Targeted Risk Assessment

Technical Report No. 93

This report describes the work of an ECETOC Task Force charged with addressing targeted risk assessment. The Task Force has developed an approach that should provide a rational basis for addressing many of the key challenges presented by the European Commission proposal for new chemical legislation REACH (Registration, Evaluation and Authorisation of Chemicals). The work remains ongoing. The Task Force are continuing to verify core concepts; validate the approach against representative case studies; and seek feedback from stakeholders on the approach's utility and shortcomings. **For this reason, *the report should not be seen as final: it constitutes a synthesis of the current rationale and may be subject to further development, commensurate with the outcome of the current stakeholder consultation.***

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SUMMARY

One of the key challenges of the proposed European chemicals legislation (REACH) is that it envisages the registration and evaluation of approximately 30,000 chemicals by producers and importers over the next 10-15 years. Faced with such a challenge, both practically and scientifically, appropriate prioritisation will be a key element of the REACH process. To facilitate such work, ECETOC has developed a tiered (step-wise) approach for identifying and prioritising scenarios where risks to human health and the environment from chemicals might reasonably be expected to be high enough to undertake a more detailed assessment of risk. The general concept of ECETOC's targeted risk assessment (TRA) is based on the premise that depending on both the degree of exposure and the hazard - considered together - different information requirements will be needed to demonstrate safe and responsible production and use of a given chemical.

The concept applies a tiered, or iterative, approach to risk assessment, consisting of three phases, i.e. Tiers 0, 1 and 2. According to this approach, the level of refinement and detail of the information required for a risk evaluation are proportional to the potential risks of a chemical, based on the consideration of both hazards and exposures together, rather than in isolation.

The process also considers existing (and new) risk reduction measures to control exposure.

The core objectives behind the approach are:

- To target assessment resources on those production and use scenarios of chemicals that constitute a likely concern for man and/or the environment;
- to ensure that all decisions are based upon risk and account for all relevant information required to reach any soundly-based judgement;
- to simplify yet maintain the scientific integrity of the risk assessment process;
- to be consistent with the requirements of existing European health and environmental legislation.

ECETOC's TRA achieves its objectives by adopting a tiered structure:

Tier 0 – The aim of the Tier 0 is to 'screen' chemicals and conditions of no immediate concern out of the process, because their general exposure and hazard potential are low, and to identify those other chemicals and conditions where further targeting risk assessment is required. The process used is straightforward, well documented and conservative.

Tier 1 – Chemicals and conditions which are not screened out at Tier 0 are evaluated in the Tier 1. The aim of Tier 1 is to use information on uses, exposure scenarios and hazard to carry out a more refined risk assessment to separate the production and uses of no immediate concern from those that require a more detailed investigation. The process necessarily involves

co-operation between producers and downstream users to identify key exposure scenarios. It is also designed to be relatively simple and well defined, in line with the common EU risk assessment principles, and aligned with the occupational, consumer and environmental legislation.

Tier 2 – Scenarios identified as being of potential concern at Tier 1 proceed to a detailed risk assessment at Tier 2. This assessment is consistent with the established EU risk assessment principles, and enables final risk assessment conclusions to be reached for those scenarios.

The advantages of the approach may be summarised as:

- It allows a systematic screening of chemicals and their uses for their possible risks, considering hazards and potential exposures together;
- the available or generated information allows chemicals and uses that are of no immediate concern to be identified quickly and easily and gives priority to the chemicals and uses that require a more detailed evaluation;
- it uses an increasing level of refinement and detail of the information (both on exposure and hazard) and allows for iteration to account for available risk management measures;
- the data and resource demands will consequently be proportionate to the likely risks of the chemical, and target the available resources to scenarios of possible concern;
- using risk assessment as the basis for defining additional information needs through targeting and exposure-driven testing encourages the appropriate use of resources and respects animal welfare;
- it helps manufacturers and the authorities to make a choice between generation of further information or implementation of more stringent risk reduction measures;
- it can be used to perform a chemicals safety assessment (CSA) and provide input for a chemicals safety report (CSR).

The concepts of the approach have been programmed into a web tool that integrates the core concepts into an easy-to-use format. The web tool has been shown to work across a range of chemicals and conditions using information and/or data that are readily available and without the need for extensive animal test data requirements or a high level of expertise. The web tool can be found at https://www.ecetoc-tra.org.

1. INTRODUCTION

1.1 Introduction

Increasing concern that the existing EU policy for the introduction and supply of chemicals on the market does not provide sufficient protection for workers, consumers or the environment (Chemicals in the European Environment: Low doses, high stakes, EEA, 1997) has led to a debate at the informal council of environmental ministers meeting in Chester in 1998. The meeting concluded that a review of the current policy on chemicals was required, in particular the operation of the primary legal instruments regulating the supply of chemicals in the Community, namely:

- Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances (EC, 1992);
- Directive 88/379/EEC relating to the classification, packaging and labelling of dangerous preparations (EEC, 1988);
- Regulation EEC/793/93 on the evaluation and control of risks of existing substances (EC, 1993a);
- Directive 76/769/EEC relating to the restrictions on the marketing and use of certain dangerous substances and preparations (EEC, 1976a).

These instruments cover a broad range of substances of different origins, e.g. industrial chemicals, substances produced from natural products, metals and minerals. Between them, the Directives regulate the evaluation of these substances and the broader determination of supply chain risks, including the need for risk reduction measures. Furthermore, they establish the duties of chemical suppliers and employers regarding the safety information to be provided to users (labelling, safety data sheets). Beyond these instruments, further legislation exists (e.g. concerning the general conditions of use of such materials (EEC, 1980; EC, 1998; EC, 1996a; EC, 1996b) or particular provisions that apply to specific classes of material (EC, 1999a; EEC, 1976b)).

Following the 1998 meeting, the Commission held a series of stakeholder events with the aim of more clearly defining the problems associated with the existing framework of European regulation and identifying potential solutions. The resulting European Commission (EC) White Paper (EC, 2001) on a strategy for a future chemicals policy, together with a draft legislation (DGEE, 2003), contains the basic elements for the proposals for a new mechanism for the control of the supply of chemicals in the EU, termed REACH (Registration, Evaluation, Authorisation of Chemicals).

Europe is the major chemical-producing region in the world and the chemical industry contributes the largest trade surplus from any area of Europe's manufacturing economy (CEFIC, 2000). There are an estimated 100,000 different chemicals registered in the EU, of which around

10,000 are marketed at volumes of more than 10 tonnes per year, and a further 20,000 are marketed at between 1-10 tonnes per year (OECD, 2001). In addition to the chemicals that are already registered, the current EU chemicals system distinguishes between 'existing substances' (those declared to be on the market before September 1981) and 'new substances' (those placed on the market after that date). Since the new substances legislation (EEC, 1979) came into force in 1981, there have been 3,000 additional new substances notified in Europe. Existing substances account for more than 99 percent of the total volume of all substances on the market (OECD, 2001). However, up to mid-2003, EU risk assessments had only been published for 38 of the priority existing chemicals (ECB, 2003), reflecting the ineffectiveness of the current regulatory system.

ECETOC has recognised that difficulties lie ahead if the proposed REACH legislation is to be workable and that some of them may be overcome by the development of a pragmatic, tiered and targeted approach to risk assessment. ECETOC consequently established a Task Force (TF) with the following Terms of Reference:

- Develop a process map for preliminary risk assessment of substances indicating where approaches for targeting may be applied;
- review which information and experimental data are needed to conduct a tiered risk assessment;
- describe how the different approaches and tools for characterising exposure and effects might be used to increase efficiency and speed of the process;
- review completed risk assessments, collate areas of concern and investigate whether the conclusions from these comprehensive risk assessments could have been arrived at via a more targeted approach;
- apply proposed tiered risk assessment scheme to case studies and evaluate effectiveness and possible implementation in REACH.

1.2 Considerations for a new approach to risk assessment

Any new system of risk assessment must be accessible to all stakeholders. In the context of the chemical's supply chain, this extends from chemical suppliers, to formulators, distributors, smaller enterprises and skilled trades. The core operating concepts of any approach must therefore aim to be simple and readily understood without compromising scientific integrity. Furthermore, it is desirable that any approach that addresses human health and environmental risks should be:

- Methodologically well documented, in order that the basis for decision-making is clear;
- adaptable and responsive to new information on chemicals that may become available and/or changes in standards arising from societal and other considerations;

- complementary with other areas of existing regulation, both in relation to human and environmental safety;
- workable, i.e. the approach is sufficiently easy to use that it can be adopted by any of the concerned stakeholders and that the resultant bureaucratic burden is not so high as to constitute a barrier to its effective adoption and implementation.

In addition to these core operational concept requirements, a number of other desirable considerations were identified by ECETOC at the outset:

- Any approach to the evaluation and prioritisation of risk must, in itself, be based upon risk, i.e. the approach has to place due account of both hazard and exposure information. Although this may appear to be an obvious consideration, several approaches to regulatory priority setting are only based upon the relative hazard of substances, rather than risk *per se* (VROM, 2001; BKH, 2000; RCEP, 2003);
- a common approach to the assessment of human (worker and consumer) and environmental risks would be desirable, but the detail may necessarily need to vary;
- in the development of a risk-based approach, due account should be given to the availability and effectiveness of different forms of risk management, e.g. child-resistant closures, on-site waste treatment, workplace ventilation, personal protection, if these are considered routine and standard practice within those parts of industry that handle chemicals.

1.3 Basic principles of targeted risk assessment

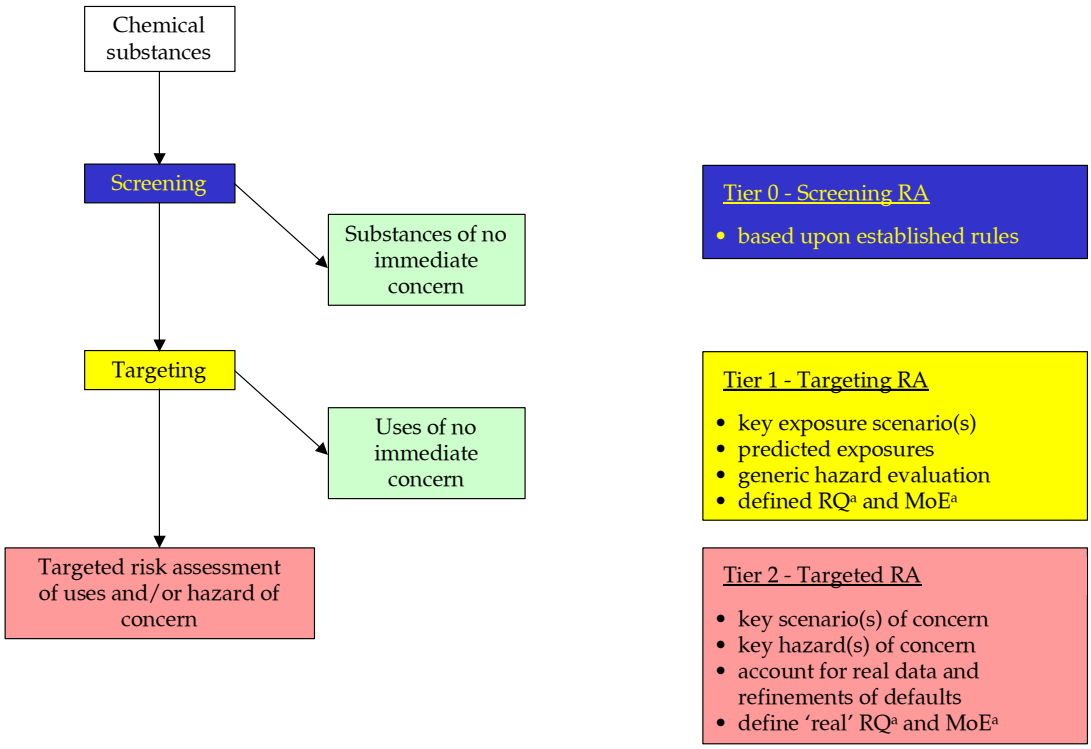
In any ideal scheme for the evaluation of risk, the effort devoted to the evaluation and management of risks would be proportionate to those risks. Risk assessment processes that place equal resource demands on each substance, or on different uses of that substance, are thus not efficient in terms of their ability to identify those substances, or particular uses of the substance, that may constitute a concern. Recognising this, ECETOC chose to develop a risk-based approach to the structured evaluation of risks to human health and the environment that accounts for the availability of (including presumptions on) information on hazard and exposure to enable estimations of risk to be made and subsequent decisions taken. This approach contrasts with, for example, those that require 'box ticking', whereby a defined minimum set of hazard or exposure information must be provided for a given situation, regardless of the use or attendant risks of that material (such as that used currently within Europe for new chemicals, (EEC, 1979)).

The tiered concept being developed adopts a common approach to human health and environmental risk assessment of chemical risks within the supply chain (see Figure 1). The underlying premise is that both hazard and exposure information are required in order to demonstrate the safe and responsible production and use of a chemical. The extent to which such

information ought to be available to support the responsible supply of the chemical changes depending upon the nature of risk; higher levels of risk demand more extensive information.

ECETOC's targeted risk assessment (TRA) approach does not address risk emanating from physico-chemical properties, for example inherent flammability or explosivity. For human health, it embraces the risks from exposure to chemicals experienced both by workers and consumers. Indirect exposure of humans to chemicals in the environment is not included at either Tier 0 or Tier 1.

Figure 1: Summary of the TRA approach



[a] RQ = Risk Quotient; MoE = Margin of Exposure

Humans can be exposed directly or indirectly to a chemical via multiple routes (dermal, oral and inhalation) and via multiple sources of exposure as varied as food, water, air and soil. Indirect human exposures are those that occur via transfer of chemicals from one medium (most frequently air) into other media (such as water, soil and the food chain), which then results in exposure of humans. A commonly used example of an indirect exposure pathway is the ingestion of meat and milk from cows that have ingested grass and soil contaminated by particulate emissions deposited from the air. As the need and demand for holistic and integrated assessments of chemical exposure increases, the contribution of indirect exposure to the total

human exposure will need to be estimated. However, estimating indirect exposures is complex. Indirect exposure assessments use many parameters and assumptions and involve more uncertainty than assessments of direct human exposure.

The considerations necessary for the assessment of indirect exposure through the environment have been documented and discussed in numerous publications (e.g. ECETOC, 1994; Mower, 1998; Reisman and Brady-Roberts, 1998; Walter, 1999). As such, for human exposure, the ECETOC TRA does not address indirect routes of exposure.

The broad concept of the ECETOC approach to targeted risk assessment consists of a series of steps (termed ‘tiers’) that serve to identify those particular uses (termed 'scenarios') of a chemical that potentially represents a risk to human health or the environment. Each tier demands more information, in order to improve the confidence in and refine the accuracy of the risk estimate. The outputs from the process are an evaluation and description of the health and environmental risks associated with the manufacture and use of the substance. These can then be used by the chemical supplier (or others with responsibilities within the supply chain) to propose and apply risk management measures.

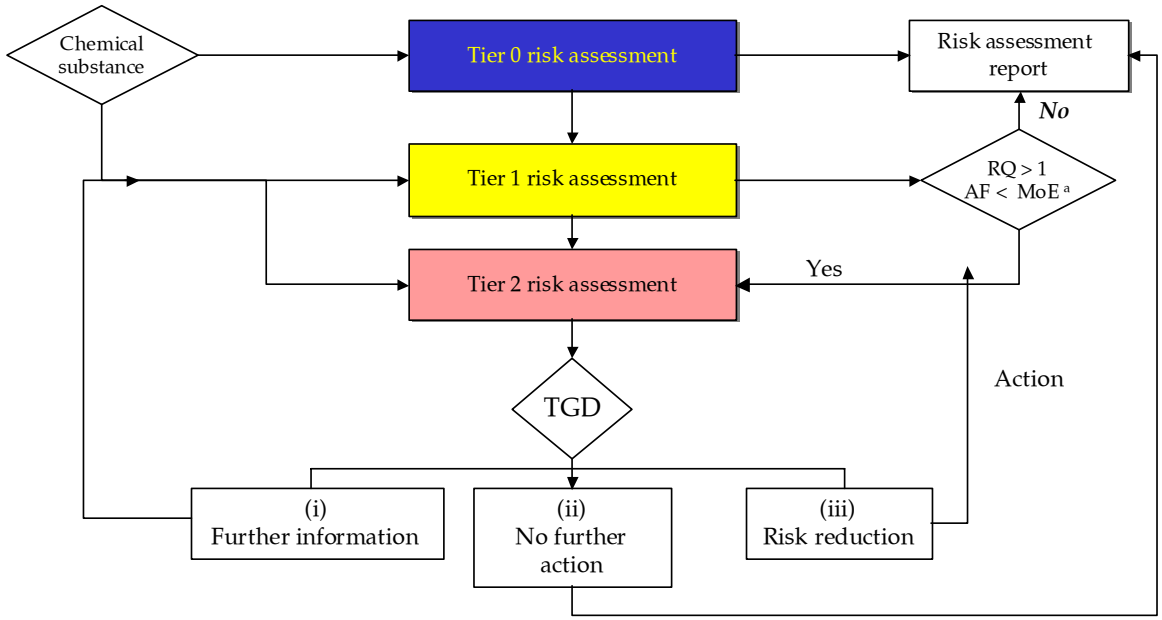
The first tier (Tier 0) establishes whether the general supply for use of a substance is of a 'low concern'. Tier 0 decisions are based on risk matrices. Such risk matrices have been applied, for example, in workplace health and safety since the early 1970s (Money, 2003). They have not, however, previously been used for the broader evaluation of chemical risks within the supply chain. The aim of Tier 0 is to identify substances that require only a limited risk assessment, i.e. to identify those chemicals with a low hazard potential and low potential for exposure where, as a consequence, the nature of the resultant risks would also be expected to be low. Such substances are therefore considered to be of no concern and require no immediate further work. All other substances progress to the higher tiers.

Tier 1 aims to identify those uses of substances that might reasonably be considered as constituting a risk and hence would warrant a more detailed evaluation (or where, for example, chemical suppliers might wish to provide additional information or advice to assist users to better manage such risks). The concept of risk at Tier 1 level is simple, well documented, conservative and verified, to provide confidence across all substances within a coherent process for evaluating workplace, consumer and environmental risks. In Tier 1, those scenarios where exposure to a substance requires ‘no further risk assessment’ are separated from those that require more detailed investigation. All scenarios identified as being of potential concern progress to Tier 2 risk assessment.

The risk assessment performed at Tier 2 is targeted at the scenarios arising from manufacture and use of substances that were identified as potential concern in Tier 1. The risks are assessed in

detail, based on the principles laid down in the EU TGD (EC, 2003a). The outcome of risk assessments at Tier 2 are also based on the EU TGD, i.e. conclusions (i) and (iii) – all scenarios identified as being of concern are candidates for further information and/or risk reduction or conclusion (ii) – no further information or risk reduction required (Figure 2). To fulfil the requirements of the proposed REACH process, if the outcome is conclusion (i) or (iii), then further information has to be gathered or adequate risk reduction measures have to be defined to finally reach conclusion (ii) as laid down in the Chemical Safety Report.

Figure 2: Tiered and targeted risk assessment



[a] RQ = Risk Quotient; AF = Assessment Factor; MoE = Margin of Exposure

There is also a need to ensure that, as far as possible, the outputs are consistent with other areas of regulation that also seek to manage human health and environmental risks. Therefore, ECETOC's TRA builds upon several concepts that are already used in different areas of relevant regulation in Member States of the European Union (e.g. HSE, 1999; UIC, 1999; BAuA, 2001; EC, 1996c, 2003a), but applies them for the first time to the broader area of the responsibilities of chemical suppliers within the chemicals supply chain. By adopting such an approach the outputs have the potential to align with the key expectations of related areas of chemical regulation.

1.4 Information requirements

Any procedure for the evaluation of a chemical substance to which there is some exposure needs at least minimum information on the hazardous properties and on the way it is used. This

information does not have to be the result of a study performed with the specific substance to be assessed. Instead, grouping of substances with similar properties or uses and bridging of information, expert judgement, (Q)SARs and alternatives to test methods, as far as generally recognised as valid, can be used to avoid unnecessary testing.

The information required at each tier is further elaborated in Sections 2 and 3 for human health and environmental risk assessment respectively. The TRA approach operates with the minimum information requirements needed to provide safety for the foreseen use.

1.5 Implementation of ECETOC's TRA

Electronic implementation of the TRA approach has been achieved through the development of a web-based tool. The tool can be accessed at https://www.ecetoc-tra.org. The tool demonstrates that, although the (eco)toxicology and exposure science behind the approach is complex, it can be automated to show the practicability of the concepts in a working model and that it need not be a resource-intensive activity. It is also designed so that the results are well documented and understandable, and to ensure that consistent answers are achieved from the set of 'rules' that have been written out in a logical pattern. The design of the tool is novel and it is believed that it will have applications (after suitable amendment) outside the scope of REACH, e.g. general product stewardship. The benefits of the electronic version are that it has simplified the verification of the approach and:

- Allows rapid assessment of substances to Tier 1;
- provides all the necessary information in one place;
- has the potential to link to other tools, models and databases;
- produces reports;
- minimises clerical activities because data need to be entered only once;
- enables easy access and understanding.

The web tool cannot provide either the hazard or exposure information needed for the assessment nor can it check the validity of data used.

1.6 Where and how the ECETOC targeted risk assessment approach helps REACH

The ECETOC TRA approach is an integrated framework which aims to readily identify the risks presented by the manufacture and use of chemicals. The approach:

- Reflects current risk assessment practice and scientific understandings;
- accounts for information that is available;

- respects resource and welfare demands;
- delivers risk-based priorities.

The use of the ECETOC TRA approach within REACH is still to be developed and agreed among stakeholders, but it is envisaged that the ECETOC TRA approach could help in the following areas:

- In the definition of core data requirements necessary to undertake risk assessments hence avoiding the duplication of work;
- when undertaking a Chemical Safety Assessment (CSA) and the production of a Chemical Safety Report (CSR) for those chemicals/uses that are not identified as being a concern at the Tier 0 and Tier 1 levels;
- identification of further work and information necessary to complete the CSA for some chemicals;
- TRA prioritises the relative risks of different substances and their conditions of use;
- TRA performs a CSA and provides a CSR for those chemicals/uses that are not identified as being a concern at the Tier 1 level;
- TRA may help authorities in their prioritisation – i.e. identify the further work and information necessary to complete the CSA as one integrates all CSRs in a community CSA to cover all uses;
- TRA enables different scenarios of concern to be evaluated easily, taking into account the effectiveness of different risk management measures;
- the prioritisation of potential risks informs and guides related regulatory and industry action plans;
- application of the TRA to substances requiring authorisation enables worker and consumer exposure scenarios of highest concern to be identified quickly and accurately, targeting resources in a subsequent detailed assessment;
- the outputs of the TRA align with existing community health and environmental regulations;
- the structure of the TRA tool is consistent with other schemes known to be understood by and taken up by SMEs;
- TRA simplifies what is often seen as a complex process only capable of being carried out by experts into a form that is simple to understand, yet maintains the required level of scientific confidence and integrity.

2. HUMAN HEALTH

2.1 Tier 0 risk assessment

The primary philosophy of Tier 0 is a risk-based process that requires that a minimal amount of relevant exposure and hazard information be available to serve as the basis for a first risk screen. The ability to describe, with some degree of confidence, the nature of likely exposure at the broad 'supply level' is a major consideration. Hence, rather than simply utilising tonnage triggers, which provide no meaningful relationship with potential exposure, a composite predictor of exposure (termed ' exposure potential') is derived to provide a more appropriate alternative.

At Tier 0 there is a need for a tool which makes the best use of any available hazard information to support strategies to protect health. Moreover, there is a need for simple and transparent approaches that are readily understood and can be applied consistently by any organisation.

2.1.1 Exposure potential

The exposure potential is determined through a combination of three separate descriptors:

- The main use category for the substance;
- basic physico-chemical properties;
  - vapour pressure (or dustiness if it is a solid)
  - physical form
- annual production volume for the substance.

The annual production volume reflects the total amount of the substance produced across all producers and importers and covering all intended uses (see Appendix A). The use category provides an indication of the nature of the exposure associated with the principal areas of use of the material (see Appendix B). The physical form has a direct bearing upon potential exposure, for example massive solids are not available for inhalation or oral exposure whilst a volatile gas usually poses little toxicological concern for dermal contact. For the determination of exposure potential at the screening level, vapour pressure and dustiness are used.

The exposure potential of a substance in the Tier 0 screening is determined by:

a) The highest value given by the physico-chemical data on vapour pressure (hPa), or dustiness as a surrogate for the fugacity of the material. This yields a banding of the substances availability according to Table 1.

Table 1: Determination of availability banding

Vapour pressure (hPa)	Dustiness	Availability banding
<5	Not dusty	Minimal
5-10	Slightly dusty	Low
10 – 100	Dusty	Medium
>100	Very/extremely dusty	High

The determination of the fugacity of materials is discussed in more detail in Appendix C.

b) Using the availability bands from (a), the following look-up tables are used to determine the overall exposure potential. The main use category associated with the use furthest down the supply chain takes precedence. Where no thorough understanding of use is known, then wide dispersive use is assumed. The shape and boundaries of the different availability categories have been derived following an initial verification exercise based upon substances that have undergone risk assessment under the Existing Substances Regulation (EC, 1993a). These boundaries are necessarily provisional, because of the limited number of substances which have been investigated. A more extensive verification is planned, dependent upon which there may be a need to refine the boundaries.

Table 2: Exposure potential for minimal band availability substances

Main category of use (TGD)	Annual tonnage					
	1-10	10-100	100-1,000	1,000-10k	10k-100k	>100k
Intermediate used on site (non-isolated and isolated)						
Isolated intermediate used/stored off site		Minimal				
Included into or onto a matrix						
Non-dispersive use - professional				Low		
Wide dispersive use						

Table 3: Exposure potential for low band availability substances

Main category of use (TGD)	Annual tonnage					
	1-10	10-100	100-1,000	1,000-10k	10k-100k	>100k
Intermediate used on site (non-isolated and isolated)						
Isolated intermediate used/stored off site		Minimal				
Included into or onto a matrix						
Non-dispersive use - professional					Low	
Wide dispersive use						Medium

Table 4: Exposure potential for medium band availability substances

Main category of use (TGD)	Annual tonnage					
	1-10	10-100	100-1,000	1,000-10k	10k-100k	>100k
Intermediate used on site (non-isolated and isolated)	Minimal					
Isolated intermediate used/stored off site						
Included into or onto a matrix			Low			
Non-dispersive use - professional						
Wide dispersive use						Medium

Table 5: Exposure potential for high band availability substances

Main category of use (TGD)	Annual tonnage					
	1-10	10-100	100-1,000	1,000-10k	10k-100k	>100k
Intermediate used on site (non-isolated and isolated)	Minimal					
Isolated intermediate used/stored off site						
Included into or onto a matrix			Low			
Non-dispersive use - professional					Medium	
Wide dispersive use	Low		Medium			High

2.1.2 Hazard potential

The hazard potential is determined by reference to all the available information for the substance. All available information sources should be included. The ECETOC approach does not implicitly demand the availability of test data. What is considered a prerequisite, however, is the availability of information sufficient to enable the approach to function effectively. For example, information derived from (Q)SAR or read across may be used to describe the likely hazards. It remains subject to expert judgement on a case-by-case basis to confirm such findings using *in vitro* or *in vivo* assays.

