the quantitative risk assessment of biocidal active substances for inclusion in Annex I of Directive 98/8/EC especially with respect to non-professional users and consumers. For professional users, evaluation often focuses on acute and long-term exposure. If intermittent exposure needs to be evaluated, relevant NOAELs for AEL and MOE derivation obtained from studies with daily administration of the test compound might in some cases be considered a conservative approach erring on the safe side. In this context, all available information on the time-dependency of toxicity should be taken into consideration.

Preferably, acute relevant NOAELs for AEL and MOE derivation should be derived based on acute studies with single exposure, which are designed to establish a dose-response relationship including NOAELs. The appropriateness of using doses and end-points from sub-acute, sub-chronic and chronic studies to establish acute relevant NOAELs needs to be carefully considered. Particular weight should be given to observations and investigations at the beginning of repeated-dose studies. However, in the absence of such initial information, all toxic effects seen in repeated-dose studies should be evaluated for their relevance in establishing acute relevant NOAEL for AEL and MOE derivation.

Table 1: Relationship between duration of human exposure and the studies required for hazard identification and establishment of relevant NOAELs for AEL/MOE derivation

Estimated duration of human exposure	Basic toxicity studies	Relevant NOAELs for AEL/MOE derivation
≤ 24 h	Single dose studies designed to determine NOAEL* or repeated dose studies demonstrating relevant acute effects e.g. - acute neurotoxicity - 28-d/90-d repeated-dose studies, acute effects developmental toxicity, acute effects * Data from LD_{50} studies can be considered supportive if appropriate acute effects were investigated	Toxic effects relevant for acute exposure
>24h – 3 (max. 6) months	Repeated-dose studies designed to determine NOAEL e.g. - 28-d/90-d repeated-dose studies - 90-d neurotoxicity - 12-m dog, depending on nature of effects - developmental toxicity - 2-generation study	Toxic effects relevant for medium-term exposure
> (3-) 6 months	Chronic studies or repeated dose studies designed to determine NOAEL and demonstrating relevant chronic effects e.g. - 18-m/24 m chronic/carcinogenicity - 2-generation study, chronic effects - developmental toxicity - 12-m dog , depending on nature of effects	Toxic effects relevant for long-term exposure

In principle, the following four situations could arise:

(1) A relevant acute NOAEL for AEL/MOE derivation is not allocated, since no acute toxic effects have been identified

(2) A relevant acute NOAEL for AEL/MOE derivation is based on an appropriately designed single-dose study

(3) A relevant acute NOAEL for AEL/MOE derivation is based on a repeated-dose study (including developmental/embryotoxicity studies), since the critical effect is also considered relevant for a single exposure

(4) A conservative relevant acute NOAEL for AEL/MOE derivation is based on a repeated-dose study if the critical effect was not adequately evaluated in a single dose study.

Most often, the medium-term relevant NOAEL for AEL and MOE derivation will be based on a repeated dose toxicity study (28-day or 90-day) or studies investigating specific end-points, e.g. reproductive toxicity, developmental toxicity or sub-acute neurotoxicity.

If there are indications that effects only become evident in chronic toxicity studies but might be initiated by sub-acute or sub-chronic exposures, the NOAEL for these effects in the long-term studies should be considered in selecting medium-term relevant NOAELs for AEL/MOE derivation. For the medium-term time frame the estimated duration of human exposure can be from >24 h to 3 (max. 6) months. The decision on whether the estimated duration of human exposure for this time frame should be 3, 4, 5 or 6 months, will be a case by case decision. The toxicokinetic properties of the active substance, such as long plasma half-life, potentially leading to prolonged internal exposure even after cessation of external contact with the biocidal product or the reversibility of the repeated-dose and chronic effects have to be considered.

In most cases, the relevant long-term NOAEL for AEL and MOE derivation will be based on a long-term toxicity study, generally a lifetime study in rats or mice, or studies investigating specific end-points such as reproductive toxicity or hormonal effects. Depending on the nature of effects the NOAEL from studies of shorter duration (e.g.: one-year dog study or developmental toxicity study) can be used for the derivation of the long-term AEL if the NOAEL is lower than the one based on a chronic toxicity study. In principle the one-year dog study is more relevant for the derivation of the medium-term AEL.

Specific points or effects

In TMII2011 is decided that when experimental data shows that the oral absorption rate exceeds 80% then the default value of 100% should be applied. Note that this is for the derivation of AELs and internal exposure levels via the oral route. The LOEP should contain a dermal absorption value including information on the derivation of this dermal absorption value (agreement TMII2012 see MOTA)

In TM III 2005 was discussed whether dental fluorosis is an adverse effect or only a cosmetic problem. The TM concluded that it is an adverse effect in animals, and should be considered as such also in humans. It was discussed whether dental fluorosis could be used as a marker for skeletal fluorosis if information on fluoride in bones is missing. However, the bone effects of fluoride are considered at least threefold less sensitive than dental fluorosis on the basis of human observations.

More information on dental fluorosis is available in the opinion of a scientific panel of EFSA, where the conclusion was that dental fluorosis is an adverse effect when it involves staining and minute pitting of the teeth, but not adverse when only white spots and opaque striation is observed (see for PDF file appendix 4).

In TMII2007 there was a discussion on which studies can be used in setting the acute AEL for anticoagulant rodenticides?

The general problem in selecting the appropriate study for anticoagulants is that, in general, acute studies are not suitable for setting AELs due to the cumulative effect of anticoagulants. In terms of exposure and study duration, teratogenicity studies in the existing dossiers have been more relevant for AEL setting, and the developmental study in the most sensitive species should be used.

In TMIII2009 there was a discussion on “How should the systemic AELs be derived for pyrethroids, given that there is extensive first pass metabolism following oral administration?”

When appropriate data exists for dermal and inhalation routes, this data should be used to derive route-specific systemic AELs, rather than using oral data and route-to-route extrapolation. Extrapolation would be problematic due to extensive hepatic first-pass metabolism.

This approach requires that 1) appropriate route-specific data is available, and 2) large first-pass metabolism is demonstrated or likely.

2.3.3 Safety factors

A limit value is derived from the selected NOAEL by, amongst others, application of a safety factor. The safety factor applied in the EU for crop protection products is 100 for AEL, ADI and ARfD. The basis for this approach is a factor 10 for differences within the animal species (intraspecies differences) and a factor 10 for differences between animal species (interspecies differences). This last factor compensates for the wider variation in sensitivity in the population of exposed workers in comparison with the relatively small (and relatively homogeneous) group of exposed test animals.
The Biocides Directive 98/8/EC, Common Principles, stipulates that Member States should observe an appropriate safety margin, while indicating that a factor 100 is normally an appropriate safety margin but that a larger or smaller margin may be appropriate, depending on factors such as the nature of the critical toxicological effect. This means that, as for plant protection products, the normally chosen safety factor for derivation of limit values for biocides is 100. In chapter 4.1 Quantitative Risk Characterisation (TNsG on Annex I inclusion version 7 2008)) the tiered approach for human health risk characterisation of biocides for threshold-based effects based on the derivation of systemic acute, medium-term, and/or long-term AELs and MOEs is described. Both the 100-fold assessment as well as the a refinement of the assessment factors is described with special attention to route-specific contributions and protective measures. In TMII 2006 and TM V 2007 there was agreement in the standard body weight used in biocide CARs of 60 kg for an adult, amateur (general-public) and professional users. Moreover in TMIV 2007 is agreed that both the MOE and the AEL approach should be used.

The text in the grey frames below is from the TNsG on Annex I inclusion, chapter 4.1 [7]. Numbering in these grey frames follows the section.

4.1.3. Selection of Assessment Factors

Risk characterisation requires the choice of Assessment Factors (AFs), which account for extrapolation from animal toxicity data to the exposed human population.

At present, with the exception of genotoxic carcinogens and non-threshold mutagens, hazard assessment for different toxicological end-points is based on the assumption of a threshold.

The setting of the overall AF is a critical step, which considers inter-species variation and intra-species variation.

In the absence of sufficient chemical-specific data a default 100-fold AF is applied to the relevant NOAEL for AEL derivation in the first tier of risk characterisation (see Figure 1A). The basis for this approach is a 10-fold factor for inter-species variation and a 10-fold factor for intra-species variation. Variability is governed by toxicokinetic as well as toxicodynamics factors.[2]

Chemical-specific AFs as proposed by the WHO International Programme on Chemical Safety (WHO/IPCS) [17] can be introduced to replace a default AF if specific information is available on:

[2] The default value of 100 was included in the TNsG on Annex I inclusion (April 2002) and thus applied in previous evaluations of biocidal active substances. It is also included in the AOEL guidance document in the context of risk assessment of plant protection products under Directive 91/414 as well as in FAO/WHO (JEFCA, JMPR) and U.S EPA evaluations.

(1) Inter-species differences in toxicokinetics
(2) Inter-species differences in toxicodynamics
(3) Human variability in toxicokinetics
(4) Human variability in toxicodynamics

The use of scientifically valid human data reduces the level of uncertainty in comparison to extrapolation from animal models and is seen as a valuable contribution to science-based decision making. Biomonitoring studies, epidemiological data and medical poisoning records can be some of the sources of human data. Human volunteer studies should not be performed for the purposes of the BPD. However, human monitoring data can be requested for products already authorised for use under the BPD. As a prerequisite for the consideration of the use of human volunteer studies that have been performed for the purpose of regulatory frameworks other than the BPD, studies in humans should include clear statements that they were performed in accordance with internationally accepted ethical standards [18], e.g. the Declaration of Helsinki, 1997 [19]. In some cases, the use of human data in regulatory safety assessment might lead to more stringent exposure limits for some biocides than those that would have been derived on the basis of animal data only. If human data are used for AEL derivation, the 10fold inter-species AF is omitted and the 10-fold AF for intra-species variation is regarded adequate.

In addition to uncertainties in inter-species differences and intra-species variability, additional AFs for the following elements should be considered:

1. the nature and severity of the effect
2. the human (sub-)population exposed
3. deviations between the exposure in the study providing the NOAEL and the estimated human exposure as regards duration, frequency, or pattern (e.g. a sub-chronic study to a chronic study)
4. extrapolation from LOAEL to NOAEL
5. the slope of the dose-response curve
6. the overall quality of the toxicity data package

If the severity of the critical effect at the LOAEL was judged to be of particular significance an additional AF might be considered necessary. So far, this AF has not been higher than 10. Quantification should be determined on a case-by-case basis taking into account the dose-response data.

If the derivation of the AEL was based on a LOAEL and not a NOAEL, an additional AF has to be considered. This factor will vary depending on the slope of the dose-response curve and the magnitude of the effect at the LOAEL. This extrapolation step should be based on expert judgement. Other methods, such as the benchmark concept, are at present not routinely used in human health risk assessment. The use of LOAELs to set AELs should be a last resort; however, where the effects at the LOAEL are of moderate magnitude and not severe, the use of a LOAEL and an appropriate assessment factor reduces the need for additional animal studies.

For local effect at the port of entry (skin, eye, G.I. tract) it is sometimes justified to assume that either toxicokinetics or –dynamics (or both) do not contribute significantly to interspecies differences (as for example in the case of direct/pH-driven chemical action on tissue/cell membranes). In such cases, based on sound scientific reasoning, the 10-fold default factor might be reduced dependent on the mode of action. With regard to local effects on the respiratory tract, guidance is available e.g. from the EU project ACUTEX [20], which proposes to apply reduced interspecies AFs when extrapolating data obtained in rats to humans. Given that there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and when there is no data to inform on this uncertainty, it is prudent to assume that humans would be more sensitive than animals to effects on the respiratory tract.