A workable system of ranking the hazard has to be based on limited information. The primary toxicological endpoints to be considered are those defined in Appendix D (Information requirements). For human health these are acute toxicity, mutagenicity, dermal sensitisation and irritancy/corrosivity. These endpoints are mainly related to the acute hazard and indications of genotoxicity as surrogate for a possible mutagenic or carcinogenic effect. The data should be of a quality that allows a clear decision on the classification and, with that, an allocation to one of three hazard categories (see Appendix E for further details). Existing information on hazards other than those included in the information requirements outlined above should however be taken into account if they are readily available. If no further information on repeated dose toxicity is available, the substance is assigned a medium hazard category (see Appendix S) unless it is allocated to the high category based on other endpoints. The hazard information for one particular substance can, in certain cases, be replaced by information on close structural analogues (grouping of substances) or be obtained from structure activity relationships (SARs) if available.

The approach presented here is based on a simplified hazard ranking system, which categorises different toxicological endpoints into discrete hazard 'bands' and provides non-expert users with a simple comparative descriptor of the hazard. By structuring the allocation of the endpoints, including, for example, their severity and/or potency, it is possible to develop banding schemes that also account for the relative importance of the effects for man. Such 'hazard banding' is considered to be easy to understand when attempting to evaluate the consequences of exposure to a substance (Wiseman and Gilbert, 2002).

Hazard ranking and banding are not new concepts. Over the last ten years various schemes have been proposed for different occupational exposure purposes covering specific classes of chemicals, e.g. industrial chemicals, pharmaceuticals (CIA, 1993; ABPI, 1995), different endpoints (CIA, 1992) or chemicals as a whole (CIA, 1997; RSC, 1996; HSE, 1999). But in general, these schemes aim to categorise on the basis of either:

- The progression of severity of discrete toxicological endpoints, in most cases expressed by the readily available risk phrases assigned for hazard classification purposes;

- the interpretation of toxicological endpoints in the context of the principal purpose of the banding scheme, e.g. the reduction of chemical exposures or risks (HSE, 1999; UIC, 1999; BAuA, 2001; Money, 1992a), the choice of engineering control strategies (Money, 1992b), or the development of generic occupational exposure limits (CIA, 1997; ABPI, 1995).

Concerning the latter, ABPI (1995) defines Occupational Exposure Bands (OEBs) as a health-based limit of a temporary nature based on the available hazard data and using a precautionary approach. These bands should be seen as the best estimate of the concentration to which the substance should be controlled. When new data become available the bands should be refined until sufficient data are available to allow an OEL to be set.

CIA (1997) consider OEBs as hazard categories to which a substance can be allocated on the basis of available hazard information. The OEB defines the upper limit of acceptable exposure. Their OEB scheme is limited to those categories relevant for inhalation exposure.

Health effect ranking

The scheme is based upon three broad descriptors of hazard: acute and systemic toxicity, irritation/corrosion and irreversible effects. The separation of endpoints accounts for the relative importance that different endpoints have in terms of adverse health effects (whether they are life-threatening, reversible, etc.) and the consequent standard/level of handling that might be expected to be associated with the use of these materials. When assigning a substance to a particular hazard category, the most sensitive endpoint for which information is available is chosen.

With one exception, namely the allocation of a medium hazard category to substances for which no information on repeated dose toxicity is available, the approach utilises the risk phrase assigned to the substance under the EU Dangerous Substances Directive (EEC, 1967) and which might be found either within the IUCLID entry for the substance or (for preparations containing the material) on the Safety Data Sheet (SDS) supplied with the product.

The ranking scheme proposed by ECETOC is outlined in Table 6.

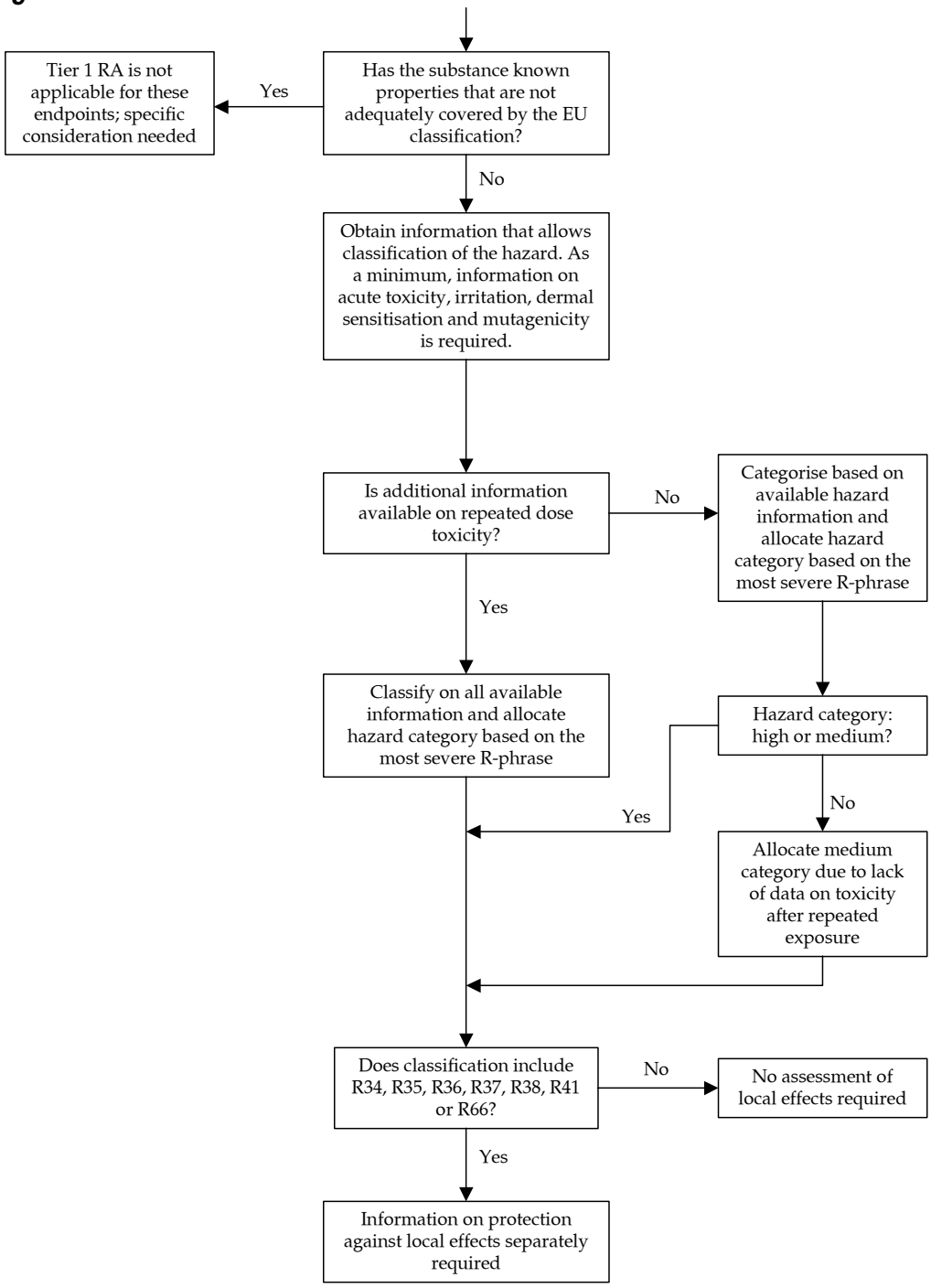
Table 6: Categorisation of hazard

Human health classification			
Risk phrase	**Classification**	**Descriptor**	**Hazard category**
	Unclassified [a]		Low
R20	Harmful	Acute toxicity inhalation	Low
R21	Harmful	Acute toxicity dermal	Low
R22	Harmful	Acute toxicity oral	Low
R65	Harmful	Aspiration	Low
R67	Harmful	Drowsiness	Low
R36	Irritant	Irritation eye	Low
R37	Irritant	Irritation respiratory system	Low
R38	Irritant	Irritation skin	Low
R66	Irritant	Irritation skin (repeated)	Low
	Unclassified or classified as acutely harmful or irritant and no information on repeated dose toxicity		Medium
R48	Harmful	Prolonged exposure	Medium
R40	Harmful	Carcinogen Cat.3	Medium
R68	Harmful	Mutagen Cat.3	Medium
R62, R63	Harmful	Reproduction Cat.3	Medium
R23	Toxic	Acute toxicity inhalation	Medium
R24	Toxic	Acute toxicity dermal	Medium
R25	Toxic	Acute toxicity oral	Medium
R39	Toxic	Irreversible effects	Medium
R43	Irritant	Sensitisation: skin	Medium
R41	Irritant	Severe eye irritation	Medium
R34, R35	Corrosive	Corrosion	Medium
R42	Harmful	Sensitisation/inhalation	High
R48	Toxic	Prolonged exposure	High
R45, R49	Toxic	Carcinogen Cat.1, 2	High [b]
R46	Toxic	Mutagen Cat.1, 2	High [b]
R60, R61	Toxic	Reproduction Cat.1, 2	High [b]
R26	Very Toxic	Acute toxicity inhalation	High
R27	Very Toxic	Acute toxicity dermal	High
R28	Very Toxic	Acute toxicity oral	High

[a] Based on data (at minimum information requirements as described in Appendix D) and sufficient information on repeated dose toxicity.
[b] Substances classified R45, R49, R46, R60 or R61 are of very high concern.

This ranking scheme is based upon a synthesis of several of the above approaches (further details of which are provided in Appendix E). The process by which data are acquired, evaluated and categorised is summarised in Figure 3.

Figure 3: Flow chart for the human health hazard assessment at Tier 1



2.1.3 Evaluation of potential risks

At Tier 0, the risk characterisation is performed using a risk matrix (see Table 7). At this level, potential risks would be evaluated based on both the exposure potential and hazard potential assigned to them. The risk assessment can be completed at Tier 0 when there is:

- Minimal to low exposure potential with a low hazard potential, or
- a minimal exposure potential with a low or medium hazard potential, or
- where the hazard category is triggered by a local effect (corrosion, irritation) and appropriate exposure management measures are in place, e.g. adequate personal protective equipment is recommended within the Safety Data Sheet (SDS), child-resistant packaging is supplied with a consumer product.

For all other cases, the risk assessment should proceed to Tier 1.

Table 7: Tier 0 risk matrix

Hazard potential	Exposure potential			
	Minimal	**Low**	**Medium**	**High**
Low	No immediate concern	No immediate concern	Higher tier RA	Higher tier RA
Medium	No immediate concern	Higher tier RA	Higher tier RA	Higher tier RA
High	Higher tier RA	Higher tier RA	Higher tier RA	Higher tier RA

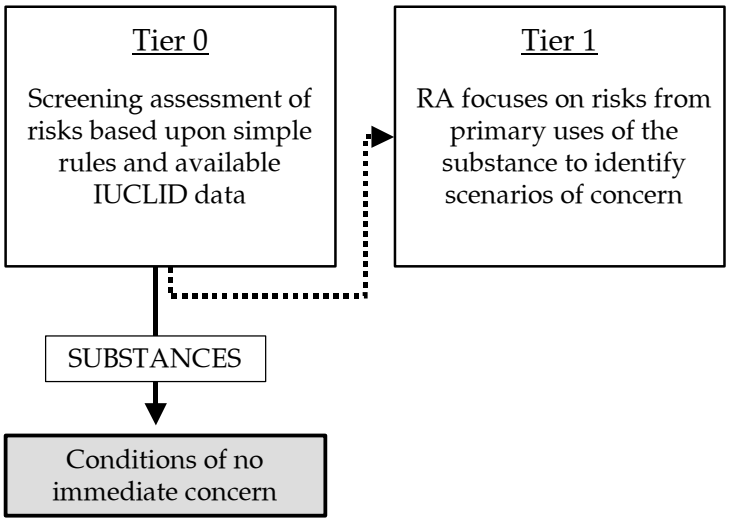
Examples describing the use of the risk matrix are given in Appendix F. A comparison of the outcomes using the ECETOC approach at Tier 0 and the published EU Existing Chemicals Risk Assessments shows that the two approaches are consistent for those substances categorised without immediate concern in the above risk matrix (Table 7).

2.1.4 Tier 0 outputs/conclusion

The first tier of the approach is a simple screening risk assessment that establishes whether further targeting within the overall risk assessment process is required. It is based upon the application of a defined set of rules to identify substances which are unlikely to constitute any immediate concern from their uses. Whilst the Tier 0 stage enables users to deliver consistent screening outputs across all substances it has undergone limited verification.

Substances that require further risk assessment progress to the next tier in order to target those uses of the substance that might constitute a risk to human health. The process is summarised in Figure 4.

Figure 4: Summary of approach to Tier 0 human health assessment



2.2 Tier 1 human health process

2.2.1 Introduction

The prime determinant of what a population's exposure to a chemical is likely to be is not *where* a substance is used but *how* it is used. The basis of the ECETOC approach to evaluate risks at the Tier 1 level is therefore to focus on those *activities* that occur throughout industry and the consumer domain and that primarily describe the subsequent nature of the exposure experienced. These are termed 'exposure scenarios' in the approach.

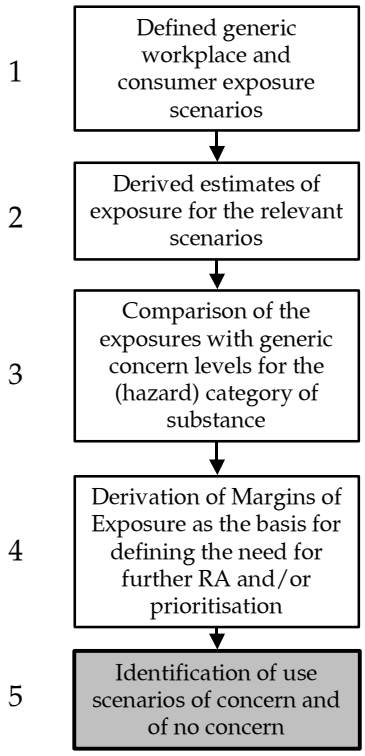
Defining exposure scenarios in this manner has the advantage that they can be expected to describe more precisely and accurately the nature of expected exposures and to identify those that are likely to be a concern. This has significant benefits in terms of industry's ability to support its obligations within the supply chain. However, it does not directly address the use of a substance in a particular industrial sector, which is a primary interest in the delineation of supply chain roles and responsibilities.

Thus in order to improve the overall confidence (in terms of reduced uncertainty) and user-friendliness of the approach as a whole, the Tier 1 process seeks to identify and describe exposure scenarios that are predominantly associated with specific industrial or product use categories. This enables Tier 1 to be progressed in a common manner regardless of whether it is addressing workplace or consumer exposures.

The process adopted to evaluate risks to human health at the Tier 1 level is summarised diagrammatically in Figure 5. The five steps consist of:

1. Identification of standard exposure scenarios that are relevant for the substance and that represent the intended conditions under which it is manufactured, sold, supplied and used both by workers and consumers. Thus, depending on the circumstances of production and use, a substance is likely to be linked to several such scenarios (the exception being site-limited intermediates that are handled in contained systems and where exposure is confined to the workplace).
2. Calculation, using suitable models, of the predicted exposure for each use.
3. Selection of an appropriate 'no concern level' for the hazard category of the substance.
4. Derivation of a Margin of Exposure (MoE) by comparison of (3) with (2).
5. Targeting those scenarios that warrant a more detailed investigation at the Tier 2 level, from those where no concern is indicated from the Tier 1 assessment, based upon the MoE. This is determined using a reference MoE that takes into account different extrapolation steps.

Figure 5: Process to evaluate risks to human health at Tier 1



Tier 1 aims at delivering a simple, transparent and consistent targeting and assessment of the risks associated with the production and use of a substance. The depth and detail of the risk assessment are proportionate to the likely risks associated with the substance. This enables resources to be directed at those scenarios that appear to be of highest concern. The RA is

consistent with existing risk assessment and management methodologies and delivers outcomes that are aligned with other worker and consumer legislation.

2.2.2 Characterisation of exposure

The particular uses of a substance determine how the expected exposures of both workers and consumers are calculated. The ECETOC approach uses established exposure-prediction models, but introduces a more structured and simplified approach for their use. This delivers consistency with established approaches for assessing risks, whilst, at the same time, simplifying them and hence ensuring their wider accessibility.

The basic philosophy for exposure assessment within the approach is that, provided suitably conservative prediction models are available to estimate exposure within a given scenario, there is no obvious need to collect measured exposure data. The exposure models will depend upon information that is sufficiently specific to describe exposure within a scenario without recourse to the use of data collected at the individual worker or consumer level. Thus, where such data are available, they can be integrated into a refined risk assessment at the Tier 2 level if necessary. This hierarchy is consistent with approaches to exposure data collection embraced within the workplace.

2.2.2.1 Workplace exposures

Personal exposures arising from the use of chemical substances at work are determined in a simple sequential manner in the Tier 1 process by describing the conditions under which a substance would be expected to be used in the workplace:

1. The generic situations (termed 'exposure scenarios') which describe how a substance is likely to be used are identified from a standard pick-list. The choice of scenarios (Appendix G) is limited (n=15) but is considered to represent the vast majority of circumstances where workplace exposures to chemicals arise. The description of the scenarios closely aligns with those used to describe successful risk management solutions in the UK COSHH Essentials scheme (HSE, 1999). These exposure scenarios also automatically identify whether there is a potential for significant dermal contact. The scenarios are not intended to address circumstances that relate to the wilful misuse of a chemical, e.g. disregarding specific precautionary advice, nor do they reflect emergency situations, e.g. spillages. However they do include small spillages such as those which might typically be encountered in day-to-day workplace activities.
2. For each exposure scenario, the likely exposure reduction measures that would be expected to be encountered with the scenario are identified (from a limited list of options). At Tier 1,

the exposure reduction options consider only the impact of local exhaust ventilation. The effectiveness of procedural measures and personal protection (other than gloves against dermal irritation and corrosivity and goggles against eye irritation/corrosivity) are considered to be elements of a Tier 2 assessment. Account is also taken of the expected duration of the activities associated with the scenarios (Appendix H).

3. Based upon the above, the predicted airborne and dermal exposure is calculated. An improved version of the EASE model (Appendix J) is applied to each of the exposure scenarios. In calculating exposures at Tier 1, there is no opportunity to override the default values that support the exposure predictions. The incorporation of actual exposure data is considered at the Tier 2 level.

The EASE exposure model is able to predict inhalation and dermal exposures for each identified scenario based upon the responses in the three stages listed above. Thus the Tier 1 process builds upon the Tier 0 assessment, not only by identifying the specific uses of a chemical that might be expected to present health risks, but also by expanding the core Tier 0 information to provide an additional level of confidence and sensitivity. Section 2.2.6.1 describes in further detail the validation exercise that has been undertaken in support of this.

The key to the success of Tier 1 is its ability to obtain an accurate generic description of the situations where a chemical is intended to be used. Moreover, incorporating a realistic estimate of exposure enables the relative risk of different uses of the substance to be compared, hence providing a mechanism for targeting any further risk assessment or risk reduction effort.

Because the EASE model is used as the basis of the predictions, exposures outside the applicability domain of EASE are consequently not reliably dealt with. In essence, such situations occur when exposures to mists or process fumes are present. A fuller description of the limitations of EASE is described elsewhere (HSE, 2003).

2.2.2.2 Consumer exposures

The exposure potential for consumer use at Tier 0 is derived by using the wide dispersive use category and only provides a limited indication of the potential number of people who may be exposed and of the likelihood that they will be exposed. Unless the substance has a low or minimal exposure potential as defined at Tier 0, it should be investigated in more detail at the Tier 1 level. Tier 1 aims to evaluate the expected level of exposure that results as a consequence of product use.

There are a number of cases and circumstances for which consumer exposure to a chemical need not be considered. These are described in Appendix K. They are either regulated by existing community legislation or other circumstances suggest that they are unlikely to present a concern,

e.g. chemicals immobilised in a matrix which precludes their bioavailability. Cases of chemicals that would not be expected to pose a consumer exposure concern include chemicals present in a product at a level lower than the concentration limit identified in the Dangerous Preparation Directive (EC, 1999b).

Estimation of human exposure to a given chemical as a consequence of its presence in consumer products requires knowledge of the type of the products where a substance may be used, the amount of the substance likely to be present in the product, together with details of frequency and duration of product use. The relevant exposure route(s) corresponding to each product use can then be identified and taken into consideration together with the appropriate physico-chemical characteristics of the chemical and the product(s) where it is present.

At the Tier 1 level, consumer exposures are estimated using an approach based upon established EU TGD algorithms (EC, 1996c). The values of the algorithm exposure parameters are derived from published information about consumer products and what is known about the routes of exposure (dermal, oral and inhalation) that arise from these uses. By examining which types of products have the greatest overall potential for consumer exposure, priority product use categories and product types can be identified. Consumer exposures to substances are assessed in the following manner:

- The use categories in which a chemical may be employed are identified from a list of defined consumer product uses (Appendix L). The list was developed from the lists that already exist within OECD and the US EPA, but excludes use categories which are subject to specific EU regulations, such as, for example, medicinal products, cosmetic products, foodstuffs, etc. Appendix L provides further background to the development of the list.
- A product default exposure profile has been developed for each use category. The profile identifies the type of exposures that are expected to be associated with any intended use of a product (dermal, oral and/or inhalation), together with default values for the key exposure determinants for each of the exposure routes. The exposure routes associated with each use have been determined by expert judgement and are detailed in Table 8. It can be seen that for some uses, potentially substantive exposures are considered to be foreseeable via all three exposure routes. But for many uses, substantive exposures are likely to be confined to two or even a single route. Appendix M summarises the default assumptions associated with each use. These assumptions reflect those that could be expected to be associated with reasonably foreseeable and intended uses of the product. They are not intended to cover extremes of use. The information reflects that found within similar product templates within the TGD, other published sources (e.g. US EPA, 1997a,b,c; HERA, 2003,) together with conservative assumptions based upon experience. Further refinement of these values will be necessary as they reflect the current understanding of use, which will change.

ECETOC will thus seek feedback on the content of Appendix M in order that it remains valid and current with time.

- Using the information in templates shown in Appendix M, consumer exposures to the substance for the individual product type can be calculated for each exposure route. Cumulative exposure across all three routes is determined for each use. However, additive exposures across different consumer product uses are not automatically defined. In this way, the proportion of the total exposure due to any product type can be estimated. The specific exposure algorithms used for the calculations are given in Appendix M.
- The approach uses a series of conservative default assumptions. Where specific information is available that indicates they are inappropriate, limited provision exists to modify these, *provided* that the basis can be justified. Specifically, the approach allows for the percentage of the substance within the product to be altered and/or the likely contact area/quantity arising from the use. Only two default values per use can be modified in this manner, further iteration being deferred until Tier 2. Appendix M identifies the modifiable parameters for each product use at Tier 1.

Table 8: Consumer product exposure routes

Product use category	**Route of exposure**		
	Dermal	**Oral**	**Inhalation**
Artists' supplies and craft/hobby materials	Yes	Yes	
Adhesives, binding agents and sealants	Yes	Yes	Yes
Automotive care products	Yes		
Electrical and electronic products	Yes		
Glass and ceramic products	Yes		
Fabrics, textiles and apparel	Yes	Yes	
Lawn and garden products (non-pesticide/herbicide)	Yes	Yes	
Leather products	Yes		
Lubricants, greases, fuel and fuel additives	Yes		
Metal products	Yes		
Paper products	Yes	Yes	
Paintings and coatings	Yes		Yes
Photographic and reprographic products	Yes		
Polishes	Yes		Yes
Rubber products	Yes		
Soaps and detergents (washing and cleaning agents)	Yes	Yes	Yes
Wood and wood furniture	Yes	Yes	Yes
Construction materials	Yes		Yes
Plastic products	Yes	Yes	

2.2.3 Characterisation of hazard

Hazard evaluation is an integral part of any health risk assessment process and the principles have been described elsewhere (for example see IPCS, 1999; EC, 2003a). In the hazard assessment all available toxicological and other relevant information (e.g. physico-chemical data, information obtained by read across from analogous substances or groupings, structure activity relationship determinations) should be taken into account in the identification of the critical endpoint.

At Tier 1, the approach addresses the properties (or surrogates of these) that represent the most relevant endpoint (or 'lead effect') that exposure to the substance may cause. The process uses the classification criteria within the Dangerous Substances Directive (EC, 1992) to derive what in effect is a generic critical endpoint for the respective hazard categories identified in Table 6. However, where acceptable data are available for an individual substance, incorporation of these are encouraged to improve the accuracy and reliability of the hazard assessment. The ECETOC approach therefore allows for (limited) iteration and thus enables the complexity and confidence of the Tier 1 risk assessment to be defined, in part by the available information. Such a cautionary approach is consistent with a tiered approach to screening risks. For the workplace, generic exposure values can be replaced by existing or expert-derived OELs. For consumers, NOAELs of rodent repeated dose studies, supported by study details on species, exposure duration and frequency can be used instead of the generic low effect values.

The Tier 1 hazard assessment concentrates on possible systemic effects after repeated exposure. Although it is applicable to most industrial chemicals, some considerations as outlined below should be made in advance of commencing a Tier 1 assessment:

1. If there is only occasional short-term exposure to the substance, then the risk assessment for repeated exposure does not have to be carried out;
2. if the substance has a local irritating potential (R-phrases 34, 35, 36, 37, 38, 41, 66), an additional assessment of possible local effects may be necessary, particularly when repeated consumer exposure could be envisaged. Substances classified as dermal sensitisers (R43) require an assessment of risk in line with the recommendations in Section 2.2.4.1.2;
3. if the substance is potentially bioaccumulative (log $K_{ow} > 5$) and is not likely to be metabolised to readily excretable metabolites or there are potentially bioaccumulative metaobolites, then an additional case-by-case assessment may be necessary in Tier 2;
4. if the substance has a potent pharmacological effect, such as exhibited by some pharmaceuticals, then it should be considered for a Tier 2 assessment.

The hazard assessment process is illustrated in Figure 3. It should be noted that as only the R48 phrase is determined by dose thresholds, then this provides a further information source upon which the accuracy of the effects assessment can be improved.

2.2.3.1 Workplace

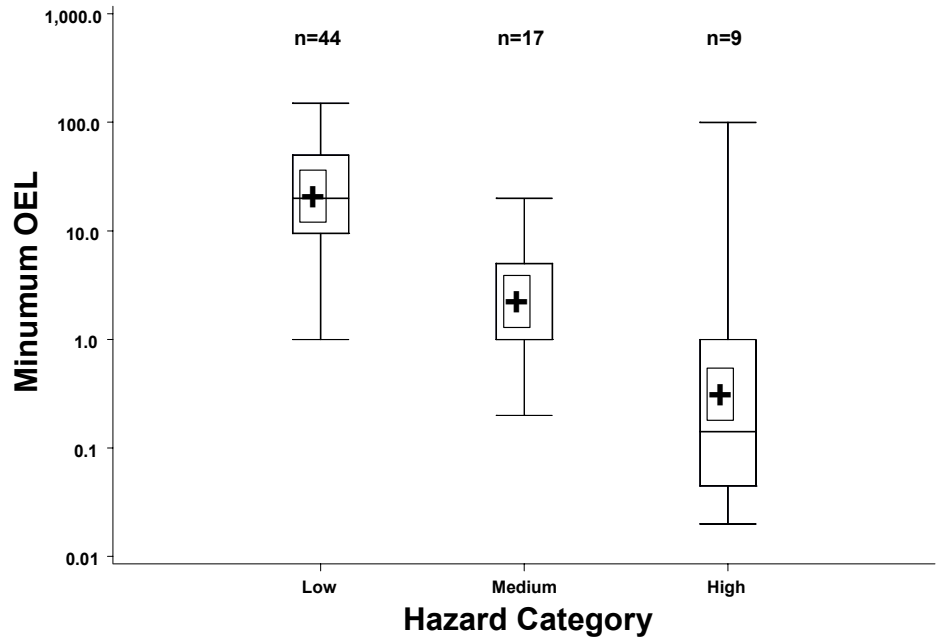
Inhalation

The hazard category is used to identify a generic exposure value which is considered to represent a workplace exposure of no concern. The values for volatile substances were derived following a comparison between the hazard category and available health-based Occupational Exposure Limits (OELs). The basis was the published list from the EU Scientific Committee on OELs. In addition, where an equivalent OEL was available from established national OEL schemes, this was also noted. A total of 63 such substances were identified. A detailed explanation of the process adopted, together with analyses, is contained in Appendix N.

Figure 6 shows the distribution of the most stringent OELs for 60 volatile substances (from the EU as well as various national schemes in Germany, Sweden, the UK, the Netherlands and the USA) compared with their hazard category. It utilises the 25th percentile value of the most stringent of available OELs for substances within a particular hazard category. From the clear demarcations (Figure 6), it can be seen that the hazard category allows for identifying values that serve as conservative surrogates for levels of no concern for the workplace. These values are referred to as Generic Exposure Values (GEVs). The GEV is not meant to replicate the role of OELs. Rather, it is designed to serve as an arbiter, at this Tier of the targeted risk assessment process, whether the workplace exposure to the substance is acceptable or not.

Unlike volatile substances, there are relatively few OELs for solid materials. It was therefore impossible to develop GEVs for solids in the manner described above. However, a number of publications describe the general relationship between generic OELs for volatile and non-volatile materials (CIA, 1997; ABPI, 1995; Brooke, 1998) and these have been used to identify equivalent GEVs for solids (Table 9). Appendix N contains details of the approach used.

Figure 6: The most stringent OEL (USA, Ger, Swe, Neth, UK and EU)



Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Table 9: Workplace GEVs for volatile and non-volatile chemicals

Hazard category	Generic Exposure Value for volatiles (ppm)	Generic Exposure Value for solids (mg/m^3)
Low	10	1
Medium	1	0.1
High	0.05	0.005
Substance of very high concern (SVHC)	Not applicable	Not applicable

Dermal

The hazard category is also used to determine a dermal equivalent of the GEV, in effect representing a workplace dermal exposure level of no concern. The dermal GEV (termed the GDEV within the approach) is derived by extrapolating the GEV to an internal dose equivalent.

This can be used as systemic dermal GEV by multiplying the dose by 10 ($10m^3$ being inhaled over a working shift by a person under light/moderate workload), and dividing by 70 (consistent with the 70 kg standard default weight for a male) and assuming 100% absorption via inhalation and dermal exposure. Appendix Q describes the considerations and underlying

assumptions in full. Such assumptions of absorption are recognised as being conservative, in particular for dermal exposures. Where information exists that indicates lower values are appropriate (for example, 100% absorption would rarely be expected to occur in practice), then these are considered at the Tier 2 level.

2.2.3.2 Consumers

To evaluate the potential risk arising from a particular consumer use of a substance, a (no or low) effect level is compared to an estimate of the exposure.

Several concepts have been developed enabling the assignment of safe human exposure levels in the absence of adequate toxicological information. Generally, these concepts are referred to as the Threshold of Toxicological Concern (TTC) (Appendix O). Because the TTC values are designed for specific applications, and only allow limited differentiation, their general use within the ECETOC approach is not considered appropriate at the Tier 1 level. The ECETOC approach is however not contradictory to those approaches and reaches similar results. Consequently, ECETOC is proposing a simple concept of generic values for substances that are derived from the hazard category. These Generic Lowest Effect Values (GLEV) can be used in tiered process of consumer risk assessment as a conservative estimate of the actual Lowest Observed Adverse Effect Level (LOAEL) for the substance's repeated dose toxicity. The ECETOC concept is based on the EU criteria for the classification of a substance for repeated dose toxicity (R48).

The criteria for applying Xn, R48 specifies thresholds at exposure levels in sub-chronic (90 day) toxicity studies in rats of 50 mg/kg/day (oral), 100 mg/kg/day (dermal) or 250 mg/m^3 (inhalation). Classification is required if significant adverse effects are observed at/or below these threshold levels. The classification T, R48 is triggered if significant adverse effects are observed at/or below 5 mg/kg/day (oral), 10 mg/kg/day (dermal) or 25 mg/m^3 (for the inhalation route). Thus for substances not meeting the requirements for classification Xn, R48 (and therefore assigned to the ECETOC low hazard category on the basis of repeated dose toxicity) the classification cut-offs represent a threshold for significant adverse toxicity (although it is possible that effects not regarded as significant may occur at these levels). Therefore, for the low hazard category, an exposure level of 50 mg/kg/day can be considered as a generic LOAEL for 'non-significant' adverse effects upon repeated oral exposure. Similarly, an exposure level of 5 mg/kg/day can be regarded as a generic LOAEL for the ECETOC medium hazard category. The classification thresholds for other exposure routes may be regarded as generic LOAELs for repeated dose toxicity (for an overview of the generic, classification-based thresholds for repeated dose toxicity, see Table 10). A similar threshold for substances in the high hazard category cannot be derived from the criteria for the classification R48. In this case, the GLEV is derived by dividing the Generic LOAEL of medium hazard category by a factor of 10.

Table 10: Consumer Generic Lowest Effect Values

Hazard category	Reference value	Oral (mg/kg/day)	Dermal (mg/kg/day)	Inhalation (mg/m^3)
Low	GLEV	50	100	250
Medium	GLEV	5	10	25
High	GLEV	0.5	1	2.5
SVHC		Not applicable	Not applicable	Not applicable

Appendix S provides further information and presents details of the validation of this approach.

Where actual data are available from good quality animal studies, these may be substituted for the GLEV. In such cases, the Assessment Factors will need to be modified in accordance with the guidance given by ECETOC (2003a).

The reference MoE cited above and the ECETOC concept for Generic LOEL have been validated for systemic effects. In-depth analyses of several databases have shown that the NOAELs for repeated dose toxicity are (at least) equal to, or lower than, the corresponding threshold for reproductive or developmental toxicity (Barlow *et al*, 2001; Mangelsdorf *et al*, 2003; Munro *et al,* 1996). Therefore, risk assessments based on a Generic LOEL and a reference MoE include, by default, an assessment for reproductive toxicity and developmental effects. Carcinogens of Category 3 are also covered by this approach, provided the lack of a mutagenic potential has been established unequivocally.

Substances within the high hazard class on the basis of a respiratory sensitisation potential (R42) should be assessed on a case-by-case basis at the Tier 2 level for their risks from consumer use. Corrosive substances (classified R34, R35 or R41) that may induce significant effects at the site of first contact without evidence of systemic toxicity (e.g. local irritation of the respiratory tract upon inhalation) are not directly covered by this approach. They require a separate assessment of these endpoints. Also excluded from this approach are those substances with a potential to bioaccumulate (see Appendix R) and those with potent pharmacological activity (e.g. pharmaceutical agents and pesticides). Further advice on how such assessments should be undertaken within the context of the Tier 1 process is contained within Appendix P.

2.2.4 Evaluation of potential risks

The Tier 1 process aims to identify those scenarios where risks to either workers or consumers would be considered to represent a potential concern. Such scenarios are then subject to a more detailed evaluation of their risks at the Tier 2 level. The different risks that might be present within any given worker or consumer scenario are assessed using the following mechanisms.

2.2.4.1 Workers

2.2.4.1.1 Inhalation exposure

Comparing the measured exposure of a worker (or working group) with an OEL is a widely established element of occupational health and safety practice. But the comparative process can also be applied to generically derived variables, whether these relate to exposure and/or effects. Thus, within the ECETOC scheme, the GEV and predicted exposure for the particular scenario are instead used for comparative purposes (unless a valid OEL is derived for the substance). In order to describe transparently the extent to which exposure relates to the GEV, a worker Margin of Exposure (MoE_w) (defined as the quotient of the GEV and the predicted exposure) is identified for each scenario.

OELs, in themselves, already incorporate safety factors, dependent upon the nature and severity of the health effect that they are intended to protect against. Therefore the process for deriving the GEV, because it is based upon a pooling and statistical evaluation of available OELs, also ensures that some margin of safety is integrated within the GEV.

The ECETOC approach has selected a discriminating MoE_w of 2 as the basis for distinguishing scenarios that are of concern from those which are unlikely to be of concern. An investigation of the acceptability of this value across 66 different workplace scenarios (Table 11) showed that use of a MoE_w of 2 or higher provides a reasonable balance between the need for a degree of inherent conservatism (within a targeting level process) and delivering conclusions that align with those that would be made if existing workplace legislation were to be applied to the situation. This value is also consistent with the general compliance rules that are routinely advocated within occupational hygiene guidance (Mulhausen and Damiano, 1998; Guest *et al*, 1993).

The MoE_w also provides the advantage that the magnitude of the MoE_w serves as a surrogate measure of the relative risk of scenarios when compared to one another. This feature potentially enables the outputs of the process to be used for priority setting or similar purposes.

Table 11: Verification of the MoE_w to determine the presence of workplace risks

Outcome of EU risk assessment	**Outcome of ECETOC method**	
	Likely risk	**Risk unlikely**
Concern (n = 23)	23	0
No concern (n = 43)	26	17

N = 66 workplace scenarios

2.2.4.1.2 Dermal contact

The risks from dermal exposures are only specifically evaluated at the Tier 1 stage of the ECETOC approach. At Tier 0, the conditions under which inhalation exposure to low hazard substances are considered to be insignificant are also considered to present a low risk from any dermal contact with such (low hazard) substances. At the Tier 1 level, dermal risks are evaluated in those scenarios that are associated with significant dermal contact with the substance. Such an assessment is made for each scenario on the basis of experiences from across industry and historical regulatory consensus (and is summarised in Appendix Q). Substances that are unlikely to constitute any dermal risk through absorption due to their physico-chemical properties are not considered. Such cases are when the substance has either high hydrophobicity (log K_{ow} > 5), high hydrophilicity (log K_{ow} < -1) or a high molecular weight (>1,000). These conditions are consistent with the advice contained within the EU TGD (EC, 2003a).

An estimate of the dermal dose (in mg/kg/day) is then determined for each scenario where significant dermal contact with the substance is likely. This is achieved by linking the descriptors of the scenario to the inputs of the dermal portion of the EASE model. The EASE output (the upper boundary of a dermal loading range) is then combined with the assumed dermal contact area (which varies according to the scenario and ranges from 420 - 1,500 cm^2 to reflect the likely exposed skin area), accounting for a mean bodyweight of 70 kg and assuming total (100%) absorption through the skin.

This philosophy of applying a tiered approach to the assessment of dermal risks is consistent with that used to identify substances that present risks from inhalation exposure. Appendix Q describes in further detail the rationale underpinning the evaluation of dermal risk, including that presented by contact allergens.

2.2.4.1.3 Mixed and aggregate exposures

In practice, many workplace exposures to chemicals will occur as a mixed exposure to several chemical entities. This may be because the chemical is encountered as a preparation or because the process uses or releases a mixture of substances. Neither the EASE nor the COSHH Essentials exposure models are designed to:

- Predict exposures to the different components of mixtures;
- describe cumulative exposure across different exposure routes within the same task or activity; or
- calculate the aggregate exposure that may arise from different exposures to the same substance across different tasks or activities.

Therefore, the ECETOC approach adopts the following convention at Tier 1:

- Regardless of the concentration of a chemical that may be present in a preparation, the predicted EASE exposure is not modified in any way, and is taken to represent the actual exposure to the substance. Such a convention is designed to 'fail safe' and accounts for any difference that the relative volatility of chemicals in a preparation may have on actual airborne exposures;
- aggregate exposure across the inhalation and dermal routes is not calculated for each scenario, but the predicted exposure for each exposure route is clearly displayed in order that such a calculation can be easily undertaken; and
- recognition that the aggregate workplace uses of a substance do not reflect the actual exposure experiences of individuals and that aggregate exposure across different tasks or activities are not calculated, but are clearly displayed, in order that such a calculation could be undertaken if relevant.

The above rules are intended to ensure that the approach to exposure prediction and interpretation at the Tier 1 level remains rigorous, conservative and transparent. There will be instances where it results in the overprediction of actual exposures. However, consideration of this is judged to require a level of detail and scientific application that is beyond Tier 1. Hence they are aspects for more detailed evaluation at Tier 2.

2.2.4.2 Consumers

Standard risk assessment procedures generally rely on the existence of a NOAEL or LOAEL for the assessment of repeated exposures. Within the ECETOC approach, the GLEV is used instead, unless an actual NOAEL or LOAEL is available for the substance.

For each identified product use scenario, the predicted exposure to the substance in the product (Section 2.2.2.2) is compared with the GLEV for each relevant route of exposure. The quotient termed the consumer Margin of Exposure (MoEc) then forms the basis for both determining whether a concern exists and ranking the relative risks of the different scenarios (and routes of exposure). Where the MoEc is less than the overall Assessment Factor (i.e the product of each of the relevant Assessment Factors), then a potential concern is considered to exist, indicating that a targeted assessment of that scenario should be undertaken at the Tier 2 level. Further discussion on the choice and use of Assessment Factors is contained in Appendix R.

In this manner, the relative contribution to risk posed by different types of consumer products can be identified. The total exposure from relevant exposure routes (dermal, inhalation, oral) within any use is calculated. Where a substance is encountered in several consumer products, then aggregate exposures are not calculated as the main intention of the Tier 1 process is to

identify scenarios for further assessment. This approach still allows aggregate exposures across different uses to be evaluated, but does not automatically assume that such a phenomenon will occur routinely. This approach is consistent with that adopted within the TGD.

Table 12: Consumer Assessment Factors applied to the GLEVs [a]

Elements of extrapolation	Assessment Factors [b]	
	Oral/dermal	**Inhalation**
LOAEL to NOAEL	6	6
Duration: sub-chronic to chronic	2	2
correction study duration (6 hours/day to 24 hours/day)	1	4
Interspecies: rat to human	4	1
Intraspecies: consumer	5	5
Reference Margin of Exposure: (= product of Assessment Factors)	240	240

[a] When real NOAELs or LOELS are used other factors are applied as outlined in Appendix P
[b] These AFs are based on systemic toxicity; local effects due to irritant properties are to be assessed separately

The GLEV approach together with the Assessment Factors applied should be inherently conservative because, for example, for a substance allocated to the low hazard category the repeated dose LOEL is determined by the LOEL value defined by the classification and labelling directive as the dose level that would lead to an allocation of an Xn, R48 classification. Together with the allocation of an Assessment Factor of 240, the accepted dose level for a 'no further risk assessment required' conclusion is conservative. (For oral administration for example, the cut-off dose in the low hazard category of 0.2 mg/kg/day is obtained by dividing the GLEV of 50 mg/kg/day (Table 10) by the default MoE of 240 (Table 12)). In the medium hazard category the oral cut-off dose would be 0.02 mg/kg bw per day, and in the high hazard category 2 µg/kg per day. The latter value is similar to the threshold of toxicological concern of 88 µg/person per day (1.5 µg/kg bw per day for a 60 kg person) for high hazard substances, while for medium hazard category substances as defined by ECETOC the value is slightly higher than the 540 µg/person/day (0.009 mg/kg bw/day) in the TTC approach for substances with structures indicating a medium level of toxicity (Barlow *et al,* 2001; Kroes *et al*, 2004; for details, see Appendix O). As the ECETOC approach requires more information than only structural indicators, the difference seems reasonable and sufficiently conservative. The approach does not set out explicitly to address the risks of particular subgroups of the population, e.g. children. However, the conservative nature of the Tier 1 assumptions (especially the magnitude of the GLEV) indicates that the conclusions would normally be valid for such subgroups as well as the broader population.

Mixed and aggregate consumer exposures

Most consumer exposures to chemicals will occur as mixed exposures because the chemical product is normally comprised of several chemicals. In line with convention, mixed exposures are not automatically assessed in the ECETOC approach. However, in the case of aggregate consumer exposures, the following convention is applied:

- Cumulative exposure across the inhalation, oral and dermal routes are calculated for each consumer scenario, but aggregate exposures across different scenarios are not calculated. Instead, the cumulative exposure for each scenario is clearly displayed in order that such a calculation can be easily undertaken if required; and
- the above approach is intended to ensure that the approach to exposure prediction and interpretation at the Tier 1 level remains rigorous, conservative and transparent. Where an understanding of the risk presented by mixed exposures is considered necessary, this is judged to require a level of detail and scientific application that is beyond Tier 1. Hence a more detailed evaluation at Tier 2 is appropriate.

Comparison between workplace and consumer assessment

Compared to the occupational assessment where the use of the generic OEL based on the 75 percentile of the occupational exposure concentrations of the respective hazard category is used together with an Assessment Factor of 2, the acceptable consumer doses for volatile substances are normally lower than the acceptable workplace dose levels depending on the molecular weight. However, for inhalation of solids this is not the case. For a low hazard category solid the 'acceptable workplace daily dose' (mg/kg bw) would amount to: (GEV/2) x 10/70 = 0.07 mg/kg bw per day. For consumers this would amount to (GLEV/240) x 10/70 = 0.14 mg/kg bw per day. For the medium category the dose levels would be 0.007 mg/kg bw for workers and 0.014 mg/kg bw for consumers and for the high category 0.7 µg/kg bw per day for workers and 1.4 µg/kg bw per day for consumers. Thus the workplace GEVs for solids are more conservative and are below the general threshold of no concern level (see Appendix P). The likely reason for this difference is that for consumers the assessment is restricted to systemic effects, while the workplace GEVs included OELs for corrosive and very irritant materials that tend to have lower occupational exposure limits based on the threshold for irritation of mucous membranes rather than systemic effects alone. As no reliable structure activity model is currently available for predicting materials exhibiting irritant effects, then use is made of the existing GEVs. However, where it can be reliably assumed that a substance is unlikely to exhibit such effects, then alternative OEL values can be substituted.

2.2.4.2.1 Irritation, corrosion and sensitisation

Within the ECETOC approach, irritants (in general) are categorised as having a low hazard. Accordingly, unless the exposure potential to such substances is other than minimal or low, they are subject to a focused risk assessment at the Tier 1 level. Substances which exhibit respiratory irritation and have a minimal/low exposure potential are not considered as constituting a significant concern at Tier 0.

Substances classified as irritant, corrosive or sensitisers should be assessed for possible effects at the site of contact. As local effects are related to the concentration of the substance coming into contact at the site of exposure, a threshold concentration can be determined for those effects. At Tier 1 the boundaries for the classification of skin and eye irritants are considered appropriate reference values. Similarly, for the risk assessment of skin sensitisers, the elicitation threshold or the regulatory threshold to induce a response in sensitised individuals for the classification of preparations is used (0.1%, unless specified otherwise; see Table 13). For substances classified as respiratory sensitisers, a case-by-case risk assessment is necessary.

Table 13: Generic concentration limits for irritants based on the concentration boundaries of the preparations directive (EC, 1999b)

Classification	Target site	Risk phrase	Basis of limit	Bounding limit (%)
Irritant	Skin	R38/R66	Irritation threshold concentration	20%
Corrosive, skin	Corrosion	R34	Irritation threshold concentration	5%
		R35		1%
Irritant	Eye	R36	Irritation threshold concentration	20%
Irritant	Eye severe	R41	Irritation threshold concentration	5%
	Skin sensitisation	R43	Elicitation threshold	0.1%

An assessment of the risk presented by exposure to an irritant or corrosive substance involves a consideration of the appropriateness of the measures put in place to prevent unintended inhalational, direct skin or eye contact. As information such as formulation, dilution or packaging is of primary relevance, the Tier 1 consumer RA simply consists of a comparison of the threshold for classification with the actual concentration of the material present in the final product or preparation. Irritant, corrosive or sensitising materials present in consumer products at levels above the classification threshold will require a specific assessment of these endpoints at the Tier 2 level that will involve several considerations. This could, in a first step, include the consideration of actual threshold concentrations of irritation from animal experiments or human experience if available and a more in-depth analysis of the exposure situation.

2.2.5 The relevance of risk reduction measures

There are a number of strategies for managing worker and consumer risks. Some of the strategies are more effective and/or robust than others, e.g. those that involve engineered solutions are typically regarded as reliable and effective, whereas those which are based upon personal behaviour are viewed with less confidence. For many workplace and consumer uses of chemicals, risk management is an integral and everyday consideration which should not be ignored. The ECETOC approach therefore addresses the effect of where such measures are likely to be associated with key uses of the substance by:

- Taking into account at the Tier 1 level some defined forms of workplace exposure controls that are generally considered to be reliable and of proven effectiveness. These controls include engineering measures, but exclude procedural controls and personal protective equipment (apart from their use for managing exposures to irritant or corrosive substances). Only those forms of control that might be associated with any given exposure scenario are considered. The effectiveness of the controls is defined by their role within the exposure prediction model. Where information exists to indicate that EASE fundamentally fails to account for the contribution of commonly encountered exposure controls for the scenario, this aspect is addressed in the modified EASE outputs (and see Appendix J);
- allowing for all other forms of exposure/risk control, e.g. specific technical controls, personal protection, job rotation, health surveillance, to be taken into consideration at the Tier 2 level.

2.2.6 Tier 1 outputs, verification and conclusions

To evaluate the validity of the proposed ECETOC approach for the Tier 1 assessment of worker and consumer health risks, exposure scenarios were developed for a range of situations that describe the exposure conditions typical of those associated with the intended manufacture and use of chemicals. The case studies are intended to be representative of the range of use conditions that are prevalent across Europe and that any risk assessment scheme might therefore be expected to address. As such, they do not include conditions of extreme use or product misuse.

2.2.6.1 Assessment of workplace risks verification

A total of 66 case studies were identified and described (n=34 for volatiles and n=32 for solids). These cover situations that are typical of both large and small organisations, as well as conditions and quantities of use. A list of the scenarios, together with full details of the validation process and its findings, is contained in Appendix T. By comparing the predicted exposure obtained from either the EASE (EC, 2003a) or COSHH Essentials (Maidment, 1998) exposure prediction

models with the OEL or GEV for the substance, it is possible to derive an MoE for each scenario. The process for deriving the GEV, (see Appendix N), because it is based upon a pooling and statistical evaluation of available OELs, also ensures that some margin of safety is integrated within the GEV. Based upon the ability of the ECETOC process to identify accurately those instances where risks are considered of concern (true positives) from those where risks are acceptable (true negatives), it is possible to explore the overall validity of the Tier 1 assessment. Tables 14 and 15 show the results for volatile substances when evaluated using either the OEL for the substance or the equivalent GEV, and using the EASE exposure prediction model. Tables 16 and 17 compare the results for non-volatile (solid) substances using different exposure prediction models (EASE and CE). Appendix N contains full details of the findings.

Table 14: Risk outcome from EASE exposure prediction versus EU OELs (volatiles)

EU risk outcome	Outcome of ECETOC Tier 1 screening for volatiles	
	Concern	**No concern**
Concern (9)	9 (True positive)	0 (False negative)
No concern (25)	14 (False positive)	11 (True negative)

Accuracy = 59% Observed sensitivity = 100% n = 34

Assuming a MoE_w of 2 and taking the 100^{th} percentile of the predicted exposure range

Table 15: Risk outcome from CE exposure prediction versus ECETOC GEVs (volatiles)

EU risk outcome	Outcome of ECETOC Tier 1 screening for volatiles	
	Concern	**No concern**
Concern (9)	9 (True positive)	0 (False negative)
No concern (25)	14 (False positive)	11 (True negative)

Accuracy = 59% Observed sensitivity = 100% n = 34

Assuming a MoE_w of 2 and taking the 100^{th} percentile of the predicted exposure range

Table 16: Risk outcome from EASE exposure prediction versus ECETOC GEVs (solids)

EU risk outcome	Outcome of ECETOC Tier 1 screening for solids	
	Concern	**No concern**
Concern (15)	15 (True positive)	0 (False negative)
No concern (17)	7 (False positive)	10 (True negative)

Accuracy = 73% Observed sensitivity = 100% n = 32

Assuming a MoE_w of 2 and taking the 100^{th} percentile of the predicted exposure range. Where EASE predicts an exposure of zero, a value of 0.01 mg/m^3 has been assumed

Table 17: Risk outcome from CE exposure prediction versus ECETOC GEVs (solids)

EU risk outcome	Outcome of ECETOC Tier 1 screening for solids	
	Concern	**No concern**
Concern (15)	15 (True positive)	0 (False negative)
No concern (17)	10 (False positive)	7 (True negative)

Accuracy = 65% Observed sensitivity = 100% n = 32

Assuming a MoE_w of 2 and taking the 100^{th} percentile of the predicted exposure range

Based upon a limited number of examples, the results suggest that the proposed scheme offers the basis for a suitably cautionary approach for the assessment of workplace health risks at the Tier 1 level. Using an MoE_w of 2 results in an observed sensitivity of 100%. In no case did a real risk fail to be identified, i.e. no false negatives were detected.