In such a situation the default factor of 2.5 to address remaining uncertainties should be applied.

For other risk evaluation programmes in the EU (DNEL methodology in the context of REACH) slightly different default approaches concerning inter- and intra-species variability are applied. As a main difference, both the MOS approach for new and existing substances and the DNEL methodology in the context of REACH extrapolate inter-species differences according to the allometric scaling principle (species differences in caloric demand) in combination with an additional default factor of 2.5 to account for remaining uncertainties. For the rat, the overall inter-species default factor is 10 and thus similar to the approach outlined above (4 x 2.5 = 10). For the dog, the default value is lower (1.5 x 2.5 = 3.75); for the mouse higher (7 x 2.5 = 17.5). The allometric scaling principle could be taken into consideration in borderline cases especially if there is a need to harmonise with decisions made in other regulatory fora. In this case allometric scaling could be used to give support to the final decision made in the risk characterisation.
In addition, when available, data from the use of PBPK modelling shall be used for the purpose of refining the assessment factors. PBPK models will not remove all of the uncertainty from the risk assessment process. The rationale for using PBPK models in risk assessment is that they provide a documentable, scientifically defensible means of bridging the gap between animal bioassays and human risk estimates. Guidance on the use of PBPK modelling is currently under preparation by IPCS/WHO and should be followed when available [21].
The choice of the appropriate AFs should be explained in the dossier or report in detail, so that the decision process can be followed step by step.

Specific situations for assessment factors
To cover the lack of data in waiving cases an extra assessment factor can be used. In a case where there was scientific justification for waiving the 2-generation study, it was decided that an extra assessment factor (AF) of 3 should be used. Using an extra AF of 10, was considered over conservative. An extra AF was however considered necessary since, although waiving was scientifically based, the data that was to be lacking could not be covered by other studies. Furthermore, there was not a possibility for reading across from a 2-generation study of another substance (see MOTA [1]; agreement TMI 2007).

The AF will depend on the available data set, and the decision will have to be made case by case. If an extra AF is concluded to be necessary, a factor of 3 is considered sufficient to provide safe margins to cover for the use of subchronic studies for chronic exposure scenarios for anticoagulant rodenticides (see MOTA [1]; agreement TMI 2007).

An extra AF of 3 will be used for all AVKs for anti-vitamin K (AVK) anticoagulants for the severity of the effect,, while it was recognised that this factor is not scientifically derived (see MOTA [1]; agreement TM III 2006).

No extra AF is normally necessary, since a 1-year dog study should be considered sufficiently chronic for deriving the long-term AEL without additional AFs, unless there is a clear justification to the contrary (agreement TMIV2009, see MOTA).

2.3.4 AEL and MOE derivation

AEL derivation
The AEL is defined as the maximum amount of a substance to which the human population as a whole can be exposed at which no adverse effects on health are expected. Where relevant, different AELs can be determined for acute, medium-term (semi-chronic/short) or long-term (chronic) exposure. Both systemic as well as local AELs can be relevant.

Systemic AEL
This procedure with respect to systemic AEL derivation is extensively described in Ch 4.1.TNsG on Annex I inclusion [4a]. The text in the grey frames below is from the TNsG on Annex I inclusion, chapter 4.1 [7]. Numbering in these grey frames follows the section.

4.1.4 AELs

Depending on use patterns of biocidal products, humans will be exposed either as non-professional or professional users or due to secondary exposure, e.g. after application of biocidal products for domestic use. Risk assessment has to consider specific effects on sensitive sub-populations where appropriate such as infants, children, the elderly or women of childbearing age.

Systemic AELs are established as general health-based reference values for the human population as a whole including sensitive sub-populations taking into account use patterns and exposure scenarios. In principle, these AELs should be derived independently of the route of exposure. Such AELs represent the internal (absorbed) dose available for systemic distribution from any route of exposure and are expressed as internal levels (mg/kg b.w/day).
AELs for biocidal active substances can be determined as a threshold estimation of a daily or interrupted exposure of the general human population or a specific sub-population likely to be without an appreciable risk of adverse effects during a specified period of time. AELs should be established for all relevant time-frames of exposure (acute, medium-term, and long-term) based on the full toxicological data package available.

The derivation of AELs should follow the same common scientific principles as the derivation of the AEL proposed by the European Commission Health and Consumer Protection Directorate-General (DG SANCO) [22], which are applied also in other regulatory frameworks, e.g. for PPPs.

4.1.5 Systemic AELs
The majority of studies submitted for inclusion of active substances into Annex I of Directive 98/8/EC are oral studies. However, risk assessment mainly focuses on the dermal and the inhalation exposure routes.
To avoid additional experimental testing of other relevant routes of human exposure, systemic AELs will usually be set on the basis of oral studies, i.e. the external NOAEL is converted to an internal NOAEL with help of the oral absorption provided that the critical endpoints of the substance (including reproductive/developmental toxicity, neurotoxicity and non-genotoxic carcinogenicity) are covered and an adequate assessment factor for irreversible effects is given.