The accuracy (measured as a combination of true positives and true negatives, together with false positives), on the other hand, varies dependent on the combination of exposure estimation model and OEL/GEV. In the case of both volatile and solid materials, the EASE appears to provide the most accurate prediction of exposure, although there is no substantive difference between it and the COSHH Essentials model. Both models have their relative strengths and weaknesses. However, the EASE model has the ability to predict both inhalation and dermal exposure and, for this reason, has been chosen as the basis for use within the ECETOC approach. These considerations are discussed in more detail in Appendix T.

The cautionary nature of Tier 1 results might, perhaps, be expected. The derived MoE_ws are inherently conservative in nature by virtue of the fact that the top end of the predicted exposure (equivalent to the 95^{th} percentile of likely exposures for that scenario) is used as the denominator. Furthermore the OEL already incorporates a safety factor, whilst the GEV represents the 25^{th} percentile of the comparable OEL range. Hence the combination of the two might be expected to yield a significant proportion of false positives. In practice, this rate is around 60%. The extent to which this is either reasonable and/or workable within the context of a screen within a tiered process is not a scientific judgement, but an area for wider stakeholder discussion and consensus.

The most accurate approach combines the use of the EASE model and published OELs. However, as established OELs are unavailable for most substances, it is proposed that the GEV serves as the default within the ECETOC approach. It is not envisaged that there would be any significant iteration for Tier 1 workplace assessments. This ensures that there is high level of consistency in outcomes across all substances and users at both the Tier 1 and Tier 0 levels. The only exception to this is where actual EU (or other regulatory) OELs (or a suitable NOAEL) may be available for the substance being evaluated. In such circumstances, scope would exist to

substitute the GEV with the relevant value (with the presumption that this would also be readily justifiable).

2.2.6.2 Assessment of consumer risks verification

The reliability of the ECETOC Tier 1 consumer risk assessment was evaluated in two verification exercises. In the first exercise the ECETOC outcome was compared to those obtained by HERA (Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products) for the substances whose consumer assessments are currently published on the HERA website (see www.heraproject.com). The second exercise compared the ECETOC outcomes with the conclusions reached for available EU Existing Chemicals Risk Assessments (located at http://ecb.jrc.it/).

The ECETOC approach was applied to eleven substances that have been assessed by the HERA project for their use in household laundry and cleaning products (and that solely correspond to the consumer exposure scenarios for 'Soaps and Detergents' in the ECETOC scheme) together with ten chemicals for which an EU risk assessment report addressing consumer health risks is available. Given the nature of the examples available for comparison, this exercise predominantly addressed soaps and detergents (i.e. the focus of the HERA project). The identity of the substances, the data used for the risk assessment evaluation of each and the findings are presented in Appendix W. The available information on exposure and hazard were used to calculate the Surrogate of Exposure (SoE) and assign the hazard category and Assessment Factors, in order to define the appropriate MoE. This was undertaken using the process described in Sections 2.2.2.2, 2.2.3.2 and 2.2.4.2.

HERA examples

Table W.2 (see Appendix W) summarises the results of the comparison between the ECETOC and HERA assessments. Actual values (taken from the HERA reports) for the fraction of substance in product were used to obtain the SoE values. Similarly, experimental hazard data (NOELs) were used to determine the value of the Assessment Factors. For each substance, the total (sum of oral, dermal and inhalation) SoE value (mg/kg bw/day) was compared to the total aggregate exposure value estimated by HERA. The overall outcome of the ECETOC consumer risk assessment (either further or no further assessment required) was compared to the outcome of the HERA consumer assessment. The result of the HERA assessment for all 11 substances is that the use of the substance in consumer soap and detergent products represents no risk to the consumer. Identical conclusions were obtained using the ECETOC approach. In addition, the following points are of note:

- For all substances studied, the total Surrogate of Exposure values calculated by the ECETOC approach were higher than those estimated by HERA, usually by at least one order of magnitude, i.e there were no 'false negatives' when estimating the Surrogate of Exposure values;
- for all substances, the outcome of the ECETOC assessment was 'no further risk assessment required'. This conclusion was reached at Tier 0 for 5 substances and at Tier 1 for 6 substances;
- the 5 substances that were cleared at Tier 0 (mainly because of low tonnage) would have been cleared at Tier 1 if taken through the process.

EU existing chemicals examples

10 consumer chemicals which are not classified as CMR (Carcinogen, Mutagen, Reprotoxin) Category 1 or 2 and for which an EU human health risk assessment report has been completed were used in the comparison. The information listed in Table F.2 of Appendix F was used to conduct Tier 0 assessments for the chemicals. Tier 1 consumer assessments were conducted for each of the consumer use categories identified for each of the chemicals. A total of 17 consumer use categories were assessed. Tier 1 assessments were conducted using exclusively the proposed default values for all exposure and hazard parameters. This is in contrast with the previous HERA comparison exercise, where actual values were used. Table W.3 (Appendix W) details the results of the comparison. Table 18 summarises the ECETOC and EU results.

Table 18: Consumer risk outcome from EU versus ECETOC Tier 1 [a]

EU risk outcome	Outcome of ECETOC Tier 1	
	Concern	**No concern**
Concern (5)	4 (True positive)	1 (False negative)
No concern (12)	4 (False positive)	8 (True negative)

[a] Outcome of ECETOC Tier 1 consumer risk assessment obtained using default values for all exposure and hazard parameters

The following points are of note:

- Of the 17 consumer use scenarios evaluated, 12 resulted in similar ECETOC and EU outcomes. Of those, 8 were of no concern and 4 required further assessment (risk reduction) referred to as 'true negatives' and 'true positives', respectively, in Table 18;
- in 4 cases the ECETOC Tier 1 approach required further assessment while the EU conclusion was of no concern ('false positives'). Three of these became of no concern at Tier 1 when actual experimental values were used for the hazard (NOELs) parameters. In

other words, 3 of the 'false positives' became 'true negatives' when experimental hazard values were substituted for the GLEVs;

- in 1 case (the use of cyclohexane in adhesives) the ECETOC Tier 1 approach deselected the chemical while the EU assessment required risk reduction measures (a 'false negative'). The EU conclusion is based on acute CNS effects that may occur when a consumer uses cyclohexane-based adhesives for carpet layering and inhales the chemical. The EU assessment uses very conservative estimates of exposure and hazard to derive its conclusion, which disregard recommended risk management measures and available data on human effects. The conclusions do not reflect conditions of intended use or the experiences arising from these and this is acknowledged within the EU risk assessment. Thus the discrepancy between the ECETOC and EU risk assessment outcomes illustrate that the ECETOC approach, while being conservative, is not so conservative that it covers extreme assumptions on use and risk.

Overall findings

The ECETOC approach has been evaluated at the Tier 0 and Tier 1 levels for 20 chemicals and 17 scenarios. One 'false negative' finding was identified, which upon closer examination did not represent a realistic example for verification purposes. Whilst the scope of the verification is limited, the overall performance of the approach for reliably targeting consumer risks appears to demonstrate considerable promise.

2.2.6.3 Tier 1 outputs and overall conclusions

All scenarios identified at the Tier 1 level as being of potential concern progress to Tier 2 for a more detailed, targeted risk assessment. Those scenarios where exposure to a substance does not constitute a concern undergo no further assessment within the ECETOC approach. The output from Tier 1 is thus two sets of worker and consumer exposure scenarios; one where a limited set of exposure/risk reduction measures are considered sufficient to manage risks (and require 'no further risk assessment' in the ECETOC process) and another that targets scenarios requiring a more detailed assessment at Tier 2.

The Tier 1 process is intended to be simple, reliable, well documented and easy to operate. It delivers outputs that are consistent with current worker and consumer health legislation and that offer the necessary balance of pragmatism and caution essential in any tiered approach with regulatory sequelae. In itself, the approach contains no new concepts of risk assessment. However, what is new about the approach is that it takes, adapts and builds upon concepts that have been used in other areas of chemicals regulation but have not previously been applied to

the regulation of marketed chemicals. For example, in the derivation of GEVs, definition of exposure scenarios, and transparent use of the MoE as the arbiter of risk.

One important attribute of the approach is its ability to deliver a ranking of the different scenarios using the magnitude of the MoE. This provides an ability to gauge the relative risk of different scenarios, and hence has consequent benefits for use in risk-based priority setting and subsequent prioritisation and targeting of necessary risk reduction measures. The ECETOC approach at Tier 1 therefore provides a robust and practical approach for the identification of exposure scenarios of concern.

To date, the approach has undergone only limited validation. Whilst the basic concept has been proven for all the workplace scenarios, only one exposure scenario (soaps and detergents) has been evaluated for consumers. Until further validation work in this area has been undertaken, the extent to which the approach is reliable for all situations cannot be guaranteed. Similarly, whilst the library of existing workplace and consumer exposure scenarios has been subject to stakeholder comment and review, the available list may not be sufficient to cover some special applications. In such cases, bespoke scenarios will need to be constructed using the abilities of the approach to incorporate alternative default values.

2.3 Limitations of the Tier 1 processes

As with all models, the approach is only valid if its use is confined to the applicability domain in which it has been developed and validated. Thus the approach:

- Should not be applied to substances exhibiting (or intended to exhibit) potent pharmacological activity such as many pharmaceuticals;
- should not be applied to substances that would be considered as very potent respiratory or contact allergens (see ECETOC, 2003b for a description);
- will not fully address endpoints considered as being insignificant within the different OEL processes, e.g. readily reversible non-debilitating symptoms;
- should be re-applied in the light of new understandings, concerning either the use of the substance or its hazardous properties;
- is not intended to address any potential for secondary poisoning that may occur for substances with high environmental exposure and the potential to bioaccumulate in organisms;
- does not accommodate forms of exposure not adequately addressed by the EASE model, i.e. mists and process fumes.

2.4 Assessment of human risk at the Tier 2 level

At the Tier 2 level, a more detailed risk assessment is undertaken of those scenarios that have been identified ('targeted') at the Tier 1 level. The level of detail that any such risk assessment will require will vary dependent upon circumstances. However, the general approach should be in line with the expectations contained within the EU TGD for risk assessment, but some of the principles will differ slightly. Specifically a) the risk assessment will only need to be targeted at those scenarios that are identified as presenting a potential concern and b) the basis for the risk assessment should be on the lead effect, rather than all endpoints. The net result of such an approach is that the resource is only directed at the relevant parameters whilst continuing to maintain the integrity of the risk assessment's conclusions.

At the Tier 2 level, specific account would be taken of:

- The availability of actual exposure data for the workplace and/or those scenarios of potential concern. Such data should be consistent with the quality expectations applied to the use of such data in risk assessment (Money and Margary, 2002);
- modifications to predicted exposures that account for specific circumstances that are not sufficiently covered within the generic exposure scenario descriptions (e.g. the common use of particular exposure controls that are different from those described in either EASE or the consumer exposure prediction models; in the case of the workplace, the content of a substance in a mixture or preparation);
- dermal penetration rates. The risk from dermal contact is assessed by comparison with an internal dose, initially assuming 100% penetration of the substance. There are several formulae to assess the penetration coefficient as indicated by ECETOC (1994) or in the US EPA DERMWIN model http://www.epa.gov/opptintr/exposure/docs/episuite.htm. Cruder estimates can also be obtained from the ratio of LD_{50}s dermal/oral (ECETOC, 1993a);
- any additional hazard information including human experience;
- the beneficial effect that personal protective equipment (including respiratory protection) and/or other forms of exposure control would have for the scenario.

Tier 2 is a targeted risk assessment using more refined hazard and exposure information to identify whether any of the use scenarios identified at Tier 1 as being of concern would require risk management. For the Tier 2 risk assessment, all available information can be used to refine the risk estimate. This includes considerations such as those outlined above, but also accommodates modifications to default values beyond those permissible at Tier 1 (Section 2.2.4.2), and can also extend to the use of probabilistic models or measured exposure data. The selection of specific tools and assumptions is on a case-by-case basis and needs to be justified for the specific substance being assessed.

3. ENVIRONMENT

3.1 Tier 0 screening risk assessment

The primary philosophy of Tier 0 is a risk-based process that requires that a minimal amount of relevant exposure and hazard information (see Section 3.1.6) be available to serve as a reliable basis for a first risk screen. The user of this process should be able to accomplish the assessment with a minimal amount of expertise and risk assessment training. Therefore an easy-to-use screening tool based on the EU TGD was developed to reduce the complexity of the current decision-support tool EUSES – which can only be used by an experienced and trained user.

3.1.1 Purpose

At Tier 0 screening risk assessment, it is established whether or not further (targeting) risk assessment is required, by means of a simple generic rule-based system.

The concept of the risk calculation, as a function of both exposure and hazard, is simple and conservative. The calculation is well defined and verified to enable consistency across substances and generic uses.

The screening risk assessment rules are based on risk calculations with the generic EUSES model following the most conservative assumptions in the EU TGD, covering major environmental compartments and release scenarios. Hence, when compared to the TGD, false negatives should not be obtained with this system, and consistency with the higher risk assessment tiers should be guaranteed.

3.1.2 Scientific justification

The Tier 0 rule base was developed from a sensitivity analysis of the EUSES model (which reflects the environmental risk assessment concepts as described in the EU TGD).

The sensitivity analysis is described in detail in Appendix AA. First, the substance-specific parameters that had a significant impact on the outcome of this environmental risk assessment were identified. These are the release scenario, the ecotoxicity, hydrophobicity, volatility and biodegradability. For two fixed release scenarios (wide dispersive use and point source emission, 100% release, 1 tonne/year) and a fixed ecotoxicity (all aquatic EC_{50} values = 0.1 mg/l, corresponding to a high hazard potential), the other identified parameters were varied to cover a relevant range for the assessment of organic chemicals. This work was conducted using a spreadsheet version of the EUSES model.

For a given release scenario and a given ecotoxicity, this research demonstrated that, at a screening level, the results of an EUSES risk assessment can be grouped into 8 classes, depending on high or low hydrophobicity, high or low volatility, and high or low biodegradability. Within each of these classes, a distribution of EUSES risk assessment results, predicted environmental concentration/predicted no-effect concentration (PEC/PNEC), was generated using Monte Carlo simulation (1,000 iterations). The worst-case PEC/PNEC for each of the PEC/PNECs for either water, sediment or soil was always used as the final result for each iteration. Hence, these assessments go beyond the aquatic compartment. For each of the 8 classes, the 5th percentile worst outcome (i.e. 95th percentile PEC/PNEC) is considered to represent a reasonable worst case, to be applied as the basis for the Tier 0 screening risk assessment. These 95th percentile risk characterisation ratios (RCR) are summarised in Table 19. The RCR is the ratio of the amount to which the ecosystem is exposed, to the level at which no adverse effects are observed (based on the hazard studies). This ratio is commonly used to determine if further work is required. Generally an RCR >1 indicates that there may be the potential for adverse effects on the ecosystem. Otherwise there is low potential for adverse effects on the ecosystem.

Table 19: RCR_{max} look-up table (95th percentile, based on 1,000 iterations)

		Production scenario		Private use scenario	
Log (K_{ow})	**Log VP**	**Readily biodegradable**	**Non-biodegradable**	**Readily biodegradable**	**Non-biodegradable**
0 → 5	-2 → 0	2.24	26.04	0.0043	0.052
	0 → 6	2.12	16.82	0.0043	0.034
5 → 7	-2 → 0	15.46	91.14	0.0384	0.181
	0 → 6	5.61	7.71	0.0150	0.017

Key assumptions: tonnage = 1 tonne/year
PNEC = 1 µg/l

Because of the linearity of the EUSES model, these results can be easily translated to other ecotoxicity values by multiplying the RCRs by an appropriate factor. Similarly, these results can be converted to fit different release rates. For example, the EU TGD estimates point-source releases during chemical production at 0.1% for High Production Volume Chemicals (HPVC) and 2% for other substances.

The re-scaling of the RCRs is shown in the equation below:

$$RCR = RCR_{table} \cdot \frac{1}{EC_{50}} \cdot T \cdot f_{release}$$

with RCR = actual RCR
RCR_{table} = RCR from look-up table
EC_{50} = actual ecotoxicity (in mg/l)
T = actual tonnage (in tonne/year)
$f_{release}$ = actual release fraction ($0<f\leq1$)

It should be noted, however, that PEC/PNEC ratios for sewage treatment plants (STPs) are not dealt with in the Tier 0 screening tool. Experience with both new and existing chemicals has shown that this is not driving the risk assessment (Bodar *et al,* 2003). Biocides are a probable exception to this rule. It should also be pointed out that the EUSES 1.0 does not cover marine risk assessment.

3.1.3 Exposure potential

The environmental exposure potential of a substance is a measure of the likelihood and the magnitude of release, emissions and exposure to the environment and depends on three factors. Factor 1 is the tonnage, factor 2 is related to the type of use and the release fraction and factor 3 is determined by chemical-specific 'fate' properties.

At Tier 0, the concept of exposure potential integrates production volumes with the main use category (and hence, the release fraction), together with a consideration of basic physico-chemical and environmental fate properties. However the exposure potential is not calculated explicitly. Instead, a rule-based system is used, in which all three exposure potential factors are considered, in combination with the hazard potential, to directly derive a risk assessment result.

3.1.3.1 Factors 1 and 2: tonnage and release

The assessment of the release involves an initial estimate of the tonnage produced and the fraction released into the environment. Potential releases of chemicals to the environment are generally the result of two basic scenarios: (i) those related to industrial facilities where an individual chemical is used, handled or processed, and (ii) those related to the use and disposal of end products.

3.1.3.1.1 Release scenarios

To standardise and simplify the release estimation, the EU TGD and supporting tools (e.g. EUSES) refer to different industrial and use categories – i.e. 'Main', 'Industrial' and 'Use'. The Main Category (MC) classifies the substances in four groups. In addition, 15 'Industrial Categories' (IC) and 55 'Use Categories' (UC) have been defined (HEDSET, 1993). In the EU TGD (A/B Tables), specific release scenarios are proposed for individual IC/UC combinations, generally further refined for different physico-chemical classes (e.g. volatility).

Next to the detailed approach as elaborated in the TGD, this classification scheme can also be used as the basis for exposure estimations in lower tier risk assessments. At Tier 0, a generic

estimate based on 'Main' Category is considered sufficient for a screening assessment. The MCs were intended originally to provide a general impression of the relevance of the exposure during the whole life-cycle. In the context of environmental risk assessment, MCs are often used to characterise release scenarios for the estimation of emissions to the environment at individual stages of the life-cycle, i.e. at production, formulation and industrial/professional use. MCs can therefore be allocated release fractions, which are used as default values where specific information is lacking. The five MCs are (I) use in closed systems (non-isolated), (II) use in closed systems (isolated), (III) use resulting in inclusion into or onto a matrix, (IV) non-dispersive use and (V) wide dispersive use.

The key information on release, required at the Tier 0 stage, is whether release is due to the wide dispersive use of a substance (MC V), or whether it is due to a point source emission (MC I, II, III or IV). It is also critical to know the fraction of the total tonnage released to the environment.

For each MC, the recommended release fractions as specified in the TGD A/B tables span a very wide range (from < 0.0001% up to 100%). As a reasonable worst-case release fraction for each MC, a high-percentile value (e.g. 90th percentile) can be derived from the values given in the A/B tables. An initial attempt to derive such percentile values based on a direct statistical analysis of the A/B tables (presented in Appendix CC) indicated that the frequency of occurrence of specific release scenarios in the A/B tables is not mirroring their actual frequency of occurrence in the chemical universe. In other words, the distribution derived from the A/B tables is biased towards rare release scenarios that are over-represented compared to the more common release scenarios. Hence, a simple statistical analysis of the A/B tables leads to an incorrect weighting of different scenarios.

A much more relevant approach would therefore be to derive the high-percentile release fractions from a large chemicals database, representing the chemical universe. To illustrate the concept, this exercise was conducted using the existing chemicals risk assessment reports. However, due to the limited number of substances covered, and due to the focus on high tonnages, the resulting distribution cannot be considered representative of the chemical universe. As a further step, this statistical work needs to be conducted on a sufficiently large and representative chemicals database.

In the interim, generic release fractions, based on expert judgment, are used as specified in Table 20. It should be noted that these values are conservative, in view of empirical data collected for intermediates (ECETOC, 1993b). For chemical intermediates it may be appropriate to divide the 'closed system' group into subgroups based on production volume, with release ranging from <0.1% for products handled only internally in strictly closed systems up to 1% for intermediates produced or processed at a large number of sites. The proposed default values can be replaced in Tier 1 if more information is available.

Table 20: Generic release fractions in the screening phase related to the main categories *(IPS, 1992; ECETOC, 1993b)*

Main category	Percentage of production volume	Examples
Closed system (non-isolated)	0.1%	Chemical intermediate
Closed system (isolated)	1%	Chemical intermediate
Enclosed in a matrix	10%	Plastic additives
Non-dispersive	20%	Photochemicals
Wide dispersive use	100%	Solvents, plant protection products, detergents

Guidance on how to select the appropriate environmental release at Tier 0 is given in Appendix CC.

Finally, for widespread use, the release is assumed to occur uniformly throughout the year, whereas for point sources the release may be discontinuous. Hence, for the latter, a quantification of the daily release is required (calculated from the number of days on which the release occurs).

3.1.3.1.2 Multiple uses or releases

If the chemical has multiple uses or releases, as a first step (at Tier 0), the total tonnage should be assigned to the 'worst-case' use or release scenario. This is a conservative approach which may result in unrealistically high exposure values.

3.1.3.2 Factor 3: substance-specific fate properties

The EUSES sensitivity analysis demonstrated that, at screening level, the fate component of the exposure potential is driven by the combination of the substance's hydrophobicity, biodegradability and volatility (Jager *et al,* 1997, 2000; Jager, 1998). Each of these three parameters can be assigned to either a 'high' or a 'low' class, within which the difference of the EUSES PEC/PNEC response is not large. This leads to 8 combinations of fate-related properties, each associated with a specific 'Factor 3' for exposure potential (Table 21):

Table 21: Exposure Potential (EP) 'Factor 3'

	Hydrophobicity	Volatility	Biodegradability
1	Log K_{ow} < 5	VP < 1 Pa	Readily biodegradable
2			Not readily
3		VP > 1 Pa	Readily biodegradable
4			Not readily
5	Log K_{ow} > 5	VP < 1 Pa	Readily biodegradable
6			Not readily
7		VP > 1 Pa	Readily biodegradable
8			Not readily

3.1.4 Hazard potential and hazard classification

The approach presented here is based on a simplified hazard ranking system, which categorises different ecotoxicological endpoints into discrete hazard bands and provides non-expert users with a simple comparative descriptor of the hazard. Such hazard banding is considered to be easier for the non-expert to understand when attempting to evaluate the consequences of exposure to a substance.

The environmental hazard potential represents a categorisation of a substance's environmental effects, designed to provide a sound and consistent basis for inter-substance comparisons and screening risk assessments.

The hazard potential (HP) can be derived according to the categorisation rules that are given in Table 22 using either the available aquatic toxicity data or environmental hazard classification of the substance. With respect to the future implementation of the Global Harmonisation System (GHS), it is considered useful to refer to the classification of the GHS, next to the corresponding current EU-classifications. If either of these classifications is available, the hazard potential can be directly derived from Table 22. If no classification is reported, but aquatic toxicity data are available, the hazard potential can be derived according to the classification rules that are also given in Table 22.

Table 22: Hazard Potential (HP) on the basis of acute aquatic toxicity information

HP	Available information	Corresponding classification	Tier 0 PNEC
High	No toxicity information available, or acute toxicity < 1 mg/l	Acute class I (R50) Chronic class I (R50/53)	0.1 µg/l
Medium	Acute toxicity 1-10 mg/l	Acute class II Chronic class II (R51/53)	1 µg/l
Low	Acute toxicity 10-100 mg/l	Acute class III Chronic class III (R52/53)	10 µg/l
Minimal	Acute toxicity >100 mg/l	Not classified [a] Chronic class IV (R53)	100 µg/l

[a] On the basis of available data, also not classified under GHS (acute class II and III)

For substances classified as 'Chronic IV' (or R53), the lowest hazard potential is assigned if the log $K_{ow} < 5$. These substances are classified based on their fate properties, not their ecotoxicity properties. The fate properties are already addressed in the exposure potential – and for the purpose of screening risk assessment, they should not be double-counted by also including them in the hazard potential. The hazard potential will be corrected on the basis of the hydrophobicity of the chemical. For substances with log $K_{ow} > 5$, the highest hazard potential should be assigned because no reliable acute toxicity can be assessed (ECETOC, 1995). This may lead to unrealistic and conservative risk characterisation ratio, requiring further refinement (e.g. use of chronic data) at Tier 1.

The PNECs used in the Tier 0 risk assessment are pre-defined, based on the hazard potential class of the substance. These Tier 0 PNECs reflect the (aquatic) exposure threshold of no concern for each hazard class – i.e. these represent the worst-case PNECs within the class. They were calculated based on the lowest possible acute toxicity values for each hazard potential class, in combination with an application factor (AF) of 1,000 (see Appendix DD). For substances with a high hazard potential, there is no lower classification linked to the acute toxicity range. For this class, the PNEC at Tier 0 is based on the generic aquatic exposure threshold of no concern.

Aquatic Exposure Threshold of No Concern ($ETNC_{aquatic}$)

The concept of the threshold of toxicological concern used in human health assessments is based on the possibility of establishing an exposure threshold value for chemicals, below which there is no significant risk to be expected. This concept may be particularly useful for general industrial chemicals where detailed toxicity studies may not always be available.

Derivation of a data-based environmental threshold of toxicological concern is currently limited to the freshwater environment due to the general lack of data for industrial chemicals for sediment, marine or soil species. Specifically for the 20,000 lower-volume chemicals, the application of the concept may help to reduce the number of animals used in testing.