By use of dermal and inhalative route-specific absorption rates the external NOAELs might also be converted to systemic reference values. On that background, any additional information from route-specific studies is of high value for risk characterisation because it reduces the uncertainties associated with route-to-route extrapolation.
In case local effects at the port of entry are to be expected or there is indication for route-specific differences in toxicity which are not reflected by absorption data, additional considerations on appropriate reference values for risk characterisation are necessary (see chapter 4.1.6 below).
For the purpose of human health risk assessment for Annex I inclusion, the AEL should generally be derived for acute, medium-term, and long-term exposure and should be included in the list of end-points (Doc I, Appendix 1 of the CA-Report). Thus, a harmonised base will be provided for later applications for Annex I Inclusion, e.g. of the same active substance in a different biocidal product type, or for the authorisation of biocidal products at Member State level.
Even in cases where the complete toxicological data package does not indicate any acute hazard, setting an acute AEL would be required for the risk characterisation of acute scenarios for certain product types. In this case, the acute AEL may be the same as the medium-term AEL value. On the other hand, if setting a long-term AEL is not supported by the data package, e.g. due to waiving of long term studies based on exposure considerations, this should also be clearly indicated in the report and in any restrictions related to the Annex I inclusion.
Data waiving arguments are quite common in biocide dossiers. Therefore, it is clearly stated in the TNsG on Data Requirements that the exposure pattern for a particular biocide may lead to the conclusion that a certain type of data are not needed and can be waived. Thus, there might be a lack of data for a certain type of study, route of exposure, or exposure duration. In these cases, caution should be taken, e.g. establishing a long-term reference value based on a NOAEL from a short-term study or a medium-term study.

Re 4.1.6 If the results of toxicokinetic or mechanistic studies give indications of a relevant first pass effect and/or fundamental differences in metabolism for different exposure routes (resulting in a route-specific effect on type or seriousness of an effect) selection of suitable route-specific studies as basis for the AEL should be considered. For systemic AEL based on dermal and inhalation studies see NL part for route-to-route extrapolation.

The following formula is used:

$AEL_{systemic}$ (mg/kg bw/day) = ($NOAEL_{oral}$ x A): 100

A is the fraction of the substance absorbed by the body after oral administration (see re. toxicokinetics and dermal absorption (2). E.g. 60% oral absorption: A = 0.6).

Local AEL
The risk Characterisation of local effects in the absence of systemic effects should be based case by case on expert judgement. During expert judgement the inter- and intraspecies factors can be adjusted. Although the paper on risk characterisation of local effects in the absence of systemic effects is not workable, the approach in the grey frames below based on that paper are still usefull.

Risk Characterisation of local effects in the absence of systemic effects
The external reference values for different routes of exposure are named here as AECdermal, AECinhalation and AECoral. These local AECs refer to external exposure, and therefore, absorption rates are not taken into account when calculating them.

Local effects
Local effects can occur on the skin, on the respiratory tract or on the GI tract.

Chapter 4.1.6 of the TNsG on Annex I Inclusion refers to an external reference value for local effects, derived as local concentration in mg/m3 air or mg/cm2.

The NOAELs/NOAECs should be compared to decide whether local effects are more critical than systemic effects. Thereafter either an AEC (if local effects are most critical) or an AEL (if systemic effects are most critical) should be derived, not both.

Observed systemic effects that are secondary to causative local effects should be considered as part of the local effects, and not as primary ("true") systemic effects.

The purpose of this document is to clarify the approach when local effects at the port of entry are seen in repeated dose studies:

• Local effects in the GI tract in a repeated dose oral study
• Local dermal effects in a repeated dose dermal study
• Local respiratory effects in a repeated dose inhalation study

This document does not concern local effects that are observed in single dose studies or sensitisation studies, although in some cases relevant information may be available only from these studies and could be taken into account. As a general rule, these effects are covered in the risk assessment/management by means of assignment of R- and S-phrases, or H and P statements in GHS:

• Irritation in an acute toxicity test (oral, dermal, inhalation)
• Irritation in an acute skin/eye irritation test
• Sensitisation in a sensitisation study

Dermal route
Local dermal effects are the critical effects when the NOAEL (in mg/kg bw) related to local effects is lower than the (overall) systemic NOAEL and the systemic NOAEL in the dermal study.
AECdermal is based on effects that are concentration dependent rather than dose dependent, and should be given as a concentration (mg/L) or percentage and, if available, in mg/cm2. These units are also appropriate for monitoring purposes. The choice of unit can be made based on a known mechanism of action: while mg/L or a percentage may be more appropriate for pH-dependent effects, mg/cm2 might be more suitable for other forms of reactivity.
AECdermal can be derived from a NOAEL value by first converting NOAEL (mg/kg bw) into a NOAEC (mg/cm²) as shown below:

NOAEC in mg/cm2 = Total dose applied in mg / Treated surface in cm2

= (average animal weight in kg) x (dose in mg / kg bw) / Treated surface in cm2

If the contact surface area is not available, the default values described in the TGD on Risk Assessment should be used. Repeated dose dermal toxicity studies are usually not submitted in the dossier under Directive 98/8/EC. These studies can nevertheless be required where potential dermal exposure is significant and route-to-route extrapolation is not possible. A dermal study may be necessary when dermal route is more relevant than other routes, or when specific effects of concern are different from the effects seen in the studies in other routes.

The exposure of laboratory animals in the repeated dose dermal toxicity study is not directly comparable to typical human exposure, mainly because the test animals are exposed under (semi-)occlusion (bear in mind that among others also the area dose and the type of formulation versus active substance could be important for non-compatibility), whereas humans will normally be exposed to bare skin (exposure on hands under gloves which may be considered as occlusive conditions is regarded as an exception). Although such differences in exposure conditions are not limited to the dermal route, this can make it difficult to use the results of animal studies for human risk assessment. If the substance produces local effects after repeated dose exposure, but does not have to be labelled for acute toxicity, skin/eye irritation or skin sensitisation, the assessment will have to be done on a case-by-case basis using expert judgement.

Inhalation route

Local respiratory effects are the critical effects when the NOAEC related to local effects is lower than the systemic NOAEC in the inhalation study or lower than the (overall) systemic NOAEL (after having converted the NOAEC related to local effects into mg/kg bw).
If critical local effects are observed in inhalation toxicity studies, the highest non-irritating concentration in animal studies should be used to calculate AECinhalation. This value is then compared with the concentrations that humans are expected to be exposed to. Both NOAEC and AECinhalation are usually expressed in mg/m3.
AECinhalation can be derived from a respiratory NOAEC, which is usually expressed in mg/m3.
Repeated dose inhalation toxicity studies are usually not submitted in the dossier under Directive 98/8/EC. For volatile substances (vapour pressure > 10-2 Pascal) or in cases where potential inhalation exposure is significant, an inhalation study is required. In some other cases (e.g. aerosols and dusts/particulate matter), studies by inhalation route should also be required in addition to studies by the oral route.

Oral route

Chapter 4.1 of the TNsG on Annex I Inclusion does not indicate how to derive an external reference value when an active substance induces local effects on the GI tract. It seems unlikely that an AECoral would need to be derived for a biocidal substance, but an approach is suggested for completeness.
Local oral effects are the critical effects when the NOAEL (in mg/kg bw/d) related to local effects is lower than the (overall) systemic NOAEL and the systemic NOAEL in the oral study. Observed systemic effects secondary to causative local GI tract effects should be considered as part of the local effects.
If critical local effects are observed in oral toxicity studies, the highest concentration with no local effects in animal studies should be used to calculate AECoral. This value is then compared to theconcentrations that humans are expected to be exposed to. AECoral is expressed as a concentration (mg/L) or percentage.

Interspecies assessment factors (AF)

Interspecies AF can be divided into a toxicodynamic component and a toxicokinetic component. For rat to human interspecies extrapolation, these components are usually set at 2.5 for the toxicodynamic component and 4 for toxicokinetic differences. In the risk characterisation of local effects, both these components can in certain circumstances be reduced. The uncertainties on the AFs can be very high for local effects, and any adjustments should be done with caution. The value by which the AF is adjusted should be considered on a case-by-case basis, and the reasons should always be justified.

- Toxicokinetic AF 4

When the mode of action is direct chemical/pH reactivity, the toxicokinetic component of 4 can be disregarded for local effects. It may be necessary to consider whether the mode of action may involve other than direct chemical/pH reactivity, resulting in a need to apply an AF for toxicokinetic differences.

For local effect at the port of entry (skin, eye, G.I. tract) it is sometimes justified to assume that either toxicokinetics or –dynamics (or both) do not contribute significantly to interspecies differences (as for example in the case of direct/pH- driven chemical action on tissue/cell membranes). In such cases, based on sound scientific reasoning, the 10- fold default factor might be reduced dependent on the mode of action (see TNsG on Annex I Inclusion; Chapter 4.1.3: Selection of Assessment Factors).

- Toxicodynamic AF 2.5

For oral and dermal local effects, a distinction has to be made between a) direct chemical reactivity which does not involve local metabolism, and b) other or unknown mechanisms. If it is known that the local effect is caused by direct chemical reactivity where metabolism has no role (e.g. simplemembrane destruction by acids/bases), the factor 2.5 can also be omitted, leaving an interspecies AF of 1. On the other hand, if the mechanism is not known, or if local metabolism may have a role, then the factor 2.5 is applied. The possible influence of local metabolism is taken into account in this AF although it does not clearly form a part of either the toxicokinetic or the toxicodynamic component of the AF.
For respiratory local effects, the toxicodynamic factor is applied because it is assumed that humans are more sensitive than animals to any effects on the respiratory tract. The AF 2.5 is therefore applied, but it is in reality an uncertainty factor rather than a toxicodynamic factor.

"With regard to local effects on the respiratory tract, guidance is available e.g. from the EU project ACUTEX, which proposes to apply reduced interspecies AFs when extrapolating data obtained in rats to humans. Given that there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and when there is no data to inform on this uncertainty, it is prudent to assume that humans would be more sensitive than animals to effects on the respiratory tract. In such a situation the default factor of 2.5 to address remaining uncertainties should be applied (see TNsG on Annex I Inclusion; Chapter 4.1.3: Selection of Assessment Factors)" [7].

Intraspecies AF

The intraspecies AF can be divided into components of 3.2 for toxicodynamic variability and 3.2 for toxicokinetic variability. It is considered that information on intraspecies variation for local effects is very scarce and it is therefore generally suggested not to refine these default factors. This is consistent with REACH [23].
In some cases it may nevertheless be possible to reduce the intraspecies AF if there is sufficient information available on either human variation (human data), or on the mechanism of action of the local effect together with knowledge on human variation of the mechanistic process involved. Thiswould be consistent with IPCS guidance [24]. For instance, intraspecies variability may be small forlocal effects exerted through a pharmacological action of a compound, or an irritant effect. In such cases it may be appropriate to reduce the intraspecies AF. A reduced intraspecies AF should always be justified.

For further reading on AF adjustment, please see JMPR 2008 [25].

Specific situations in AEL setting
In principle, a limit approach cannot be applied and no AEL can be derived for substances of mutagenicity category 1 and 2, and substances of carcinogenicity category 1 and 2 (see 67/548/EEC for the classification). Deviation from this is only possible if there is convincing evidence for the existence of a limit value for this effect.

This is not possible as the BPD Article 5 (2) clearly indicates that CMR substances cannot be authorised for marketing to the general public or for use by the general public (taking into account the concentration limits) (agreement TMIII 2007).

Any available suitable human data are taken into consideration and may be used to support test animal data.
These data may originate from humans exposed during production or application of pesticides or from volunteer studies conducted under ethical criteria (Helsinki Convention 1971) [26], e.g. into dermal absorption.
In case human data are not available, however, it is not desirable to conduct human studies [4].

Besides duration and frequency of exposure, the choice of the most relevant study can also be determined by the excretion rate of the active substance and its metabolites, and by the rate at which the effects that may be caused by exposure to a substance are reversible.