De Wolf *et al* (2004) have addressed the issue of environmental thresholds of toxicological concern for freshwater systems ($ETNC_{aquatic}$) for organic chemicals (see Appendix EE). They analysed existing environmental toxicological databases (acute and chronic endpoints) and substance hazard assessments. Only data sources were used for which a data quality assurance is available. Lowest numbers and 95th percentile values were derived with data stratification based on Mode of Action (MOA) (assignment using the Verhaar *et al,* 1992, categorisation). Derivation of $ETNC_{aquatic}$ values was done by multiplication of these values by appropriate application factors.

Using long-term toxicity information, the $ETNC_{aquatic,MOA1-3}$ is consistently above 0.1 µg/l, irrespective of the data sources or the approach (lowest value or 95th percentile) taken. This is also supported by analysis of fish acute toxicity databases. A preliminary analysis with complete MOA stratification of the databases shows that for MOA 1 or 2 chemicals, the $ETNC_{aquatic}$ value could be even higher than 0.1 µg/l. In contrast, a significantly lower $ETNC_{aquatic,MOA4}$ was observed based on the long-term toxicity information in the ECETOC database (ECETOC, 2003c).

Application of the $ETNC_{aquatic}$ in a tiered risk assessment scheme may help chemical producers to set data generation priorities and thus refine or reduce animal use, for instance for low-volume chemicals and those used in process-oriented research and development. It may also help to inform downstream users on the relative risk associated with their uses, and be of value in putting environmental monitoring data into a risk assessment perspective.

Appendix FF provides an overview of the use of (Q)SARs to characterise effects and their link to toxic modes of action (see Appendix EE).

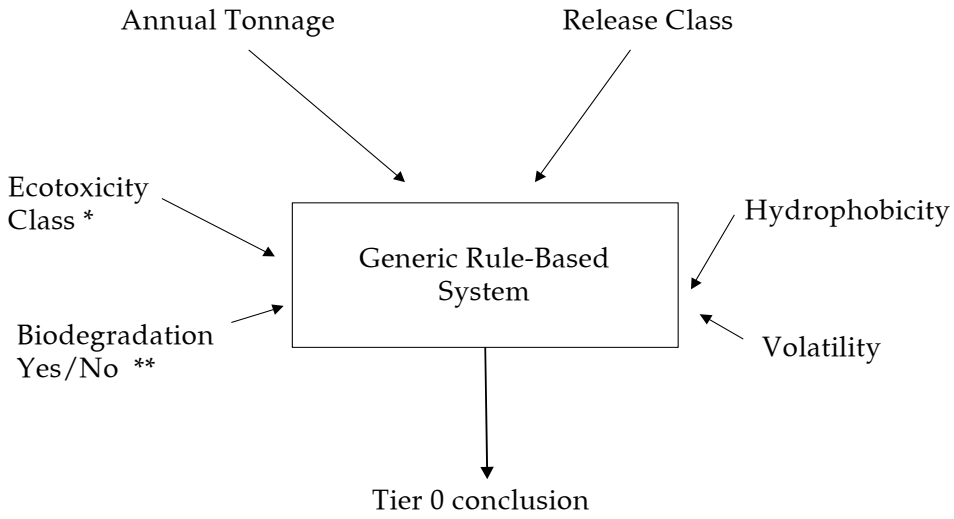
3.1.5 PBT substances

At Tier 0, information on both the degradability (expressed by the result of a biodegradation test or a corresponding (Q)SBR) and the bioaccumulation potential (expressed as the log K_{ow}, measured or predicted by QSAR) is required for organic substances. Consequently, if the substance is considered as not readily biodegradable and has a log $K_{ow} > 5$, it will be triggered automatically for further risk assessment at Tier 2, even if the PEC/PNEC ratio calculated at this stage is <1. The exception would be if measured Bioconcentration Factor (BCF) data are available, showing that BCF < 100. The results of such a risk assessment can be used in the new

REACH approach in which persistent, bioacumulative and toxic (PBT) chemicals are subject to an authorisation process based on the results of a risk assessment.

However, in the revised TGD (EC, 2003a), the assessment of PBT is only hazard-based and not risk-based as it should be for the authorisation process. ECETOC has established a Task Force to establish a scientifically sound way of assessing the risk of PBT chemicals. The methodology developed by this Task Force may then be used at Tier 2 of the ECETOC targeted risk assessment approach with a focus on the specific uses considered for authorisation.

3.1.6 Tier 0 risk assessment summary scheme



* If no data: assume ETNC ** If no data: assume non-biodegradable

3.1.7 Tier 0 minimum information requirement

The following information is required as a minimum to run a Tier 0 screening risk assessment:

- Substance tonnage (total and/or per intended use);
- characterisation of intended uses and release scenarios;
- hydrophobicity classification (low or high octanol-water coefficient, i.e. log K_{ow} < 5 or > 5);
- volatility classification (low or high, i.e. vapour pressure < 1 Pa or > 1 Pa).

In addition, the following information is recommended for a refined screening assessment:

- Actual aquatic toxicity information or environmental hazard classification (EU or GHS) (no information leads to worst-case toxicity assumption 'high hazard potential');

- biodegradability classification (readily biodegradable or not) (no information leads to the assumption the substance is not biodegradable).

3.2 Tier 1 targeting risk assessment

3.2.1 Purpose

Tier 1 is a simple, well-documented targeting risk assessment, using more refined information to identify whether any of the emission scenarios and/or environmental compartments require a more detailed targeted risk assessment (Tier 2).

The EU TGD (EC, 1996c, 2003a) is used as the basis for evaluating and targeting in a simple, well-documented and consistent way the environmental risks associated with production and uses of chemicals.

3.2.2 Key concepts

The approach proposed here to identify scenarios and compartments of possible concern is essentially based on the application of the TGD as they are implemented in the generic rule-based system or EUSES, via a user-friendly interface.

For effect assessment, application factors are used as described in the EU TGD (EC, 1996c, 2003a). However, when the MOA has been identified as lethal narcosis, then guidance on the reduction of the conservative EU TGD application factor for acute effects is given in Appendix DD. If data are available for 3 trophic levels, then the factor is reduced from 1,000 to 100; and if data are available for 2 trophic levels, then a value of 500 is recommended.

3.2.3 Option 1 – rule-based system

As a first option, the simple generic rule-based system can be run with specific information on dilution and release factors, instead of the generic defaults of Tier 0.

Release refinement

- If the chemical has multiple uses or releases, the different uses/releases may be assessed independently, provided it can be demonstrated that these different uses or releases have no cumulative effect on the environment. In other words, it has to be demonstrated that the individual releases do not impact the same environmental compartment in a single region.

If this can be shown, the PEC/PNEC ratios can be calculated for the different uses/releases and assessed separately. If, on the other hand, this cannot be demonstrated, PEC/PNEC values for the different uses/releases should be added to obtain a cumulative PEC/PNEC;

- specific (known) release fractions for point sources can be considered by the rule-based system, as well as specific dilution factors in the receiving water.

Effects assessment refinement

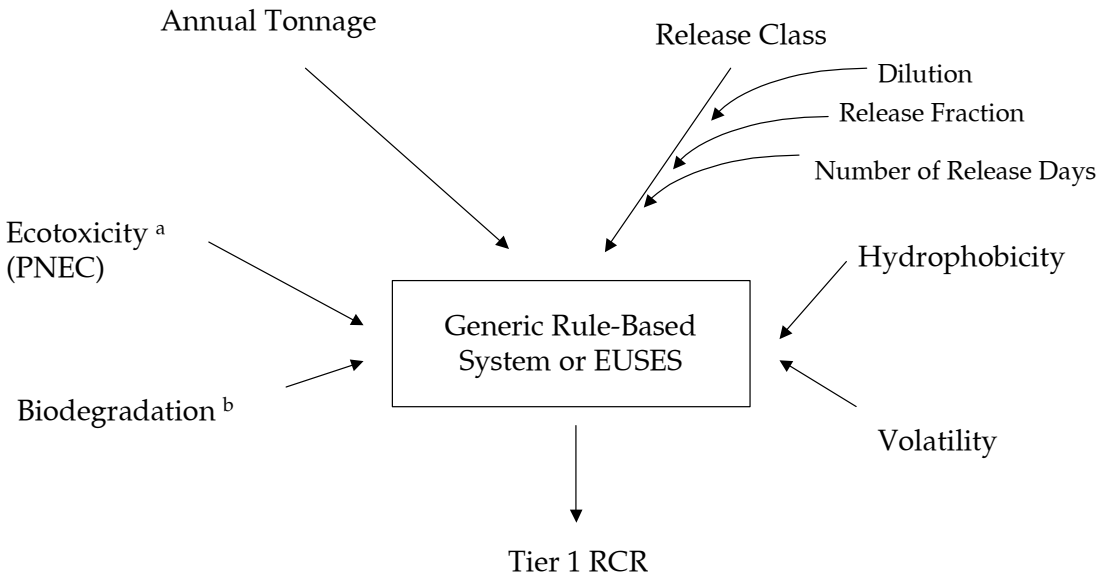
Specific (known) PNEC or WQS (Water Quality Standard) can be used to override the generic effect levels of no concern.

3.2.4 Option 2 – EUSES model

Alternatively, the EUSES model can be applied, which implements the approach described in the TGD. A user-friendly interface (see Appendix BB) has been developed to facilitate the use of this programme. All environmental release scenarios described in the TGD can be easily reviewed in order to identify those emission scenarios and compartments that appear to be of concern and, consequently, those that do not require further risk assessment. All realistic release scenarios linked to the production and the different intended uses of the substance are reviewed and, for each scenario, the environmental exposure is evaluated on the basis of the EUSES model. This model systematically considers the water, sediment and soil compartments. From the results, compartments of concern can be identified for each scenario, using the concept of an RCR. Generally an RCR >1 indicates that there may be the potential for adverse effects on the ecosystem. Otherwise there is low potential for adverse effects on the ecosystem.

As both the TGD and EUSES were formulated always to consider the worst-case situation and default values, any scenario identified as being of no concern for a given compartment should not be submitted to a further risk assessment for this compartment. If a scenario appears to be of possible concern (RCR >1) for a given compartment, then a more detailed targeted risk assessment should be carried out at Tier 2.

3.2.5 Tier 1 risk assessment summary scheme



[a] If no data: assume ETNC
[b] If no data: assume non-biodegradable

3.2.6 Tier 1 information requirements

The substances subjected to the Tier 1 risk assessment are the substances identified of possible concern at Tier 0, where the information used is limited to the TGD default values. At Tier 1, more realistic information should be used wherever necessary to demonstrate safe production and/or use.

For the rule-based system, the additional information requirements are:

- Specific release fractions at production/formulation or industrial or private use sites, and/or;
- specific dilution factors at production/formulation or industrial or private use sites, and/or;
- specific PNEC value;
- for EUSES, it is important to consider the use of measured or predicted (via valid QSAR) values, in particular:
  - physico-chemical properties: measured or predicted K_{ow}, water solubility and vapour pressure and other relevant input parameters;
  - specific release fractions at production/formulation or industrial or private use sites;
  - specific dilution factors at production/formulation or industrial or private use sites;

- fate parameters: information on (bio)degradability and information related to bioconcentration where necessary;
- ecotoxicity data: ecotoxicity information can be used rather than ETNC or hazard classification with appropriate derivation of PNEC (see Appendix DD).

In the EUSES calculation, default values will continue to be used, in particular those related to the application (assessment) factors in estimating the PNEC value and those linked to specific exposure scenarios.

Depending on the use profile of the substance, more or less detailed exposure scenarios can be considered at this stage.

3.2.7 Verification of the approach

A preliminary verification was performed in order to explore the conservativeness of the look-up table for Tier 0 and Tier 1.

The approach was applied to 41 HPV chemicals that were identified by the authorities as priorities for detailed and comprehensive risk assessments. The data were extracted from the current draft and finished EU Risk Assessment Reports (RARs) on these chemicals (downloaded from ECB, 2003). The outcome was then compared with the risk assessment outcome based on the full EUSES assessment. The RARs indicated that all chemicals had a RCR_{max} >1. The screener, based on the proposed look-up table (95th percentiles were used), indicated a potential concern for all chemicals and therefore required further assessment for all chemicals. The preliminary validation exercise has therefore demonstrated that the substances selected as priority chemicals within the EU existing substances work would also be triggered for further risk assessments when applying the look-up table approach. This suggests that there may be a low risk of false negatives for these HPVs.

The approach was also applied to 8 LPV chemicals (see Appendix GG). The Tier 0 approach was compared with the Tier 1 EUSES outcome. The results for all 8 LPVs were consistent with the outcome of the EUSES run, confirming the risk assessment conclusions at Tier 0 and Tier 1 when further specific information (e.g. release fraction and dilution) was provided. In 7 out of 8 cases further risk assessment was required at Tier 0, whereas the conclusion at Tier 1 resulted in no further risk assessment required for 7 out of 8 LPVs. This conclusion was obtained by either a refinement of the release fraction (5 out of 8) and/or refinement of the release fraction and dilution together (2 out of 8). For one LPV, a further risk assessment was required.

Clearly, a more extended validation study is needed based on a more diverse database of chemicals (with representatives from all main, industry and use categories and with different

physico-chemical and biodegradation properties) in order to further assess both the absence of false negatives and the limited occurrence of false positives. In particular, the database should also contain chemicals of no concern, with RCR_{max} <1, to check whether the look-up table is overly conservative (and identifies a need for further assessment for essentially all chemicals) or not. The availability of such a database will also enable the determination of conservative and representative release fractions for each main category in order to further refine the look-up table.

Outputs

At the end of Tier 1, exposure scenarios leading to possible concern in at least one environmental compartment will be identified and submitted to a more detailed risk assessment, targeted at the identified concern.

There will be a separation of those scenarios where exposure to a substance requires 'no further risk assessment' from those that require more detailed investigation. The exposure scenarios should be described in such a way that downstream users can use them to assess the risk in their application.

3.3 Tier 2 targeted risk assessment

3.3.1 Purpose

Tier 2 is a targeted risk assessment using more refined information to identify whether any of the use scenarios and/or environmental compartments identified at Tier 1 as being of concern would require risk management.

3.3.2 Key concepts

For the Tier 2 risk assessment any appropriate tools can be used. The assessment can be based on EUSES calculations, possibly with modifications to default values and scenarios, but it can also be based on targeted higher-tier models such as GREAT-ER (ECETOC, 1999; http://www.great-er.org/), probabilistic models or monitoring data. The use of GREAT-ER as a higher-tier confirmatory model for chemical risk assessment was recently evaluated by Klein (2004).

The selection of specific tools and assumptions should be made on a case-by-case basis, and be justified for the specific substance that is being assessed.

4. CONCLUSIONS

One of the key challenges of proposed European chemicals legislation (REACH) is that it envisages the registration and evaluation of approximately 30,000 chemicals by producers and importers over the next 10-15 years. Faced with such a challenge, both practically and scientifically, appropriate prioritisation will be a key element of the REACH process. To facilitate such work, ECETOC has developed a tiered or step-wise concept for identifying and prioritising scenarios where risks to human health and the environment from chemicals might reasonably be expected to be high enough to undertake a more detailed assessment of risk. The general concept begins with the premise that depending on both the degree of exposure and the hazard - considered together - different information requirements will be needed to demonstrate safe and responsible production and use of a given chemical.

The concept applies a tiered, or iterative, approach to risk assessment – Tier 0, 1 and 2 – whereby the level of refinement, detail, and information required for a risk evaluation is proportional to the potential risks of a chemical, based on consideration of both hazards and exposures together, rather than in isolation. The process also considers existing (and new) risk reduction measures to control exposure, where it is concluded that such measures are needed to enable a 'no immediate concern' conclusion to be reached.

The core objectives behind the approach are:

- To focus assessment resources on production and use scenarios of chemicals that constitute a likely concern for man or the environment;
- to ensure that all decisions are based upon risk and account for the relevant information that might be expected to be available and necessary to make such judgements;
- to simplify yet maintain the scientific integrity of the risk assessment process;
- to deliver consistency with expectations of other existing European health and environmental regulations.

The ECETOC approach delivers its objectives by adopting a tiered structure:

- The aim of Tier 0 is to identify substances that require only a limited risk assessment, i.e. to identify those chemicals with a low hazard potential and low potential for exposure where, as a consequence, the nature of the resultant risks would also be expected to be low. Such substances are therefore considered to be of no concern and require no immediate further work. All other substances progress to the higher tiers.
- The aim of Tier 1 is to identify the uses and exposure scenarios of substances that might reasonably be considered as constituting a risk and hence would warrant a more detailed evaluation (or where, for example, chemical suppliers might wish to provide additional information or advice to assist users to better manage such risks). The concept of risk at

Tier 1 level is simple, well documented, conservative and verified, to provide confidence across all substances within a coherent process for evaluating workplace, consumer and environmental risks. In Tier 1, those scenarios where exposure to a substance requires 'no further risk assessment' are separated from those that require more detailed investigation. All scenarios identified as being of potential concern progress to Tier 2 risk assessment.

- The risk assessment performed at Tier 2 is targeted to the scenarios arising from manufacture and use of substances that were identified as of potential concern in Tier 1. The risks are assessed in detail, based on the principles laid down in the EU TGD (EC, 2003a). The outcome of risk assessments at Tier 2 are also based on the EU TGD, i.e. conclusions (i) and (iii) – all scenarios identified as being of concern are a candidate for further information and/or risk reduction or conclusion (ii) – no further information or risk reduction required (Figure 2). In order to fulfil requirements of the proposed REACH process, if the outcome is conclusion i or iii, then further information has to be gathered or adequate risk reduction measures have to be defined to finally reach conclusion ii as laid down in the Chemical Safety Report.

It should be noted that at each tier (but especially Tier 1 and 2), existing risk reduction measures already in place to control exposures are considered. If unacceptable risks are identified during the process, then manufacturers or importers would need to consider additional controls, as necessary, to support the ultimate goal of ensuring all uses of a given chemical are of 'no concern.'

The advantages of the approach may be summarised as:

- It allows for a systematical screening of chemicals and their uses for their possible risks, considering hazards and potential exposures together;
- the available or generated information allows chemicals and uses that are of no immediate concern to be rapidly identified and gives priority to the chemicals and uses that require a more detailed evaluation;
- the tiered approach uses an increasing level of refinement, detail and information (both on exposure and hazard) and allows for iteration to account for available risk management measures;
- the data and resource demands will consequently be proportionate to the likely risks of the chemical thereby targeting available resources to scenarios of possible concern;
- using risk assessment as the basis for defining additional information needs through targeting and exposure-driven testing encourages the appropriate use of resources and respects animal welfare;
- the approach will help manufacturers and the authorities to make a choice between the generation of further information and the implementation of more stringent risk reduction measures.

The concepts of the approach have been programmed into a web tool that integrates the core concepts into an easy-to-use format. The web tool has been shown to work across a range of chemicals and conditions using information and/or data that are readily available and without the need for extensive animal test data requirements or a high level of expertise. (It can be found at https://www.ecetoc-tra.org).

5. CONSIDERATIONS FOR FUTURE WORK

The work of the Task Force has been presented and discussed at several international fora during the period 2003-2004. Furthermore, many useful suggestions concerning where the TRA approach might be further developed have been forthcoming either as the result of user feedback (from the web tool) or from user dialogue, e.g. the ECETOC TRA workshop report (ECETOC, 2004). Some of these observations concern the potential for the TRA approach to be extended and applied to other areas of chemicals risk management. But some observations relate to fundamentals of the scientific methodology underpinning the approach. As such, the work elements can be divided into those where further work is recommended in order to improve the integrity and utility of the approach and those that relate more to style and presentation, i.e. where further work might be considered. The core elements are summarised below. A fuller description is available in the TRA workshop report (ECETOC, 2004) and on the website (https://www.ecetoc-tra.org).

5.1 Recommendations for further work

5.1.1 General

- Further work should be undertaken to verify the chosen cut-off values used to ascribe the exposure potential and risk outcome for human health at Tier 0 and explore values identified for environmental assessments at Tier 0;
- there is a need to continue to verify the approach quantitatively and confirm its accuracy and sensitivity at Tier 1, i.e. to ensure that the approach remains duly conservative (no false negatives).

5.1.2 Human health

- Further verification of the Tier 1 generic hazard values (GLEVs) and GEVs is desirable. The quality-assured information contained in the EU new substances database would represent an ideal data source in order to evaluate whether the values are sufficiently conservative;
- the available exposure scenarios should be subject to continued review with a view to increasing their number if the current scenarios are incapable of adequately accommodating commonly encountered conditions of workplace exposure or consumer use;
- an equivalent degree of justification is required for the chosen default values used for the various consumer exposure scenarios.

5.1.3 Environment

- Further refinement of the release fractions is needed to enable an easy selection of the relevant main, industrial and use categories. The simplification that has been introduced should be further verified to ensure that the release fractions are sufficiently conservative at each stage of the risk assessment;
- the screening tool needs to be verified for substances with a high log K_{ow}. This will allow determination of whether or not an additional category should be introduced for this class of substances;
- the screening tool should be modified in its structure and reporting to ensure that the compartment that has triggered the concern at Tier 0 is clearly identified. This will simplify verification and enable the testing strategy to be optimised on the endpoints and compartments of concern.

5.2 Considerations for further work

5.2.1 General

- Integrate the work in the REACH implementation projects;
- develop stakeholder consensus on input data set and approach;
- further improve the transparency, functionality, security, reliability and user-friendliness of the tool;
- establish a User Group which can be used to capture suggestions as experience with the tool develops.

5.2.2 Human health

- It would be useful if clear guidance could be developed for how an assessment could be performed on a preparation, rather than each of the component substances. Thus, for example, could the R-phrases for the composite preparation be used together with information on volumes and use categories/scenarios?
- the recommended approach (Appendix Q) for evaluating the risk from substances classified as dermal sensitisers (R43) should be integrated into the web tool RA. Consideration should be given to formulating a reliable mechanism for identifying substances likely to be considered as high potency dermal sensitisers.

5.2.3 Web tool

Further work is recommended to improve the utility of the web tool and how key concepts are integrated into the tool. In particular:

- The TRA tool demands a minimum level of information to make risk-based judgements which may be seen as being inconsistent with certain REACH expectations (e.g. Annex V);
- the tool does not address the quality of input information, rather it *assumes* this is of an adequate quality;
- it is not designed as a registration tool but as a risk assessment tool enabling CSAs to be carried out;
- it does not define the order in which substances should be registered, but could be used at a pre-registration step to help set priorities;
- although the tool prioritises risk, it does not identify actions necessary to address these.

GLOSSARY

Application Factor: A factor for converting data from one exposure period or endpoint to another, e.g. from acute EC_{50} (measured) to chronic NOEC (predicted).

Assessment Factor: A factor applied to a data point or set when assessing a substance in order to derive an acceptable level of that substance in the environment.

EC_{50} Value (median effective concentration): A statistically derived concentration which, over a defined period of exposure, is expected to cause a specified toxic effect in 50% of the test population.

Exposure:
1. Concentration, amount or intensity of a particular physical or chemical agent or environmental agent that reaches the target population, organism, organ, tissue or cell, usually expressed in (numerical) terms of substance concentration, duration, and frequency (for chemical agents and microorganisms) or intensity (for physical agents such as radiation), and
2. process by which a substance becomes available for absorption by the target population, organism, organ, tissue or cell by any given route. *

Exposure Scenario: Describes the probable upper boundary conditions of use where exposure might be expected but which are not reflective of circumstances which describe the wilful misuse or abuse of the substance. More that one scenario may be identified for a single substance, depending on where it is likely to be used (worker, consumer and environmental exposure) and how exposure can be expected to occur (the exposure route). In any case, the total of key exposure scenarios should cover the entirety/emission emanating from a substance.

Generic Exposure Value: A quantitative measure of the relative harm of a substance based upon comparison of the substance's hazardous properties (as classified under EU chemicals supply regulation) with established OELs.

Generic Low Effect Value: A measure of the relative harm of a substance based upon comparison of the substance's hazardous properties (as classified under EU chemicals supply regulation) with identified repeated dose LOAELs contained within publicly available data sources.

Hazard: The set of inherent properties of a substance or mixture that makes it capable of causing adverse effects in man or to the environment when a particular level of exposure occurs. cf. risk.*

* From van Leeuwen and Hermens (1996)

Hazard Category: A descriptive measure of the relative hazard of a substance based upon consideration of the substance's hazardous properties as classified under EU chemicals supply regulation.

Key Exposure Scenarios: These represent the worst case. More than one key scenario may be identified for a single substance, depending on use (worker, consumer and environmental exposure) and exposure route. In any case, the total of key exposure scenarios should cover the entirety of exposure/emission emanating from a substance.

LC_{50} Value (median lethal concentration): A statistically derived concentration which, over a defined period of exposure, is expected to cause 50% mortality in the test population.

LOAEL (Lowest Observed Adverse Effect Level): The lowest exposure level at which there are statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control.

LOEC (Lowest Observed Effect Concentration): The lowest test concentration at which the substance is observed to have a statistically significant and unequivocal effect on the test species.

Margin of Exposure: The quotient of the GEV for the substance and the predicted exposure for the use. For consumers, the MoE is represented by the quotient of the NOAEL (or LOAEL), modified by appropriate Assessment Factors, with the predicted exposure for the use.

Narcotic Mode of Action: Inert chemicals are chemicals that are not reactive when considering overall acute effects, and that do not interact with specific receptors in an organism. The mode of action of such compounds in acute aquatic toxicity is called narcosis. Narcosis-type toxicity is considered to be brought about by an absolutely nonspecific mode of action, in that the potency of a chemical to induce narcosis is entirely dependent on its hydrophobicity (Verhaar *et al*, 1992).

NOAEL (No Observed Adverse Effect Level): An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Some effects may be produced at this level, but they are not considered as adverse or precursors to adverse effects (US EPA, 1995).

NOEC (No Observed Effect Concentration): The highest tested concentration below the LOEC where the stated effect was not observed. The NOEC is usually connected with chronic effects.

PNEC (Predicted No-Effect Concentration): Environmental concentration which is regarded as a level below which the balance of probability is that an unacceptable effect will not occur.

RCR (Risk Characterisation Ratio): The ratio of the amount to which the ecosystem or target is exposed, to the level at which no adverse effects are observed (based on the hazard information). Generally an RCR >1 indicates that there may be the potential of adverse effects; an RCR <1 indicates that there is a low potential for adverse effects.

Reasonable Worst Case: Reasonably unfavourable but not unrealistic situation. Combining the most adverse environmental circumstances and worst-case release parameters necessarily results in an unrealistic overall worst-case estimation, which is extremely unlikely to occur.

Risk: The probability of an adverse effect on man or the environment resulting from a given exposure to a chemical or mixture. It is the likelihood of a harmful effect or effects occurring due to exposure to a risk factor (usually some chemical, physical or biological agent). Risk is usually expressed as the probability of an adverse effect occurring, i.e. the expected ratio between the number of individuals that would experience an adverse effect in a given time and the total number of individuals exposed to the risk factor.*

TRA (Targeted Risk Assessment): Means, targeted to identified uses of concern. In a tiered approach, use scenarios of highest concern for a substance are defined, which are supposed to represent the worst case, and therefore to cover all other existing uses.

Tier 0: The aim of the Tier 0 is to 'screen' chemicals and conditions of no immediate concern out of the process, because their general exposure and hazard potential are low, and identify those other chemicals and conditions where further targeting risk assessment is required.

Tier 1: Chemicals and conditions that are not screened out at Tier 0 are evaluated in the Tier 1. The aim of Tier 1 is to use information on uses, exposure scenarios and hazard to carry out a more refined risk assessment to separate the production and uses of 'no immediate concern' from those that require a more detailed investigation. The process necessarily involves co-operation between producers and downstream users to identify key exposure scenarios. It is also designed to be relatively simple and well defined, in line with the common EU risk assessment principles, and aligned with the occupational, consumer and environmental legislation.

Tier 2: Scenarios identified as being of potential concern at Tier 1 proceed to a detailed risk assessment at Tier 2. This assessment is consistent with the established EU risk assessment principles, and enables final risk assessment conclusions to be reached for those scenarios.

* From van Leeuwen and Hermens (1996)

ABBREVIATIONS

ACR	Acute to Chronic Ratio
BCF	Bioconcentration Factor
COSHH	Control of Substances Harmful to Health
EASE	The UK Estimation and Assessment of Substance Exposure model
EC	European Commission
EP	Exposure Potential
ETNC	Environmental Exposure Threshold of No Concern
$ETNC_{aquatic}$	Aquatic Exposure Threshold of No Concern
EU	European Union
GDEV	Generic Dermal Exposure Value
GEV	Generic Exposure Value
GHS	Global Harmonisation System
GLEV	Generic Lowest Effect Value
GREAT-ER	Geographically Referenced Exposure Assessment Tool for European Rivers
HERA	Human and Environmental Risk Assessment (on Ingredients of Household Cleaning Products)
HP	Hazard Potential
IC	Industry Category
LOEC	Lowest Observed Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MC	Main Category
MOA	Mode of Action
MoE	Margin of Exposure
MoE_c	Consumer Margin of Exposure
MoE_w	Worker Margin of Exposure
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
OEB	Occupational Exposure Bands
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
PPM	Parts Per Million
QSAR	Quantitative Structure Activity Relationship
QSBR	Quantitative Structure Biodegradability Relationship
RA	Risk Assessment
RCR	Risk Characterisation Ratio

REACH	Registration, Evaluation, Authorisation and restrictions of Chemicals
RQ	Risk Quotient
SAR	Structure Activity Relationship
SDS	Safety Data Sheet
SoE	Surrogate of Exposure
STP	Sewage Treatment Plant
SVHC	Substance of Very High Concern
TGD	Technical Guidance Document
TRA	Targeted Risk Assessment
TTC	Threshold of Toxicological Concern
UC	Use Category
US EPA	United States Environmental Protection Agency
WQS	Water Quality Standard

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APPENDIX A: TOTAL ANNUAL PRODUCTION TONNAGE

Annual production and import tonnages have been used as the driver for many regulatory initiatives and voluntary action programmes. This is because the annual production and import volume of a substance has been used as a readily available guide to the maximum quantity of the substance that the environment and humans (occupational or consumer application) could potentially be exposed to. It is also reasonable to assume, in general, that more individuals will be exposed to a substance that is produced or imported at higher tonnages than lower ones. Thus, tonnage also gives an indication of the priority for assessment. At the screening level, overall tonnage per annum should be easily available. More detailed information on specific quantities in specific uses may be required at later stages.

The banding of tonnages for the determination of exposure potential (EP) used are given in Table A.1:

Table A.1: Banding of tonnages for the determination of EP

Tonnes/annum production + import
1-10
10-100
100-1,000
1,000 – 10,000
10,000 – 100,000
>100,000

These logarithmically scaled bands are those used in the data collection for the EU Existing Substances Regulation and as implemented into the current version (4.0) of IUCLID. Currently regulatory schemes use 1,000 tonnes per annum (TPA) as a maximum value for decision-making and other requirements such as testing. However, there are a significant number of materials that are produced at much higher tonnages, and which need to be encompassed in a screening and prioritisation scheme so appropriate differentiation can be made.

APPENDIX B: MAJOR USE CATEGORIES

Although production figures deliver a crude estimation of the potential nature and scale of exposure, the use of the substance is at least as important a determinant. The uses of many chemicals are varied and often technically complex. However, for the purposes of a screening step, the headline or main category of use suffices to give a broad indication of possible use. The uses below are those main uses given in the TGD as implemented in the current version of IUCLID.

Table B.1: Main use category

Intermediate used on site (non-isolated)
Isolated intermediate used/stored off site
Included into or onto a matrix
Non-dispersive use - professional (industry point sources)
Wide dispersive use

The information on use categories enables assumptions to be made about the nature of exposure controls that are likely to be encountered during the use of the substance and the confidence that might be invested in their ability to reliably control exposures. For example, the use of a material within defined sectors of industry will be related to a restricted range of operations and operating conditions. These operating characteristics, which are an integration of a range of individual factors that affect exposure (nature of process controls, operating conditions, etc.), not only affect the magnitude of likely exposure, but also the confidence of that prediction.

An ***intermediate used on site (non-isolated)*** will be used in a very limited number of specialist companies whose business is to process chemicals. They are subject to extensive workplace legislation. Consequently it is highly likely that emission and exposures are well controlled and low. These materials are out of the scope of the proposed REACH legislation.

An ***isolated intermediate used/stored on or off site*** is likely to be used within a limited number of companies who are used to routinely handling chemicals and, as a consequence, will have developed systems and procedures in place for ensuring emissions and exposures remain well controlled. For example, these will include the availability of suitable engineering control technologies, as well as extending to the positive impact that good standards of operator training/understanding (and related work practices) will have. There is also considerable workplace legislation in place to ensure minimum standards. Because of these conditions, it is highly likely that emissions and exposures are routinely well controlled and low.

A substance that is ***included into or onto a matrix*** has the emission pattern similar to the off-site intermediate but has a potential for exposure to a wider population from subsequent use of the matrix into which it is included. Whilst this latter aspect is likely to yield low exposures there are theoretically increased environmental emissions and human exposures compared to process chemicals. It should be noted that many such substances are the subjects of specific legislation, e.g. food contact regulations.

Non-dispersive use - Professional (industry point sources) substances are likely to be used both by companies who are familiar with handling chemicals and by organisations who are not. As a consequence, although some firms will have developed systems and have procedures in place for ensuring emissions and exposures remain well controlled, others are likely to seek to control emissions and exposures in a less systematic manner. The consequence of this is that whilst emissions and exposures will undoubtedly be low in some areas, the same confidence in the prediction cannot be made throughout the spectrum of use. This uncertainty is reflected in how the estimates of exposure potential are interpreted within the context of the risk matrix.

A substance marketed for wide dispersive use is likely to reach consumers, and it can be assumed that such a substance will be emitted into the environment for 100% during or after use. Because these substances have the potential to expose a higher number of individuals, there are a number of conditions that must be met before substances are placed on a wide market. European legislation seeks to prohibit very hazardous chemicals from being sold to consumers. Secondly, direct exposures of the public to hazardous chemicals are generally via the use of consumer products/preparations, where the chemical is usually encountered at low concentrations. Thirdly, in contrast to workplace exposures, the public use much lower amounts of consumer products at any one time than is the case in industry. However, exposures to the public are very different to those in industry in that (a) the exposed population is far wider (for example, it includes the young, sick and elderly), (b) the exposure is very often to a mixture of chemicals (as consumer products are usually preparations) and not to single substances, and (c) because the public are not specifically trained to use a consumer product in the specified manner, they may use consumer products in ways in which they were not originally intended and are not intentionally sold for. Although consumer exposures to chemicals are invariably far lower than those within the workplace, there is often less confidence in any exposure estimate.

In their applications, many substances are used in more that one main use category. For simplicity, the main use, which leads to the highest exposure potential, is used at this level of assessment. In some cases this will lead to an overestimate of potential exposure, and it is a conservative approach. However, it will be transparent that this has been done for the level of risk assessment required and will be modified by factoring in different uses at a higher level assessment, should it be required.

APPENDIX C: THE TENDENCY OF SUBSTANCES TO BECOME AIRBORNE ('FUGACITY')

The form of a substance has a direct bearing on its availability to biological systems and the requirements for toxicological information and risk assessment. The inherent tendency of a substance to become airborne and thus constitute a likely source of airborne exposure can be described as its fugacity. Most commonly, the vapour pressure is used as a surrogate for the rate of emission of volatile chemicals. For solids, dustiness can be taken as the surrogate for their relative emission.

There are currently no standard techniques available to quantify the effects that the physical characteristics of a material have on resulting exposures. However, several investigations have been undertaken which seek to describe the contribution that different parameters have on the ability of solids to become airborne (and in particular, with respect to workplace conditions) (BOHS, 1985, 1988; Burdett and Chung, 2000). Broadly speaking, solids can be ranked into several categories of dustiness (Chung and Burdett, 1994). This categorisation can be further refined depending on the material's particle size distribution (proportion of respirable, inhalable matter, etc.). In general, however, the distinctions that can be made are showin in Table C.1.

Table C.1: Categories of dustiness of solid materials

General description	Relative dustiness potential	Typical materials
Not dusty	1	Plastic granules [a], pelleted fertilisers
Slightly dusty	10 - 100 times dustier	Dry garden peat, sugar, salt
Dusty	100 - 1,000 times dustier	Talc, graphite
Very/extremely dusty	More than 1,000 times dustier	Cement dust, milled powders, plaster, flour, lyophilised powders, (process fumes [b])

[a] Exposures to materials where a substance is contained and bound in a matrix (e.g. pigment within a plastic, filler within paint) should also be included in this category. Although the real exposure is actually determined by a combination of physical form and the bioavailability of the substance within the matrix, because the bioavailability is very low under such circumstances, then this will result in a low exposure potential.

[b] Process fumes (e.g. rubber, welding, soldering) behave like gases and would be considered within this category if exposures to such complex mixtures are considered in any risk assessment.

These principles can also be extended to other situations where there is concern about potential human exposure to chemicals. For example, the fact that granular or pelleted materials do not give rise to significant exposures in the workplace also applies to non-occupational situations. What is important about the characteristic being described is not the characteristic in itself, but how that property relates to comparable descriptors of exposure. Thus materials used by consumers in the form of solutions, pastes, creams, or encased/ combined in some other material to form a matrix, would similarly be considered to be non-dusty (i.e. a low potential for airborne

exposure). In contrast, materials marketed in aerosols or sprays (with a particle size in the respirable range) would be considered to be very dusty.

The dustiness of solids is only one determinant of probable exposures to these materials. Other factors such as the quantity in use, the nature and effectiveness of controls in place and the dampness/humidity of material are equally important (Maidment, 1998). The ECETOC proposals for determining the exposure potential of a substance therefore build on these elements by identifying suitable qualitative descriptors that reflect (either alone or in combination) the principal determinants of exposure.

APPENDIX D: INFORMATION REQUIREMENTS

General principles

Any procedure for the evaluation of a chemical to which exposure occurs needs at least a minimum of information describing how it is used, as well as basic information on the hazardous properties. The term 'information' does not necessarily mean the result of a study performed with the specific substance to be assessed. Rather, grouping of substances with similar properties or uses and bridging of information, expert judgement, (Q)SAR and alternative test methods, as far as generally recognised as valid, can be used to avoid unnecessary animal testing. Similarly, exposure can invariably be characterised by the use of suitable modelled estimates as opposed to the collection of actual measurements.

Whenever available, use should be made of data from human experience. In these cases, extrapolation from animal to humans can be avoided. Data that have been generated by reliable non-standard tests (for example, those that may not conform fully to the current requirements of Good Laboratory Practice) should also be reviewed regarding their acceptability on a case-by-case basis using expert judgement. Testing should only be necessary if the additional information generated could be reasonably expected to have a consequence on risk management measures already in place.

For the selection of an appropriate risk assessment procedure based on a banding concept, there is a need to define the information on the physico-chemical, toxicological and ecotoxicological properties of a substance considered necessary to enable soundly-based judgements to be made. In considering the hazard data that may be desirable, the uses to which the chemical is intended to be put, as well as animal welfare considerations, will serve as primary information determinants. Testing should account for relevant exposure situations and allow for flexibility in the final decision on test requirements (waiving). In-depth testing should only be required where basic testing results indicate a need.

For substances which result in human exposure, information should be available on substance identity, use, physico-chemical properties and possible effects on humans.

Information relevant for the Tier 0 human health risk assessment

Use information

Use information should be provided to an extent that allows an estimation of the exposure of humans to the substance:

- Main use category (as defined within the TGD).

Substance identity by molecular structure and unique identification number

- Molecular structure enables SAR and categorisation;
- molecular weight less or greater than 1,000 enables the determination of whether or not the substance has a potential for substantial dermal penetration or bioavailability for aquatic organisms;
- the identity of substances (e.g. CAS number) is required for reference purposes and for identification within the regulatory process.

Physico-chemical properties

Essential for the assessment of environmental behaviour are:

- Aggregation form;
- melting point/boiling point;
- information complementary to aggregation form.

Of relevance to both human health and environment are:

- Description of dustiness (if a solid, i.e. having a vapour pressure of <5hPa);
- vapour pressure (25°C);
- relevant for the determination of the potential occupational exposure route and of the entrance pathway into the environment;
- pH value - extreme values indicate corrosive potential and/or environmental impact;
- log K_{ow} value. Used in the Tier 0 environmental risk assessment to evaluate bioaccumulation potential and in Tier 1 worker exposures to evaluate dermal penetration (can be derived by modelling or measured).

Information on human health hazards

The information should be obtained accounting for the considerations described in Section 2.1.2. Deduction from structural analogies may be possible and is encouraged for:

- Acute toxicity (route determined by the principal exposure route);
- irritation/corrosivity;
- if the substance is presumed to be irritant or corrosive, based on defaults from pH and structural analogies, the test is not to be performed;
- sensitisation (if indicated by structural alerts);
- mutagenicity from *in vitro* testing (or if indicated by alerting structure).

At Tier 0, initial testing is being performed to confirm or rule out mutagenic properties. If the initial test is positive then further testing or an assessment of the structural concerns is necessary to conclude a classification for mutagenicity.

Table D.1: Minimum information requirements at Tier 0 for human health risk assessment

Information	Purpose	Remark
Use category	Define broad exposure category	
Molecular structure/impurities	Enables SAR and categorisation	
Dustiness	Exposure categorisation	
Vapour pressure	Exposure categorisation	
pH	Prediction of possible corrosivity	
Acute toxicity	Leads to categorisation and allocation of R-phrases	R20, 21, 22 R23, 24, 25 R26, 27, 28
Irritation potential skin, eye	Leads to categorisation and allocation of R-phrases	R38, 34, 35 R36, 41, 66
Skin sensitisation potential	Leads to categorisation and allocation of R-phrases	R43
Mutagenicity *in vitro* e.g. Ames test	Does not lead to allocation of R-phrase	If negative no immediate concern for R68, if positive further testing or information required that allows mutagenicity classification

If no information on repeated dose toxicity is available and the substance is not allocated to the high hazard category based on the above information, the substance is allocated to the medium hazard category (see Appendix S).

Information relevant for the Tier 1 human health risk assessment

At Tier 1, limited additional information is required in order to refine the exposure situation and to target the assessment to certain exposure scenarios of concern.

Use information

- Consumer product types in which the substance is used, chosen from a series of generic consumer product use categories (Appendix L);

- an indication of how the substance is intended to be used at the workplace, chosen from a series of generic unit activities and control measures likely to be in use (see Appendix G).

Substance information

Molecular weight for volatile substances (for conversion of ppm to mg/m^3 and systemic dose dermal).

APPENDIX E: HAZARD RATING SYSTEMS BASED ON R-PHRASES

Comparison of exisiting hazard rating schemes

ECETOC has compared its proposals for hazard categorisation with other existing schemes based on R-phrases. For comparison the ranking schemes presented in Table E.1 have been grouped into three levels: high, medium and low. In some of the schemes certain R-phrases have not been assigned or did not exist when the scheme was created.

Some general observations concerning the different schemes:

- All schemes use, as a basis, the EU classification which expresses the progression of severity of discrete toxicological endpoints (Xn, T, T+) and allocate the corresponding risk phrase to the hazard levels low (R20, R21, R22), medium (R23, R24, R25) and high (R26, R27, R28), respectively.
- The CMR class 1 and 2 substances (R45, R46, R49, R60, and R61) are in almost all schemes part of the highest hazard level or are to be considered separately on a case-by-case basis. The exception is TRGS 440 (BAuA, 2001) which considers reproductive hazards (R60, R61) as medium.

The main differences between the rankings of R-phrases are the following:

Irritation/corrosion

Most schemes group R36, R37 and R38 either as low hazard or of no concern. In the UK, ABPI (1995) does not consider R37 (respiratory irritation), whilst the Chemical Industry Association (CIA, 1997) scheme does not take R36 (eye irritation) into account. Brooke (1998) considers R37 of medium importance. In the ECETOC scheme R36, R37 and R38 are ranked together as low hazard, because OELs are often based on these direct effects.

In all schemes, corrosion (R34, R35, and R41) is seen as a higher hazard than irritation. However, some schemes differentiate between R34 and R41, as still being in the same hazard category as irritation (low), and R35 as being a higher (medium) hazard. As R34, R35 and R41 are classified as corrosive (C), and the difference in criteria of hazard between R34 and R35 is based on the contact time (4 hours versus 3 minutes) needed to provoke the corrosive effect, the ECETOC scheme considers them for general risk assessment purposes of being in the same (medium) hazard category.

Sensitisation

In most schemes sensitisation through skin contact (R43) or by inhalation (R42) are seen as medium hazards. In many schemes sensitisation by inhalation is considered to be of high hazard or should be treated on a case-by-case basis. ABPI (1995) ranks skin sensitisation as low hazard.

Chronic effects

For general chronic effects most schemes distinguish between R48Xn (harmful) and R48T(toxic), and assign them to different hazard levels (medium and high). ABPI (1995) attributes R48 to low hazard as does CIA (1997) for R48Xn. In some schemes a similar distinction is made for acute danger for very serious irreversible effects between R39T and R39T+ (medium and high hazard). Similarly R33 (danger of cumulative effects) has been assigned mostly to the medium hazard category.

The other chronic effects considered in the different schemes are CMR category 3 (R40, R62, R63, R68) effects. As the EU classification scheme assigns Xn to them it seems logical to treat these the same way as R48Xn, i.e. as medium hazard. However, in some schemes (HSE, 1999; CIA, 1997) the category 3 CMRs are seen as high hazard, i.e. similar to the category 1 and 2 CMRs.

Specific effects

There are a number of risk phrases use in the hazard schemes which refer to specific effects:

- R6: Possible risk to the unborn child;
- R65: Harmful, may cause lung damage if swallowed;
- R66: Repeated exposure may cause skin dryness or cracking;
- R67: Vapours may cause drowsiness and dizziness.

These R-phrases have only recently been created. Thus they are not included in all the schemes. Where they are, they have been assigned to the low hazard level, which is justified because they are of a descriptive nature.

Some schemes also include the following risk phrases:

- R29: Contact with water liberates toxic gas;
- R30: Can become highly flammable in use;
- R31: Contact with acids liberates toxic gas;
- R32: Contact with acids liberates very toxic gas.

Health effect scoring

As an alternative to hazard bands one can also attribute a more quantitative judgment to the different toxicological effects and their severity. Such health hazard potential or effect scores are used by the EU to evaluate the hazard of industrial chemicals in the IUCLID database. In this EU Risk Ranking Method (EURAM) the human health effects score is determined by using the R-phrases and the test results from genetic and reproductive toxicity as well as the presence or absence of test results for repeated dose toxicity. So not only the R-phrases but also the underlying data are taken into consideration in the scoring.

The score associated with the Human Health Effects score (HEF) is the maximal score the substance achieves by considering all the R-phrases and the specified test information for that substance and their corresponding scores (see Table E.2).

For genetic toxicity a distinction is made between three different types of tests *in vivo*:

- Germ cell *in vivo* test;
- somatic cell test with chromosome aberrations;
- any other type of somatic cell test *in vivo.*

A substance scores zero for genetic toxicity if:

- Test(s) for gene mutation (*in vitro*) and for chromosome aberrations in somatic cells (*in vivo* or *in vitro*) have been conducted and were all negative;
- possible positive in *in vitro* test(s), but with at least two *in vivo* tests conducted and both were negative (i.e. no positive or ambiguous *in vivo* data).

For reproductive toxicity and for teratogenicity a distinction is also made in Table E.2 between full and screening test (e.g. Chernoff/Kavlock results). The test results generated using Directive 87/302/EEC (cf. EEC, 1987) Part B, pages 24, 43 or 47 or OECD Test Guidelines numbers 414, 415 or 416 (OECD, 1981, 1983a, 1983b) have been considered as full test results for Table E.2. All other acceptable test results are considered to be results from screening tests. A substance scores zero for reproductive toxicity if full *in vivo* fertility and teratogenicity tests have been conducted and only negative results obtained.

From Table E.2 it follows that it is necessary to know if a particular genetic toxicity test or reproductive toxicity test is negative or positive. Ambiguous test results are treated as positive for scoring purposes.

Table E.1: Hazard rating systems based on R-phrases

Hazard rating systems based on R-phrases	ABPI (UK) 1995[b]	CIA (UK) 1997[b]	HSE (UK) 1998[b]	TRGS 440(G) 1996, 2001	UIC-DT63 (F) 1999[b]	Solvay 2000	SOMS (NL) 2001[b]	ECETOC
HIGH (SVHC)[a]	42 45 46 49 60 61	26 27 28 60 61 (40 42 43 45 46 49)	26 27 28 48T 60 61 62 63 (40 42 45 46 49)	26 27 28 32 45 46 48T 49	26 27 28 32 33 35 39 42 48T 62 63 64 (45 46 49 60 61)	26 27 28 45 46 49 60 61	26 27 28 39T+ 48T (45 46 49 60 61)	26 27 28 42 48 (45 49 46 60 61)
OEBs								
Vapour (ppm)	< 0.1	< 0.5	< 0.5					< 0.05
Dust (mg/m^3)	< 0.01	< 0.1	< 0.01					< 0.005
MEDIUM	23 24 25 26 27 28 34 35 39 41	23 24 25 34 35 48T 62 63 (unknown)	23 24 25 34 35 37 39 41 43 48Xn	23 24 25 29 31 33* 35 40 42 43 48Xn 60* 61*68	23 24 25 29 31 34 37 40 41 43 48Xn	23 24 25 33 35 39 40 42 43 48T 48Xn 62 63 64	23 24 25 29 31 32 39T 40T 48Xn 42 43 62 63 64 67 68	23 24 25 34 35 39 40 41 43 48 62 63 68
OEBs								
Vapour (ppm)	0.1- 1	0.5 - 5	0.5 – 5					<1
Dust (mg/m^3)	0.1- 0.01	0.1 – 1	0.01 - 0.1					< 0.1
LOW	20 21 22 36 38 40 43 48 62 63	20 21 22 37 38 48Xn	20 21 22 40Xn	20 21 22 34 41*62 63 64	20 21 22 36 38 65 66 67	20 21 22 34 36 37 38 41 65 66 67	20 21 22 33 34 35 41 40Xn 65	20 21 22 36 37 38 65 66 67
OEBs								
Vapour (ppm)		5 - 50	>5 - 50					<10
Dust (mg/m^3)		1.0 - 10	0.1 - 1					<1

[a] Under REACH, substances categorised as CMR, categories 1 and 2, are considered SVHC and will need to undergo Authorisation

[b] These approaches also extend to consideration of the risks of substances considered as CMR categories 1 and 2.

Table E.2: The Human Health Effects (HEF) scoring system

R-Phrase	Genetic toxicity (a)	Reproductive toxicity (b)	Respiratory sensitisation	Repeated dose	Acute	Irritation	Skin sensitisation	Score (HEF)
R45 or R49	R46	R47, R60 or R61	-	-	-		-	10
R40	R40	R62, R63 or R64	-	-	-		-	9
-	Positive in at least one *in vitro* test but no *in vivo* somatic cell test conducted	Positive in an *in vivo* screening test but no appropriate full *in vivo* test conducted (c) or positive in OECD reproductive screening test (OECD, 1995)	-	-	-		-	8
-	NO TEST	NO TEST and NO REPEAT TEST or positive Chernoff/Kavlock screen test	R42	R48 (Toxic)	-		-	7
-	-	NO TEST and NO REPEAT TEST available or positive in screening test	-	R48 (Harmful)	-	R34 or R35 or R41	R43	6
-	-	Negative in screening test	-	R33	-	R36 or R37 or R38	-	5
-	Positive in at least one *in vitro* test, with only one negative *in vivo* somatic cell test	Negative in OECD reproductive screening test	-	NO TEST	-		-	4
-	-	Only negative in full *in vivo* test(s) for teratogenicity or in Chernoff/Kavlock teratology screening test	-	-	R26, R27 or R28		-	3
-	Only negative in *in vitro* gene mutation test(s) or only negative test(s) for chromosomal aberrations in somatic cell (*in vitro* or *in vivo*)	Only negative in full *in vivo* test(s) for fertility	-	-	R23, R24 or R25		-	2
-	-	-	-	-	R20 or R21 or R22		-	1
No R-phrase	A	B	No R-phrase	No R-phrase and test performed	No R-phrase	No R-phrase	No R-phrase	0

APPENDIX F: EXAMPLES OF PUBLISHED RISK ASSESSMENT AND COMPARISON WITH THE ECETOC TIERED APPROACH

The outcome of Tier 0 risk assessments using the ECETOC approach for substances that are not classified as CMR Category 1 or 2 and for which comprehensive risk assessment under the EU Existing Chemicals Regulation are available on the website (http://ecb.jrc.it/) and are given in Table F.1. The information extracted from the EU risk assessment reports and used for allocation of these substances to the exposure potential and hazard category bands is shown in Table F.2.

Substances for which the uses are allocated to the minimal – low exposure potential with a low hazard potential category and those allocated to the minimal exposure potential with a medium hazard potential category are regarded to be without immediate concern.