The most relevant studies are selected from the dossier on the basis of these considerations. The selection must be justified in the decision making.

The study with the most relevant NOAEL, obtained with the most relevant test animal, is selected. This does not necessarily always have to be the lowest NOAEL found in the most sensitive test animal. The choice of the NOAEL as starting point depends on the total package of available toxicity studies and the mutual relationships in dose regimes. The most suitable NOAEL on which the AEL is based should be selected on a case-by-case basis, for which expert judgement is required.

Local effects are not taken as starting point for derivation of a systemic AEL. Generally, the risk of local effects such as inhalatory effects, skin irritation, eye irritation, and skin sensitisation, are included in the risk management process by placing hazard symbols and risk and safety phrases on the label. Exposure can, e.g., be minimised by prescribing suitable personal protection measures or other exposure-mitigation measures (see [8]).

In TMII 2007 was discussed which studies can be used in setting the acute AEL for anticoagulant rodenticdes. The general problem in selecting the appropriate study for anticoagulants is that, in general, acute studies are not suitable for setting AELs due to the cumulative effect of anticoagulants. In terms of exposure and study duration, teratogenicity studies in the existing dossiers have been more relevant for AEL setting, and the developmental study in the most sensitive species should be used.

MOE derivation
This procedure with respect to MOE derivation is extensively described in Ch 4.1.TNsG on Annex I inclusion [7]. The text in the grey frames below is from the TNsG on Annex I inclusion, chapter 4.1 [7]. Numbering in these grey frames follows the section.

4.1.7 The MOE approach

The Margin Of Exposure (MOE) represents a direct comparison of exposure and toxicity. The MOE approach is not intended to provide a health-based limit-value but serves primarily as an instrument for risk characterisation. The MOE is calculated as:

$$MOE = \frac{\text{NOAEL (mg/kg b.w/day)}}{\text{Exposure (mg/kg b.w/day)}} \quad \text{or} = \frac{\text{NOAEC (mg/m}^3\text{)}}{\text{Exposure (mg/m}^3\text{)}}$$

The MOE approach is identical to that used in the U.S.A. and the Margin Of Safety (MOS) approach used in the EU TGD or the Toxicity Exposure Ratio (TER) approach used in some other countries.

The MOE should be calculated using the most relevant toxicity endpoint derived from the most relevant study, considering explicitly the exposure scenario under evaluation. From this it follows that acute exposure is compared to NOAELs (or LOAELs) for relevant effects in (sub) acute studies whereas chronic exposure is compared to N(L)OAELs from long term studies. If relevant good quality epidemiology data are available these data prevail over animal studies in certain cases (see section 4.1.3 regarding suitable human data). The selection of endpoints and studies involves expert judgement on a case-by-case basis. According to the TGD for new and existing substances the risk characterisation, based on the MOE approach, is performed for each toxicological endpoint separately. In addition, if more than one study is available with an exposure duration relevant to the exposure scenario under evaluation, it is possible to calculate more than one MOE based on the NOAELs from the different studies to provide more insight in the range of the possible risk.

Based on a calculated MOE, the risk assessor needs to conclude whether the involved exposure to the substance is of concern or not. If the MOE is higher than the overall assessment factor, then the risk under the circumstances specified for the risk characterisation is acceptable. If the MOE is lower than the overall assessment factor the possibility of refining the pattern of use to reduce exposure can be considered by the Applicant. Subsequent revision of the risk characterisation would indicate whether the risk was now acceptable. This process should be exceptional since the Applicant should have resolved these situations while conducting the risk assessment with their dossier.

Tiered approach for risk characterisation

In the EU the tiered approach is described in Ch 4.1.TNsG on Annex I inclusion, chapter 4.1 [7] (see chapter human exposure EU part). In the EU refinement of the risk assessment can be based on several refinement situations as allometric scaling, new dermal absorption data, route specific mitigation measures (as PPE).

2.3.5 Derivation ADI and ARfD

The ADI is defined as the estimated amount of active substance, expressed per kg body weight, that can life-long be absorbed daily without adverse health risk.
The ARfD (Acute Reference Dose) is defined as the amount of a substance in food or drinking water, expressed in mg per kg body weight per day, that can be absorbed during a meal or a day, without adverse health risk for the consumer, based on all available knowledge at the moment of assessment.

The limit values that are considered acceptable from a health point of view, such as ADI and ARfD, are derived from the available toxicological studies. The ADI is derived for chronic exposure. An ARfD is derived as well for a substance with acute toxic properties. This is described in the TNsG on Annex I inclusion [6].

The text in the grey frames below is from the TNsG on Annex I inclusion. Numbering in these grey frames follows the section numbering in the TNsG on Annex I inclusion.

4.1.6 The ADI/ARfD approach

For the assessment of health risk after subchronic or chronic exposure to pesticides, the ADI has been established. The World Health Organisation 1989 publication “Guidelines for predicting the dietary intake of pesticide residues” (WHO, 1989) had formed the basis for this ADI approach of consumer risk assessments of food residues. The ADI is usually based on NOAELs from lifespan or subchronic studies. Concerns have been recently expressed that acute toxic effects may sometimes be elicited following consumption of food containing residues of certain pesticides.
The 1994 JMPR (FAO/WHO, 1994) considered that situations in which the ADI derived from subchronic or long-term studies were probably not an appropriate toxicological benchmark for assessing risk posed by short-term exposure to acutely toxic residues. Certain biocides might present an acute hazard, however, so that such excesses are of toxicological concern. As a matter of standard practice in the risk assessment of residues in food and drinking water, the case for setting an acute reference dose (ARfD) should be considered for all compounds (EC2001 b). The ARfD of a chemical was defined by the 1998 JMPR as ’an estimate of a substance in food or drinking water, expressed on body weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation‘ (FAO/WHO, 1998).