Inspection of the risk matrix indicates that the outcome of the EU risk assessment and the screening assessment (Tier 0) of the ECETOC approach are quite similar. There are three cases (1,2,4-trichlorobenzene, acetonitrile, 1,4-dichlorobenzene) where the EU risk assessment highlights a potential concern, while the ECETOC Tier 0 approach does not identify a concern. These inconsistencies were all associated with minor use scenarios which were not taken into account in the initial evaluation using the ECETOC Tier 0 approach. When these scenarios are taken into account in the ECETOC approach, these three substances are allocated to the medium exposure potential band and further assessment at Tier 1 is indicated.

Table F.1: Tier 0 risk assessment using the ECETOC approach of substances with published risk assessments

	Exposure potential band			
Hazard category	**Minimal**	**Low**	**Medium**	**High**
Low	Bis(pentabromophenyl) ether *(ii)* [a, b] 1,2,4-trichlorobenzene (*iii)* [c] Cumene *(ii)* 1,4-dichlorobenzene *(iii)* [d]	Acetonitrile (*iii)* [c] Ethyl acetoacetate *(ii)* Di-isononyl phthalate (DINP) *(ii)* Di-isodecyl phthalate (DIDP) *(ii)*		Methyl acetate (*iii)* Cyclohexane (*iii)* Methyl tert-butyl ether (iii)
Medium	Dimethyl dioctadecyl ammonium chloride *(ii)* Diphenyl ether pentabromo derivative *(i)* [b]	Naphthalene (*iii)* 4-chloro-o-cresol *(ii)* Methacrylic acid (*iii)* 1,4-dioxane (*iii)* Hydrogen peroxide *(iii)* Nonylphenol (*iii)* Alkanes, C10-13, chloro *(ii)* Alkanes, C14-17, chloro *(Inc)*[e]	Acrylic acid (*iii)* Methyl methacrylate (*iii)* 4,4'-isopropylidene diphenol (*iii)* Styrene (*iii)(Inc)* [e] Toluene *(iii)* Tetrachloroethylene *(Inc)*[e]	
High		Acrylaldehyde *(iii)* Aniline (*iii)* Hydrogen fluoride *(iii)*		

[a] Conclusion EU Existing Chemicals risk assessment:

(i) There is need for further information and/or testing

(ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

(iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

[b] Substance of Very High Concern (SVHC) based on environmental criteria

[c] EU risk assessment included use categories not covered in the main use category selected by ECETOC; the exposure potential of this substance is of 'medium' category if these additional use categories are included

[d] Outcome of EU risk assessment based on a scenario using elevated temperatures; taking into account a vapour pressure at elevated temperatures this substance is of a 'medium' exposure category.

[e] (Inc) = risk assessment incomplete

Table F.2: Information used to allocate substances to exposure potential band and hazard category

Chemical name or generic descriptor	CAS number	Availability band, basis	Critical use category	Production volume (tpa)	Exposure potential	Risk phrase [a]
Aniline	62-53-3	Minimal VP 0.4 hPa	Isolated intermediate	> 100k	Low	R20/21/22, 40, 48/23/24/25, 50
Acetonitrile	75-05-8	Medium VP 98.6 hPa	Isolated intermediate	1k - 10k	Low	R11, 20/21/22, 36
Acrylic acid	79-10-7	Low VP 3.8 hPa	Wide dispersive	> 100k	Medium	R10, 20/21/22, 35, 50
Methacrylic acid	79-41-4	Minimal VP 0.9 hPa	Non-dispersive	10k - 100k	Low	R21/22, 35
4,4'-isopropylidenediphenol	80-05-7	Medium Solid: Dusty	In a matrix	> 100k	Medium	R37, 41, 43, 62 [b]
Methyl methacrylate	80-62-6	Medium VP 42 hPa	Wide dispersive	> 100k	Medium	R11, 37/38, 43
Methyl acetate	79-20-9	High VP 217 hPa	Wide dispersive	10k - 100k	High	R11, 36, 66, 67
Naphthalene	91-20-3	Minimal VP 0.105 hPa	Wide dispersive	> 100k	Low	R22, 40, 50/53 [b]
Cumene	98-82-8	Minimal VP 4.96 hPa	Isolated intermediate	> 100k	Low	R10. 37, 51/53, 65
Styrene	100-42-5	Low VP 6.67 hPa	Wide dispersive	> 100k	Medium	R10, 20, 36/38 (Risk assessment incomplete; allocated to medium hazard category)
Tetrachloroethylene	127-18-4	Medium VP 19 hPa	Wide dispersive	> 100k	Medium	R 40, 51/53

Table F.2: Information used to allocate substances to exposure potential band and hazard category (cont'd)

Chemical name or generic descriptor	CAS number	Availability band, basis	Critical use category	Production volume (tpa)	Exposure potential	Risk phrase [a]
1,4-dichlorobenzene	106-46-7	Minimal VP 1.6 hPa	Wide dispersive	10k - 100k	Low	R36, 50/53
Acrylaldehyde	107-02-8	High VP 293 hPa	Isolated intermediate	10k - 100k	Low	R11, 24/25, 26, 34, 50
Dimethyl dioctadecyl ammonium chloride	107-64-2	Low; solid slightly dusty	Non-isolated intermediate	1k - 10k	Minimal	R41, 50/53
Toluene	108-88-3	Medium VP 30 hPa	Wide dispersive	> 100k	Medium	R11, 38, 48/20, 63, 65, 67
Cyclohexane	110-82-7	High VP 103 hPa	Wide dispersive	> 100k	High	R11, 38, 50/53, 65, 67
1,2,4-trichlorobenzene	120-82-1	Minimal VP 0.468 hPa	Isolated intermediate	1k - 10k	Minimal	R22, 38, 50/53
1,4-dioxane	123-91-1	Medium VP 40 hPa	Non-dispersive	1k - 10k	Low	R11, 19, 36/37, 40, 66
Ethyl acetoacetate	141-97-9	Minimal VP 1 hPa	Wide dispersive	1k - 10k	Low	Not classified
Bis(pentabromophenyl) ether	1163-19-5	Minimal VP < 5 hPa	In matrix	1k - 10k	Minimal	Not classified
4-chloro-o-cresol	1570-64-5	Medium VP 26 hPa	Isolated intermediate	10k - 100k	Low	R23, 35, 50 SVHC [c]
Methyl tert-butyl ether	1634-04-4	High 270 hPa	Wide dispersive	> 100k	High	R11, 38 [b]

Table F.2: Information used to allocate substances to exposure potential band and hazard category (cont'd)

Chemical name or generic descriptor	CAS number	Availability band, basis	Critical use category	Production volume (tpa)	Exposure potential	Risk phrase [a]
Hydrogen fluoride	7664-39-3	High VP 1,033 hPa	Isolated intermediate	> 100k	Low	R26/27/28, 35
Hydrogen peroxide	7722-84-1	Minimal VP 3 hPa	Wide dispersive	> 100k	Low	R5, 8, 20/22, 35 [b]
Nonylphenol	25154-52-3	Minimal VP 0.3 hPa	Non-dispersive	10k - 100k	Low	R22, 34, 50/53
Diphenyl ether pentabromo derivative	32534-81-9	Minimal VP <0.1 hPa	In matrix	1k - 10k	Minimal	R48/21/22, 50/53, 64 SVHC [c]
Di-isononyl phthalate (DINP)	28553-12-0	Minimal VP <0.1 hPa	In matrix	> 100k	Low	Not classified
Di-isodecyl phthalate (DIDP)	26761-40-0	Minimal VP <0.1 hPa	In matrix	> 100k	Low	Not classified
Alkanes, C10-13, chloro	85535-84-8	Minimal VP < 5 hPa	Non-dispersive	10k - 100k	Low	R40, 50/53

[a] According to Annex 1 of Directive 67/548/EEC

[b] According to the 29th ATP of Directive 67/548/EEC; classification agreed but awaiting adoption

[c] SVHC - Substance of Very High Concern, based on environmental criteria

APPENDIX G: DESCRIPTION OF WORKPLACE EXPOSURE SCENARIOS FOR USE AT THE TIER 1 LEVEL

Scenario	Description	Significant dermal exposure?	Assumptions concerning dermal exposures
Use in a closed process with no likelihood of exposure	The use of the substances in a high integrity contained system where little potential exists for exposures, e.g. any sampling is via closed loop systems.	No	None
Use in closed process with occasional controlled exposures, e.g. during sampling	A continuous process but where the design philosophy is not specifically aimed at minimising emissions. It is not high integrity and occasional exposures will arise, e.g. through maintenance, sampling and equipment break-downs.	No	Significant dermal exposure only likely to arise from break-downs and maintenance. Routine elevated exposure expected to be low.
Use in a closed batch process, i.e. where only limited opportunity for breaching arises, e.g. sampling	Batch manufacture of a chemical or formulation where the predominant handling is in a contained manner, e.g. through enclosed transfers, but where some opportunity for contact with chemicals occurs, e.g. sampling	No	Sampling unlikely to give rise to significant exposures.
Use in a batch or other process (including related process stages, e.g. filtration, drying) where opportunities for exposure arise, e.g. sampling, discharging or charging of materials	Use in the batch manufacture of a chemical where significant opportunity for exposure arises, e.g. during the charging, sampling or discharge of materials, and when the nature of the design can reasonably be predicted to result in exposures.	Yes	Two hands, face only (480 cm^2) assumed.
Use in a batch process including chemical reactions and/or the formulation by mixing, blending or calendering of liquid and solid-based products	The manufacture or formulation of chemical products or articles using technologies related to mixing and blending of solid or liquid materials and where the process is in stages or provides the opportunity for significant contact at any stage.	Yes	Two hands, face only (480 cm^2) assumed.
Spraying of the substance or preparations containing the substance in industrial applications, e.g. coatings	Spray applications of a substance or preparations containing it, e.g. paints, adhesives, lacquers. Also includes uses where substantial thermal or kinetic energy is applied to the substance, e.g. welding or grinding.	Yes	Two hands and forearms (1,500 cm^2) assumed.
Discharging or charging of the substance (or preparations containing the substance) to/from vessels	Covers the situation where a material is transferred from one vessel to another, including the filling of large containers, but at facilities that are not dedicated for the purposes.	Yes	Two hands, face and upper surface (960 cm^2) assumed.

APPENDIX G: DESCRIPTION OF WORKPLACE EXPOSURE SCENARIOS FOR USE AT THE TIER 1 LEVEL (CONT'D)

Scenario	Description	Significant dermal exposure?	Assumptions concerning dermal exposures
Filling containers with the substance or its preparations (including weighing)	Relates to filling lines which are specifically designed for the purposes of both capturing vapours or aerosols emissions *and* minimisation of spillage	Yes	Two hands, face only (480 cm^2) assumed.
Roller application or brushing of adhesives and other surface coatings	Covers the application of adhesives and similar coatings using low energy sources, e.g. brushes or rollers. Also applies to printing activities.	Yes	Two hands, face and upper surface (960 cm^2) assumed.
Use as a blowing agent in the manufacture of foams, etc.	Self explanatory	No	Process precludes contact with agent. Dermal exposure not considered to be significant.
Use for coating/treatment of articles, etc. (including cleaning) by dipping or pouring	Covers the treatment or coating of articles by low energy techniques such as dipping and pouring. Would include metal finishing activities, degreasing activities, and the cold formation of products from resin-type matrices.	Yes	Two hands, face only (480 cm^2) assumed.
Production of products or articles from substance by compression, tabletting, extrusion or pelletisation	Self-explanatory	No	Activities not considered to be associated with substantive dermal exposure.
Use as a laboratory reagent	Covers the use of a substance at the laboratory scale. This does not extend beyond one litre or one kilogramme of substance. Large scale laboratories and pilot evaluations should be treated as industrial processes.	No	Small scale use of laboratory reagents not considered to represent a substantive dermal exposure.
Use as a fuel	Covers the use of materials as fuel sources where limited exposure to the product in its unburned form can be expected. The scenario would not cover exposures arising as a consequence of spillage or combustion products.	No	Fuel manufacture, distribution and use assumed to occur via enclosed systems with limited potential for substantive dermal contact.
Use as a lubricant (including metal working fluids)	Use as a lubricant where significant energy or temperature is applied between the substance and moving parts. Would include metal working fluids and greases.	Yes	Two hands, face and upper surface (960 cm^2) assumed.

APPENDIX H: EXPOSURE MODIFICATION FACTORS FOR NON-CONTINUOUS ACTIVITIES

The EASE model is intended to provide exposure estimates that equate to the shift average (8-hour) exposure for the activity, assuming that the activity continues for the duration of the shift. For many activities, however, their duration is significantly less than 8 hours. In such circumstances, the EASE exposure estimate will be an overestimate of the true exposure. In order to account for circumstances where a scenario involving the use of chemicals does not extend for the full shift, then the ECETOC approach incorporates factors that are applied to the EASE output to provide a more realistic estimate of exposure for those circumstances. The factors are shown in Table H.1.

Table H.1: Factors applied to EASE output

Duration of activity	Exposure modifying factor
> 4 hours	1
1 - 4 hours	0.6
15 mins - 1 hour	0.2
< 15 mins	0.1

The modifying factors remain conservative, when seen in the context of the relative weighting assigned to the duration of the different activities, yet enable a higher degree of flexibility and accuracy to be incorporated into the approach. The EASE model does not address working periods longer than 8 hours. As a consequence, neither does the ECETOC approach. In such circumstances, the resulting risks need to be evaluated on a case-by-case basis in accordance to established guidance on novel work patterns.

APPENDIX J: REVISIONS TO THE EASE MODEL FOR ESTIMATING WORKPLACE EXPOSURE

Because of the high incidence of false positive outcomes that arose during the preliminary validation of the approach (see Section 2.2.2.1), an investigation was carried out concerning the extent to which the targeting performance at Tier 1 might be improved. The Generic Exposure Values (GEVs) are based upon published Occupational Exposure Limits (OELs). OELs, for the most part, take as their starting point the no-effect levels, derived from human and animal data, which, when combined with suitable margins of safety, deliver values that provide health-based guidelines for risk assessment and management. Because the GEVs are based directly on published OELs, the scope for revising the GEVs is restricted. On the other hand, the model used to predict exposures for each workplace scenario (the EASE model) is recognised to overpredict exposures in many scenarios (Mark, 1999; ECETOC, 1997; Bredendick-Kämper, 2001; Dervillers *et al*, 1997; Van Rooij and Jongeneelen, 1999). Part of the reason why EASE has an inherent tendency to overpredict, is that it was developed to be able to be used for almost any exposure scenario. The platform for such a broad performance standard has been built by calibrating EASE's outputs with the range of historical exposure data held by the UK Health and Safety Executive (HSE), which, in themselves, are positively biased because much have been obtained from enforcement situations. However, where the EASE model is being applied to a narrowly defined scenario, as is the case with those in the ECETOC scheme, then the basis for its validation ought to be based upon the data available for the scenario, rather than an extrapolation from general industrial situations.

The predictive power of the inhalation component of the EASE model was therefore reviewed for the range of identified workplace scenarios (Appendix T). EASE is acknowledged to provide a reasonable prediction of 'worst-case' exposures, for both volatile and solid materials. However, in several circumstances, EASE clearly overpredicts exposure (HSE, 2003). This may be for several reasons, although, in most likelihood, they can be restricted to three. Firstly, EASE fails to adequately account for the surface area of the substance in contact with the workplace air (or a suitable surrogate for this, e.g. the quantity of material being handled within the scenario). EASE assumes tonne quantities are routinely handled, whereas in practice, actual amounts are often much smaller. Secondly, the calibrating database for the model is influenced by HSE's enforcement strategy in the 1980s and 1990s. This focused on higher risk establishments and is therefore not necessarily representative of current workplace exposures or indeed those across Europe in general. Thirdly, EASE provides insufficient consideration of the real effectiveness of any extract ventilation associated with that scenario (although this may, in turn, be a reflection of the effectiveness at the time of those controls when the model was first developed).

ECETOC has therefore developed modified EASE exposure estimates for the specific exposure scenarios used within the approach (and which are outlined, together with a justification, in Appendix U). For the 15 current exposure scenarios (which cover circumstances of controlled

manufacture, use by trained and knowledgeable workers, as well as routine dispersive uses of chemicals within industry), there are a possible 176 outcomes (based upon three different categories of volatile and non-volatile materials, each including or excluding the presence of some form of local extract ventilation). Of the 176 EASE predictions, it was considered that 86 (49%) are likely over-estimates of real 'worst-case' exposures for the specific scenario. The rate of overprediction is in line with the findings of previous investigators (Mark, 1999; ECETOC, 1997; Bredendick-Kämper, 2001; Dervillers *et al*, 1997; Van Rooij and Jongeneelen, 1999) who have typically found that EASE overpredicts current exposures in around half of cases. In contrast to the overpredictive tendency, 10 instances (2%) were considered to be underestimates of the typical worst-case exposures for the scenario, a figure which is slightly higher than found previously (Mark, 1999; Bredendick-Kämper, 2001; Dervillers *et al*, 1997). Most of the instances where EASE was considered to underestimate exposure were associated with situations where dusty, solid materials are handled.

The range of the exposure estimates remains in line with EASE predictions (i.e. 0.001-1,000 ppm for volatile materials and 0.001-50 mg/m^3 for solids). The concept of using the worst-case estimates of EASE has therefore been retained. However, because they are now applied to specific exposure scenarios this provides a better basis for reliably validating them against practical experiences.

Table J.1 summarises the findings of a repeat of the validation exercise but using the modified exposure estimates (again for the 66 scenarios summarised in Appendix V). The overall false positive frequency is slightly reduced from 60% to 58%, whilst still maintaining a complete absence of false negatives. This ratio is still high. ECETOC is therefore undertaking a more extensive validation exercise, not only by increasing the number and range of scenarios to improve the power of the validation *per se*, but also to investigate the extent to which further modifications to the GEV values and magnitude of the MoE might further reduce the inherent caution without compromising the approach's ability to reliably identify potential scenarios of concern.

Table J.1: The impact of revised EASE exposure estimates within the validation exercise

Outcome of EU risk assessment	Prediction using revised EASE and ECETOC GEVs	
	Risk likely	Risk unlikely
Concern	23	0
No Concern	25	18

N = 66 workplace scenarios

APPENDIX K: CIRCUMSTANCES WHERE AN ASSESSMENT OF HUMAN RISK IS NOT REQUIRED

Certain uses of substances can be identified which need not undergo an assessment of consumer risk at the Tier 1 level, because they are covered by other relevant legislation, because there will be insignificant exposure or because they are generally regarded as being of low concern.

Substances evaluated in detail and authorised for certain uses

To avoid duplication of effort, detailed evaluations that have already been performed in the context of existing and generally accepted regulations should not be repeated. The result of the evaluation, i.e. the authorisation for a certain use or the conclusion that the substance is generally of very low toxicity, is used as such.

Uses that have been extensively reviewed and are listed in one of the following legislations:

- Commission Directive 89/109/EEC on materials and articles intended to come into contact with foodstuffs;
- Commission Directive 90/128/EEC on plastic materials and articles intended to come into contact with foodstuffs;
- Council Directive 89/107/EEC on food additives authorised for use in foodstuffs;
- the substance is listed in one of the positive lists of the Cosmetic Directive (76/768/EEC); (Annex IV, Annex VI, Annex VII) or is listed in Annex III and complies with the restriction provided in this Annex;
- Regulation 2309/93 for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products;
- Council Directive 91/414/EEC on the placing of plant protection products on the market;
- Council Directive 98/8/EC concerning the placing of biocidal products on the market;
- fertilisers.

Substances that have been extensively reviewed and are listed in one of the following legislations:

- Notified new substances (EC, 1993b);
- priority substances according to Existing Chemical Regulation (793/93/EEC) (EC, 1993a) for which a completed risk assessment report has been published and all relevant uses have been addressed;
- radioactive substances.

Substances to which exposure is insignificant

Included in this category are:

- Substances which are not isolated from reaction processes and handled in closed system;
- uses of substances in preparations only present at a level lower than the concentration limit provided in the Dangerous Preparation Directive (1999/45/EEC) for CMR properties, i.e 0.1% for CM Cat. 1 and 2 and 0.5% for R Cat. 1 and 2;
- uses of substances for which exposure has been minimised because they are only handled in conjunction with other substances which are much more hazardous.

This applies to by-products and impurities resulting from the production process, as well as to intentionally added components, e.g. solvents, stabilisers or colourants. If the most hazardous component requires risk reduction measurements that minimise exposure, as it is the case with substances classified mutagenic, or carcinogenic Cat. 1 or 2, then it should be sufficient to limit the risk assessment to this component and disregard the other constituents.

Substances of low concern

Included in this category are:

Natural substances of which exposure related to an anthropogenic use is minimal compared to the already existing natural exposure. For food additives JECFA (1998) uses this concept in the evaluation of the addition of naturally occurring flavours to food. If the natural occurrence is dominant to the intentional addition of the substance to food, then this addition is not of concern:

- The substance is on the FDA list for use as food additives and that are Generally Recognised As Safe (GRAS);
- substances evaluated by JECFA, SCF, etc. used in food contact materials or as food additive and without ADI.

Chemicals that are generally considered to be unreactive or inert

This is a synonym for 'inactive' with respect to biochemical reactions. In toxicological terms it is defined as not producing any toxic effect at dose levels that are several magnitudes above any possible exposure. The noble gases, including helium, neon, argon, krypton, xenon and nitrogen are considered to be inert.

Substances which are in general not bioavailable

Substances with a M Wt > 1,000 and diameter of a molecule > 950 µm (MMAD) (e.g. many polymers) and substances of which the aggregate form (in or on a matrix) makes exposures unlikely.

APPENDIX L: LIST OF CONSUMER PRODUCT USE CATEGORIES

Identification of the consumer product use categories in which a chemical is employed is the first basic step in the process of estimation of consumer exposure to the chemical. To that purpose it is useful to define a 'master' list of consumer product use categories. The OECD use categories list (Table L.1), which has been widely accepted and is used in IUCLID and international SIDS assessments, is an excellent starting point. However, the OECD use categories actually represent a mixture of product uses and functional uses for chemicals, as it covers both occupational and consumer-related scenarios. To use this list in the context of consumer exposures, it would be necessary to focus and condense the list, and identify those OECD use categories that represent nontrivial exposures to the general consumer population. These are tentatively identified in ***bold italics*** in Table L.1.

Table L.1: List of OECD/IUCLID/SIDS chemical use categories

Absorbents and adsorbents	Heat-transferring agents
Adhesive, binding agents	Hydraulic fluids and additives
Aerosol propellants	Impregnation agents
Anti-condensation agents	Insulating materials
Anti-freezing agents	Intermediates
Anti-set-off and anti-adhesive agents	Laboratory chemicals
Anti-static agents	***Lubricants and additives***
Bleaching agents	***Non-agricultural pesticides***
Cleaning and washing agents and disinfectants	Odour agents
Colouring agents	Oxidising agents
Complexing agents	pH regulating agents
Conductive agents	***Pesticides***
Construction materials additives	***Pharmaceuticals***
Corrosion inhibitors	Photochemicals
Cosmetics	Process regulators
Dustbinding agents	Reducing agents
Electroplating agents	***Reprographic agents***
Explosives	Semiconductors
Fertilisers	***Softeners***
Fillers	***Solvents***
Fixing agents	Stabilisers
Flame retardant and fire-preventing agents	***Surface active agents***
Flotation agents	***Tanning agents***
Flux agents for casting	Viscosity adjusters
Foaming agents	Vulcanizing agents
Food/foodstuff agents	Welding and soldering agents
Fuel	Others
Fuel additives	

In addition to the OECD list, there are other lists of product use categories that have been proposed. For example Table L.2 contains the recently proposed Inventory Update Rule's (IUR) consumer end-use category list. This list was developed by the US EPA based on the potential for consumers to be exposed during product use. This potential for exposure was estimated based on product survey data, the percentage of the population that use that product and the potential dose. Dose was assumed to be nontrivial if it could be greater than 1 mg/year (US EPA, 1996).

Table L.2: List of US EPA IUR product end-use categories

Artists' supplies
Adhesives and sealants
Automotive care products
Electrical and electronic products
Glass and ceramic products
Fabrics, textiles and apparel
Lawn and garden products
Leather products
Lubricants, greases and fuel additives
Metal products
Paper products
Paints and coatings
Photographic chemicals
Polishes and sanitation goods
Rubber and plastic products
Soaps and detergents
Transportation products
Wood and wood furniture
Other

Building on the OECD/EU use categories and the IUR consumer end-use categories list, Table L.3 was prepared as a proposal for a product use category list that tries to combine both previous approaches. Excluded from this list are product use categories that are subject to specific, generally accepted regulations, such as:

- Materials and articles intended to come into contact with foodstuffs;
- food additives;
- cosmetics;
- medicinal products;
- plant protection products;
- biocides;
- fertilisers;
- radioactive substances.

Table L.3: Description of product use categories

Consumer use number	Name	Description
C01	Artists' supplies and craft/hobby materials	Substances contained in commercial and consumer products for use in artwork and hobbies. Subcategories/Product Types: paints, crayons, stained glass fluxing/soldering agents, clay and glazes, electrodes, flux, powdered metal, wire.
C02	Adhesives, binding agents and sealants	Substances contained in consumer products that are used to adhere two surfaces to each other. Subcategories/Product Types: glues, caulking compounds, sealants, tile and rubber cements, spray adhesives, hot melt glues, resins for polymer-based hardening adhesives, and solvent-based adhesives.
C03	Automotive care products	Substances contained in commercial and consumer products intended for use in cleaning and care of the external and internal vehicle surfaces. *** Could be the same products as C16, cleaning/washing products and C14 polishes. Subcategories/Product Types: antifreeze, de-icing products, washing fluids, polishes.
C04	Electrical and electronic products	Substances contained in electronic equipment intended for commercial and consumer use. These may include substances that are residual from manufacturing of electronic components as well as refrigerants, lubricants, hydraulic fluids. Subcategories/Product Types: computers, office equipment, household appliances, electrical tools, electrical lighting and wiring, video and audio recording and communication equipment.
C05	Glass and ceramic products	Substances contained in commercial and consumer glass and ceramic products. These would include substances in the finished products that could be released by heating or normal use (e.g. plates for eating food). Subcategories/Product Types: dinner ware, pots/pans for food preparation, storage containers.
C06	Fabrics, textiles and apparel	Substances contained in consumer products made of cotton, silk, wool or man-made fibres. These substances could include dyes, fixing agents, softening agents, etc. used in manufacturing of these materials and final treatments like flame retardants and fire-prevention agents and anti-static clothing/textile treatments. Subcategories/Product Types: curtains, bedding, upholstery, clothing, carpeting, rugs.