Calculation ADI

Consumers may via their food throughout their life be exposed to residues of plant protection products. The corresponding limit value (ADI) must therefore represent the dose that life-long be ingested via food without adverse health effects. The JECFA (Joint FAO/WHO Expert Committee on Food Additives) has defined the ADI as follows: ’the estimated amount of active substance, expressed per kg body weight, that can life-long be absorbed daily without adverse health risks.
The ADI is usually derived from test animal research in which the effect of prolonged exposure to the test substance has been studied. This concerns the chronic toxicity research.
The ADI is based on the most sensitive, also most critical effect.
‘Effect’ is understood to be: an effect that is considered as undesirable.
Usually, data on several species are available (rat and mouse and sometimes also dog). The data of the most relevant animal species for the most critical effect serve for derivation of the ADI. The relevance of the observed effect for man is also important.

In principle, a limit value approach cannot be applied and no ADI can be derived for substances of mutagenicity category 1 and 2, and substances of carcinogenicity category 1 and 2 (see 67/548/EEC for classification). Deviation from this is only possible if there is convincing evidence for the existence of a limit value for this effect.

Where suitable human data are available, these can possibly be taken as starting point (above animal studies). These data may originate from people exposed during production or application of biocides, or from volunteer studies carried out under ethical criteria (Helsinki Convention 1971) [26], e.g. into dermal absorption.

If, however, no human data are available, it is not desirable to conduct human studies [4].

A safety factor of 100 is usually applied for extrapolation of the NOAEL from test animal research to the ADI.

The following formula is used:
ADI = NOAEL / 100 (test animal research)

If further data about the kinetics and mode of action of the substance in test animals or humans are available, these data can justify the use of a deviating safety factor. If too little is still known about the mode of action of the substance, this may be reason for derivation of a 'provisional' ADI.
In such cases an extra safety factor is usually applied to compensate for the uncertainty. The value of this factor depends on the nature of the effects [27].
Furthermore, it can be decided to apply an additional safety factor if the margin between NOAEL and LOAEL is very small and depending on the observed effects at the LOAEL.

Calculation ARfD
A national guideline has been developed, together with RIVM, for derivation of the ARfD [28] and there is a draft Guidance Document of the European Commission [29] (with the RIVM report as one of the supporting documents). It is briefly described below in which cases an ARfD must be derived. The documents mentioned above also attempt to give a guideline on how the ARfD should be derived, which studies can be used as starting point, and which effects are relevant for acute exposure.

Some substances have specific acute toxic properties or may after a short-term (single) (high) exposure induce prolonged effects. In such a situation it is possible that a short-term exceedance of the ADI entails a health risk. The ARfD is defined as "the amount of a substance in food or drinking water, expressed in mg per kg body weight per day, that can ingested during a meal or a day, without adverse health risk for the consumer, based on all available knowledge at the moment of evaluation".

An ARfD is always derived unless the toxicological profile of the substance meets all following conditions:
- The substance induces no effects (including behaviour, clinical symptoms, or pathology) in an acute oral study at a dose of 2000 mg/kg bw or higher.
- No embryonic, fetotoxic, or developmental effects were found at dose levels that are not maternally toxic.
- There are no indications or triggers from studies with repeated exposure which indicate toxic effects after acute exposure (e.g. acute neurological behaviour effects or effects on the gastrointestinal, cardiovascular or respiratory system).
- The substance shows no acute neurotoxicity or this is not expected on the basis of the available toxicological information.
- No other toxicological alerts such as hormonal or biochemical changes have been found in studies with repeated exposure which may also occur after a single dose.

As a general rule, the ARfD should be based on the most sensitive acute toxicological endpoint of human relevance, derived from the most suitable study in the most suitable (animal) species. Selection of the most relevant effect should be based on the complete, available toxicity research.

Knowledge about the mode of action of a substance may be very valuable when selecting the most relevant endpoint for acute exposure. The fact that the current database is not yet geared to the derivation of an ARfD makes it difficult to identify the correct endpoint and the most suitable study. Sound justification of the derivation of an ARfD is therefore important.
Some relevant effects for which an ARfD can be derived are: certain clinical effects (tremors, mucus formation/drivelling), acetyl cholinesterase inhibition, delayed neuropathy, neurotoxicity, methemoglobin formation, disturbance of oxygen transport or dissociation mitochondria, embryonic or foetotoxic effects, developmental effects, developmental neurotoxicity, direct effects on gastrointestinal tract, pharmacological effects.
When no ARfD is derived, this should be also be justified in the evaluation.

Where suitable human data are available, these can possibly taken as starting point (above animal studies). These data may originate from people exposed during production or application of biocides, or from volunteer studies carried out under ethical criteria (Helsinki Convention 1971) [26], e.g., into dermal absorption. If, however, no human data are available, it is not desirable to conduct human studies [4].

A safety factor of 100 is usually applied for extrapolation of the NOAEL from test animal research to the ARfD.

In principle, a threshold approach cannot be applied and no ARfD can be derived for substances of mutagenicity category 1 and 2, and substances of carcinogenicity category 1 and 2 (see 67/548/EEC for classification). Deviation from this is only possible if there is convincing evidence for the existence of a limit value for this effect.

The following formula is used:
ADI = NOAEL / 100 (test animal research)

If further data about the kinetics and mode of action of the substance in test animals or man are available, these data can be used to substantiate a deviating safety factor. If too little is still known about the mode of action of the substance, this may be reason for derivation of a ‘provisional’ ARfD.
In such cases an extra safety factor is usually applied to compensate for the uncertainty. The value of this factor depends on the nature of the effects [27]. Correction of the safety factor for exposure duration is not applicable because the ARfD is preferably based on a study in which a short-term (single) exposure took place.

2.4 Approval

The actual permissibility of a biocide follows from the risk assessment for human exposure, which has been elaborated in EU exposure part.

2.5 Developments

Biocides dossiers are currently being evaluated in EU framework. This process will result in amendments of the already existing TNsGs, and new documents will be prepared.

3 APPENDICES

Appendix 1 Racemic mixtures

Paper on the use of toxicological research carried out with a racemic mixture for the risk evaluation of (products with) the biologically active enantiomer

1. Introduction

The racemic mixture of several active substances in pesticides is replaced by the biologically active enantiomer. This raises the question to what extent toxicological research carried out with the racemic mixture can be used in the risk evaluation of pesticides based on the biologically active enantiomer. This question has been raised in view of the risks for those who apply pesticides and those who work in treated spaces or in treated crops.
This paper thus specifically deals with labour protection.

2. Problem

The question about the suitability of toxicological data obtained with a racemic mixture for risk evaluation of pesticides based on the biologically active enantiomer cannot be answered unequivocally.
Literature research shows that stereoselectivity often plays a role in the biological activity of pesticides, qualitatively (type of reaction) as well as quantitatively (reaction speed). These differences in reaction may in turn affect toxic side effects.
It can therefore without further research not be ruled out that acute effects and effects after longer exposure are associated with the stereochemical structure.

3. Irritation effects

No stereoselectivity is to be expected as regards skin and eye irritation and corrosivity. This means that as regards irritation and corrosion potential of a pesticide based on the biologically active enantiomer, the data obtained with the identical pesticide based on the racemic mixture can be used.
Interpretation may sometimes be difficult because the concentration active substance in the pesticide based on the biologically active enantiomer will be about half (whereas the concentration active enantiomer is the same).
This means that supplementary research may be required.

4. Systemic effects

For the other toxicological effects it cannot be said beforehand whether the already existing data, obtained with the racemic mixture, can be used for the risk evaluation of pesticides based on the biologically active enantiomer. The following approaches are possible when seeking an answer:

- providing complete insight into the determinative mode of action of the toxic effect, in view of the risk for man, and in particular the (higher) exposure during work;
- providing results of a comparative study with the racemic mixture on the one hand and the biologically active enantiomer on the other in an (e.g. short-term) experimental set-up with the emphasis on the mode of action of the most critical effect for man, with a particular in view on labour protection. Such research can generally only be carried out if there is a certain extent of insight into the mode of action;
- providing insight into the metabolism of the biologically active enantiomer as well as the other enantiomer in a test animal that is representative of metabolism in man, or providing insight into the metabolism of the biologically active enantiomer as well as the other enantiomer in man.

The results of one of the three approaches mentioned above will usually make it possible to judge about the need for further supplementary research, and the content thereof. The chosen approach will depend on the already available data.

The order of the three options above indicates the preference.

Authorisation holders who (consider to) replace a racemic mixture by a biologically active enantiomer can approach the CTGB for consultations about the approach to be chosen in a specific case.

Appendix 2 Derivation systemic AEL on the basis of an inhalation study

A number of examples to determine whether a systemic AEL must be derived from an oral study or from an inhalation study have been elaborated below. If a systemic AEL must be derived on the basis of an inhalation study, this AEL can be expressed as concentration in air (mass/m^3) or as body burden (mass/time unit).
In practice it will usually not be difficult to make a well-based decision about the way in which the AEL must be expressed (provided that a good dossier is available).

This is not an exhaustive review but it serves as illustration of possible situations and choices that can then be made.

An inhalation study with repeated exposure will usually not be available. There are several options in such cases:

a. No acute inhalation study needs to be submitted in accordance with data requirements. Inhalatory exposure/risk is considered low in that case. Only a systemic AEL will be derived on the basis of an oral study.
b. An available LC_{50} does not indicate a significantly higher toxicity via the inhalatory route or gives no cause for classification for acute inhalatory toxicity (other routes can also be very harmless). In principle, no large problems are expected via the inhalatory route. A systemic AEL is derived on the basis of an oral study.
c. An LC_{50} gives cause for concern as regards toxicity via the inhalatory route (much lower than oral). This would have to be reason for submission of an inhalation study with repeated exposure (28 or 90 d) but the data requirements do not provide for this. Expert judgement/consultations are required in such cases to decide what is required.
   Calculations are in principle carried out with a systemic AEL where a study with repeated exposure is not available.
   The toxicological profile of the substance plays an important role as well (are problems expected via the inhalatory route). If necessary, an inhalatory study with repeated exposure must be requested.

An inhalation study with repeated exposure is available. There are several options in that case as well.

a. The toxicological profile via the inhalatory route is comparable to that via the oral route and the NOAEL (as body burden) is of the same order of magnitude for both routes.
   The risk is in that case calculated with a systemic AEL based on an oral study.
b. The toxicological profile via the inhalatory route is comparable to that via the oral route but the NOAEL (body burden) is more than a factor 10 lower for inhalation. Expert judgement is in that case necessary to determine whether a separate evaluation needs to be carried out for the risk via inhalatory exposure, and with what AEL (air concentration or body burden).
c. The inhalatory route shows a different critical effect than the oral route. In principle, a separate risk evaluation for inhalatory risk must be carried out in that case.
   In that case one AEL should wherever possible be chosen for inhalation (concentration or body burden) as well. The toxicological profile will often give sufficient indications to make a choice through expert judgement.
   The effect will in most cases be related to body burden. Only if the target organ is in fairly direct contact with air (upper respiratory tract, lungs and possibly in some cases also blood) an AEL on the basis of concentration will sometimes be necessary. The nature of the effect and the mode of action play an important role in this as well, which again requires expert judgement.

Appendix 3 OECD SERIES ON TESTING AND ASSESSMENT, Number 80, Guidance on grouping of chemicals

OECD Guidance grouping chemicals

Appendix 4 Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Fluoride


EFSA fluorosis

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