Table L.3: Description of product use categories (cont'd)

Consumer use number	Name	Description
C07	Lawn and garden products (non-pesticidal/herbicidal)	Substances contained in ready-to-use agricultural products for commercial and consumer use. Subcategories/Product Types: soil amendments, fertilisers, soil conditioners.
C08	Leather products	Substances contained in finished leather products made from hides and skins and artificial leather products for commercial and consumer use. These substances may include tanning agents, bleaching agents, dyes, fixing agents, waxes, dressing agents, etc. Subcategories/Product Types: apparel, upholstery.
C09	Lubricants, greases, fuel and fuel additives	Substances contained in gasoline, kerosene, diesel fuel, and heating oils after refining and commercial or consumer products that are added to these fuels to enhance performance or clean components of combustion devices. This category also includes lubricants, and greases used in motorised equipment. Note that the lubricants and greases may overlap with substances in products found in category C04. Subcategories/Product Types: gasoline, diesel fuel, heating oil, natural gas, anti-fouling agents, antiknock agents, deposit modifiers, fuel oxidisers, oils, fats, waxes, friction-reducing additives.
C10	Metal products	Substances contained in or associated with finished metal furniture and furnishings for consumer use (e.g. rust preventives) Subcategories/Product Types: furniture, cutlery, cooking utensils, pots/pans for food preparation, toys.
C11	Paper products	Substances contained in commercial and consumer paper products. Subcategories/Product Types: tissue, towels, disposable dinnerware, nappies, writing paper, newspaper, feminine hygiene products, adult incontinence products.
C12	Painting and coating	Substances contained in consumer household paints, varnishes, etc and removers of these products from surfaces. These products are not those used generally in smaller quantities by artists (C01) and does not apply to the exposure to the finished product (e.g. wood furniture, C17) Subcategories/Product Types: house paints (interior and exterior), wood finishing materials (varnishes, lacquers, paints), paint and varnish removers, putty and wood fillers, wallpaper.

Table L.3: Description of product use categories (cont'd)

Consumer use number	Name	Description
C13	Photographic and reprographic products	Substances contained in photographic and reprographic equipment and final products (e.g. pictures, copies). Also includes commercial and hobbyist use of photographic developing/printing products. Subcategories/Product Types: cameras, video cameras, film, printed photographs, toner for photocopying machines, toner additives, desensitisers, developers, fixing agents, photosensitive agents, sensitisers, anti-fogging agents, light stabilisers, intensifiers.
C14	Polishes	Substances (both natural and synthetic) used in furniture, metal, glass, and other polishes. Subcategories/Product Types: metal and wood polishes.
C15	Rubber products	Substances contained in commercial and consumer rubber products. Subcategories/Product Types: tyres, footwear, flooring, toys.
C16	Soaps and detergents (washing and cleaning agents)	Substances used to remove dirt or impurities from clothing, household and commercial establishment surfaces. Subcategories/Product Types: detergents, soaps, dry cleaning solutions, surface cleaners; dishwashing liquids, scouring compounds.
C17	Wood and wood furniture	Substances contained in finished wood products for consumer use. Subcategories/Product Types: furniture, flooring, toys.
C18	Other	Subcategories/Product Types: sporting equipment, water filters.
C19	Construction materials	Substances used in building materials and constructional articles. Subcategories/Product Types: wall construction materials, road surface materials, ceramic, metal, plastic and wooden construction materials, insulating materials.
C20	Plastic products	Substances contained in commercial and consumer plastic products. Subcategories/Product types: disposable dinner ware, food storage, food packaging, toys, baby bottles.

APPENDIX M: SURROGATES OF EXPOSURE FOR CONSUMER USE CATEGORIES

Table M.1: Overall process for determining the total surrogate of exposure for consumer use scenarios

Default values are shown - selecting the variables for each consumer use scenario will alter the values shown											
Consumer Exposure Scenarios	Product Ingredient - fraction of substance in product/article (all routes of exposure)	**Dermal**			**Oral**			**Inhalation**			Total surrogate of exposure Dermal + Oral + Inhalation mg/kg/day
		Contact area of article/product with skin (cm^2)	Product of other exposure factors[a]	Surrogate of Exposure mg/kg/day [c]	Contact area with mouth (cm^2)	Product of other exposure factors [a]	Surrogate of Exposure mg/kg/day	A = amount of substance used per application (g)	Product of other exposure factors [a]	Surrogate of Exposure mg/kg/day	
	Default (or value) [b]	Default (or value) [b]			Default (or value) [b]			Default (or value) [b]			
Artists' supplies and craft/hobby materials	0.5	50	1.67E-03	4.17E-02	50	2.50E-05	6.25E-04				4.23E-02
Adhesives, binding agents and sealants	0.3	30	2.50E-03	2.25E-02	5	8.33E-05	1.25E-04	5	6.25E-03	9.38E-03	3.20E-02
Automative care products	0.5	100	2.50E-04	1.25E-02							1.25E-02
Electrical and electronic products	0.2	30	1.67E-04	1.00E-03							1.00E-03
Glass and ceramic products	0.2	420	1.67E-06	1.40E-04							1.40E-04
Fabrics, textiles and apparel	0.2	1200	1.67E-06	4.00E-04	30	1.67E-04	1.00E-03				1.40E-03
Lawn and garden products (non-pesticide/herbicide)	0.5	100	1.25E-03	6.25E-02	15	2.50E-04	1.88E-03				6.44E-02
Leather products	0.1	640	1.68E-04	1.07E-02							1.07E-02
Lubricants, greases, fuel and fuel additives	1	50	1.25E-03	6.25E-02							6.25E-02

Table M.1: Overall process for determining the total surrogate of exposure for consumer use scenarios (cont'd)

Default values are shown - selecting the variables for each consumer use scenario will alter the values shown

Consumer Exposure Scenarios	Product Ingredient - fraction of substance in product/article (all routes of exposure)	**Dermal**			**Oral**			**Inhalation**			Total surrogate of exposure Dermal + Oral + Inhalation mg/kg/day
		Contact area of article/product with skin (cm^2)	Product of other exposure factors[a]	Surrogate of Exposure mg/kg/day [c]	Contact area with mouth (cm^2)	Product of other exposure factors[a]	Surrogate of Exposure mg/kg/day	A = amount of substance used per application (g)	Product of other exposure factors [a]	Surrogate of Exposure mg/kg/day	
	Default (or value) [b]	Default (or value) [b]			Default (or value) [b]			Default (or value) [b]			
Metal products	1	50	1.67E-05	8.33E-04							8.33E-04
Paper products	0.1	50	1.67E-03	8.33E-03	50	3.33E-04	1.67E-03				1.00E-02
Painting and coating	0.3	240	1.67E-05	1.20E-03				20	1.25E-02	7.50E-02	7.62E-02
Photographic and reprographic products	0.1	30	1.67E-04	5.00E-04							5.00E-04
Polishes	0.5	120	2.50E-05	1.50E-03				15	6.25E-03	4.69E-02	4.84E-02
Rubber products	0.05	480	1.67E-05	4.00E-04							4.00E-04
Soaps and detergents (washing and cleaning agents)	0.2	840	1.67E-01	2.80E+01	1000	3.33E-06	6.67E-04	10	3.75E-03	7.50E-03	2.80E+01
Wood and wood furniture	0.3	420	1.67E-05	2.10E-03	100	3.33E-04	1.00E-02	10	6.25E-03	1.88E-02	3.08E-02
Construction materials	0.2	240	1.67E-05	8.00E-04				10	3.33E-01	6.67E-01	6.67E-01
Plastic products	0.5	400	1.67E-05	3.33E-03	50	1.67E-04	4.17E-03				7.50E-03

[a] For details of the factors that make up the surrogate of exposure for a particular route, see the route specific tables (M2-M4)

[b] Conservative standard defaults subject to modification where data indicate alternative value more appropriate. Values in red are selectable in the Tier 1 assessment for each scenario

Not relevant for this exposure scenario

Table M.2: Calculation of dermal surrogate of exposure for consumer product use categories

Factors	**P**roduct **I**ngredient fraction of substance in product/article	Skin **C**ontact **A**rea with article/product	**FreQ**uency of use	**T**hickness of **L**ayer in contact with skin	**C**oncentration of **P**roduct/ article	**P**ercent **T**ransferred to skin	**C**onversion **F**actor	**P**ercent **A**bsorbed into body from skin	**B**ody **W**eight (female)		
Calculation of intake	**PI x**	**CA x**	**FQ x**	**TL x**	**CP x**	**PT/100 x**	**CF x**	**PA/100**	**/BW x**	**Time =**	**Surrogate of Exposure**
Units		cm^2	#/day	cm	g/cm^3	%	g to mg	%	kg	hr	mg/kg/day
Product use category	**Exposure determinant defaults**										
	Tier 1 - Selectable		**Tier 1 - Fixed**								
Artists' supplies and craft/hobby materials	0.5	50	1	0.01	1	1	1000	100	60	24	4.17E-02
Adhesives, binding agents and sealants	0.3	30	0.15	0.01	1	10	1000	100	60	24	2.25E-02
Automotive care products	0.5	100	0.15	0.01	1	1	1000	100	60	24	1.25E-02
Electrical and electronic products	0.2	30	1	0.01	1	0.1	1000	100	60	24	1.00E-03
Glass and ceramic products	0.2	420	1	0.01	1	0.01	1000	100	60	24	1.40E-03
Fabrics, textiles and apparel	0.2	1200	1	0.01	1	0.01	1000	100	60	24	4.00E-03
Lawn and garden products (non-pesticide/herbicide)	0.5	100	0.15	0.01	1	5	1000	100	60	24	6.25E-02
Leather products	0.1	640	1	0.01	1	0.1	1000	100	60	24	1.07E-02
Lubricants, greases, fuel and fuel additives	1	50	0.15	0.01	1	5	1000	100	60	24	6.25E-02
Metal products	1	50	1	0.01	1	0.01	1000	100	60	24	8.33E-04

Table M.2: Calculation of dermal surrogate of exposure for consumer product use categories (cont'd)

Factors	**P**roduct **I**ngredient fraction of substance in product/article	Skin **C**ontact **A**rea with article/product	**FreQ**uency of use	**T**hickness of **L**ayer in contact with skin	**C**oncentration of **P**roduct/ article	**P**ercent **T**ransferred to skin	**C**onversion **F**actor	**P**ercent **A**bsorbed into body from skin	**B**ody **W**eight (female)		
Calculation of intake	**PI x**	**CA x**	**FQ x**	**TL x**	**CP x**	**PT/100 x**	**CF x**	**PA/100**	**/BW x**	**Time =**	**Surrogate of Exposure**
Units		cm^2	#/day	cm	g/cm^3	%	g to mg	%	kg	hr	mg/kg/day
Product use category	**Exposure determinant defaults**										
	Tier 1 - Selectable		**Tier 1 - Fixed**								
Paper products	0.1	50	1	0.01	1	1	1000	100	60	24	8.33E-03
Painting and coating	0.3	240	1	0.01	1	0.01	1000	100	60	24	1.20E-03
Photographic and reprographic products	0.1	30	1	0.01	1	0.1	1000	100	60	24	5.00E-04
Polishes	0.5	120	0.3	0.01	1	0.05	1000	100	60	24	1.50E-03
Rubber products	0.05	480	1	0.01	1	0.1	1000	100	60	24	4.00E-03
Soaps and detergents (washing and cleaning agents)	0.2	840	1	0.01	1	100	1000	100	60	24	2.80E+01
Wood and wood furniture	0.3	420	1	0.01	1	0.01	1000	100	60	24	2.10E-03
Construction materials	0.2	240	1	0.01	1	0.01	1000	100	60	24	8.00E-04
Plastic products	0.5	400	1	0.01	1	0.01	1000	100	60	24	3.33E-03

Table M.3: Tier 1 calculation of oral surrogate of exposure for consumer product use categories

Factors	**P**roduct **I**ngredient fraction of substance in product/article	Oral **C**ontact **A**rea with article/product	**FreQ**uency of use	**T**hickness of **C**ontact layer	**P**ercent **T**ransferred from article available for ingestion	**P**roduct **C**oncentration	**P**ercent Deposited onto article[a]	**P**ercent **A**bsorbed into body	**B**ody **W**eight (female)	
Calculation of intake	**PI x**	**CA x**	**FQ x**	**TC**	**PT/100 x**	**PC x**	**PD/100 x**	**PA/100**	**/BW =**	**Surrogate of Exposure**
Units		cm^2	#/day	cm	%	mg/cm^3	%	%	kg	mg/kg/day
Product use category	**Exposure determinant defaults**									
	Tier 1 - Selectable		**Tier 1 - Fixed**							
Artists' supplies and craft/hobby materials	0.5	50	0.15	0.01	0.1	1000	100	100	60	6.25E-04
Adhesives, binding agents and sealants	0.3	5	1	0.01	0.1	1000	50	100	60	1.25E-04
Fabrics, textiles and apparel	0.2	30	2	0.01	0.1	1000	50	100	60	1.00E-03
Lawn and garden products (non-pesticide/herbicide)	0.5	15	0.15	0.01	10	1000	10	100	60	1.88E-03
Paper products	0.1	50	2	0.01	0.1	1000	100	100	60	1.67E-03
Soaps and detergents (washing and cleaning agents)	0.2	1000	2	0.01	1	1000	0.1	100	60	6.67E-04
Wood and wood furniture	0.3	100	2	0.01	0.1	1000	100	100	60	1.00E-02
Plastic products	0.5	50	1	0.01	0.1	1000	100	100	60	4.17E-03

[a] e.g. from solution containing the substance

Table M.4: Calculation of inhalation surrogate of exposure for consumer product use categories

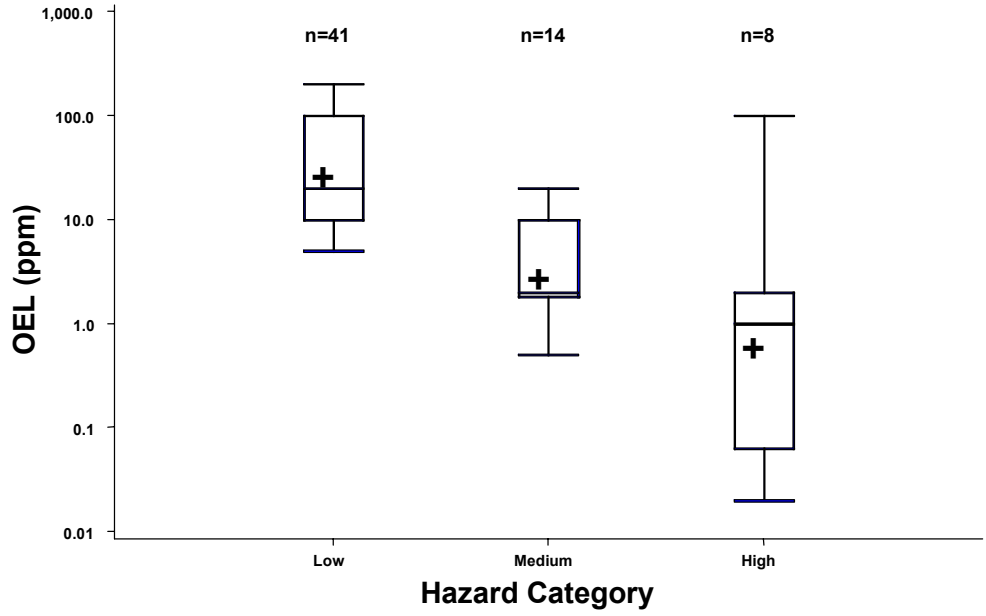
Factors	**P**roduct **I**ngredient fraction of substance in product/article	**A**mount of product used per application	**FreQ**uency of use	**P**eriod of **U**se	**I**nhalation **R**ate	**F**raction transferred from article/product to air	**C**onversion **F**actor	**P**ercent **A**bsorbed into body through lungs	Room **V**olume representative of conditions of use	**B**ody **W**eight (female)	
Calculation of intake	**PI/100 x**	**A x**	**FQ x**	**PU x**	**IR x**	**F x**	**CF x**	**PA /100**	**/ V x**	**BW =**	**Surrogate of Exposure**
Unit		g	#/day	hr	m^3/hr		g to mg	%	m^3	kg	(mg/kg/day)
Product use category	**Exposure determinant defaults**										
	Tier 1 - Selectable		**Tier 1 - Fixed**								
Adhesives, binding agents and sealants	30	5	0.15	0.5	1	0.1	1000	100	20	60	9.38E-03
Painting and coating	30	20	0.15	1	1	0.1	1000	100	20	60	7.50E-02
Polishes	50	15	0.15	1	1	0.05	1000	100	20	60	4.69E-02
Soaps and detergents (washing and cleaning agents)	20	10	0.15	0.3	1	0.1	1000	100	20	60	7.50E-03
Wood and wood furniture	30	10	0.15	1	1	0.05	1000	100	20	60	1.88E-02
Construction materials	20	10	1	8	1	0.05	1000	100	20	60	6.67E-01

APPENDIX N: DERIVATION OF GENERIC WORKPLACE EXPOSURE VALUES

Background and process followed

In order to evaluate the extent to which the hazard categorisation scheme might also usefully serve as a mechanism for determining levels that would be regarded as reflecting acceptable occupational risks, a comparison was made between the ECETOC hazard banding scheme and Occupational Exposure Limits (OELs). Utilising the current published OELs of the EU Scientific Committee on OELs (EC, 2000, 2002), and those of Germany (BAuA, 2002), the Netherlands (SZW, 2002), the UK (HSE, 2002), Sweden (SWEA, 2000) and the USA (ACGIH, 2001), a list was compiled of volatile substances for which a recommended OEL is available. The list only covered substances where a hazard category could be assigned. It therefore omitted Category 1 and 2 carcinogens, mutagens and reprotoxins. For each substance, the hazard category was determined by assigning a R-phrase to the substance, by reference either by its Annex 1 entry, IUCLID classification, or in the absence of both, through access to standard texts and the literature. A total of 63 such volatile substances were identified with established OELs.

Figure N.1: Comparison of OEL (ppm) by hazard category



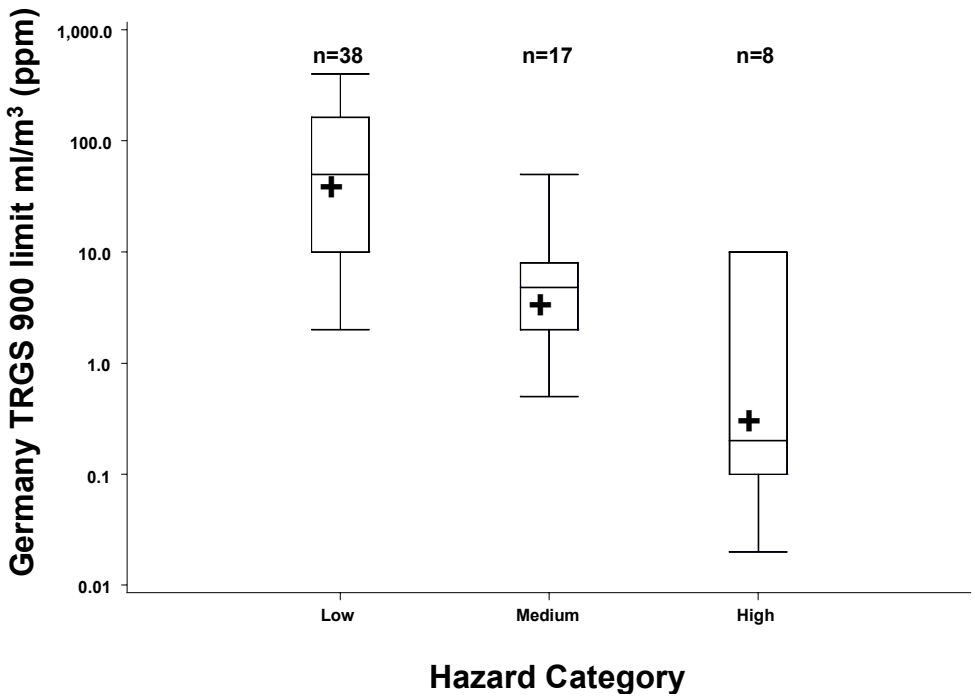
Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Figure N.1 plots the published EU volatile OELs against ECETOC hazard category. Based upon the clear demarcation of the stepped difference between categories, it can be seen that the basis for the hazard category also provides a mechanism for identifying values that would serve as conservative surrogates for inhalation risk. These values are referred to in the ECETOC scheme

as Generic Exposure Values (GEVs). Analysis of the range of values for OELs shows that they cover a range of at least four orders of magnitude (0.1 to 1,000 ppm for volatiles). Any scheme that might therefore be intended to replicate OELs on a generic basis must also be able to cover a similar range.

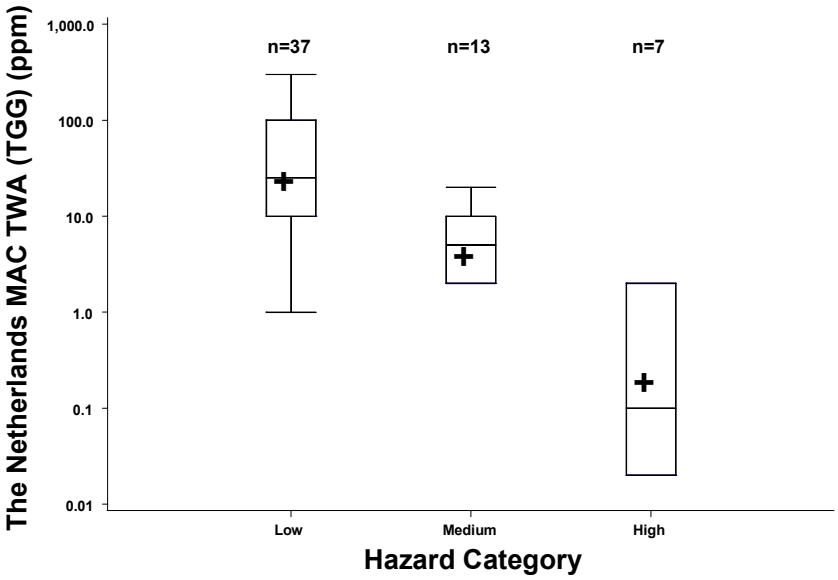
The distribution of the OELs for equivalent substances in each of the national OEL schemes is shown in Figures N.2 – N.6. The data provide a good level of confidence that the proposed hazard categories are broadly consistent with accepted approaches for the management of workplace risk. Figure 6 (Section 2.2.3.1) plots the most severe OEL from any of the national OEL schemes (including that of the EU) against hazard category. Using the data in Figure 6 (Section 2.2.3.1) GEVs have been derived, based upon the 25th percentile values of each whisker plot (Table N.1). These GEVs are intended to serve as a pragmatic surrogate for workplace OELs (in the absence of an established regulatory OEL) when used in the context of a tiered process of risk assessment.

Figure N.2: Comparison of OEL (ppm) by hazard category



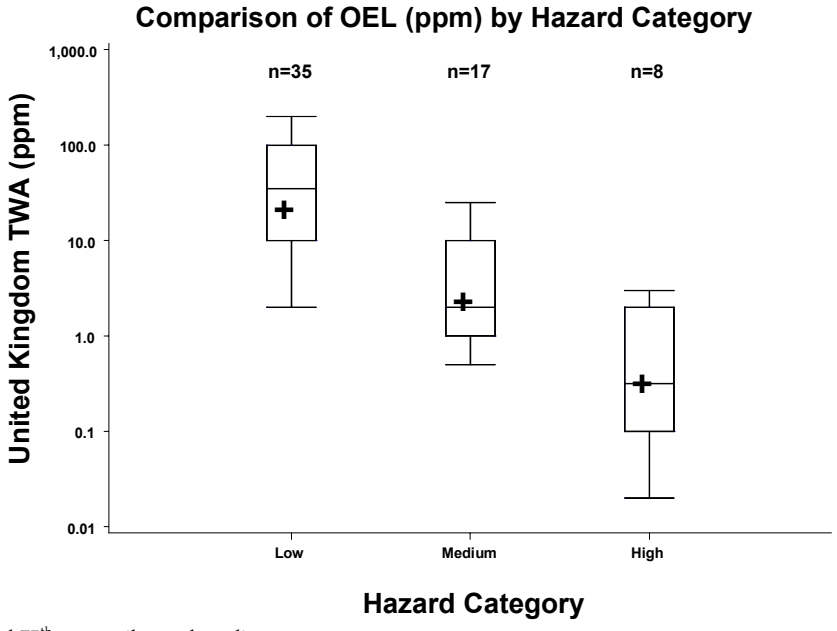
Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Figure N.3: Comparison of OEL (ppm) by hazard category



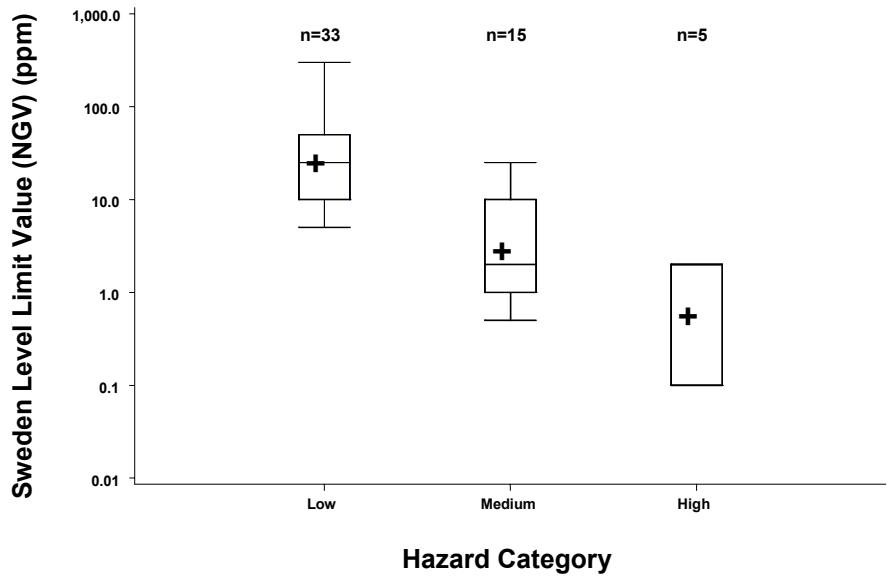
Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Figure N.4: Comparison of OEL (ppm) by hazard category



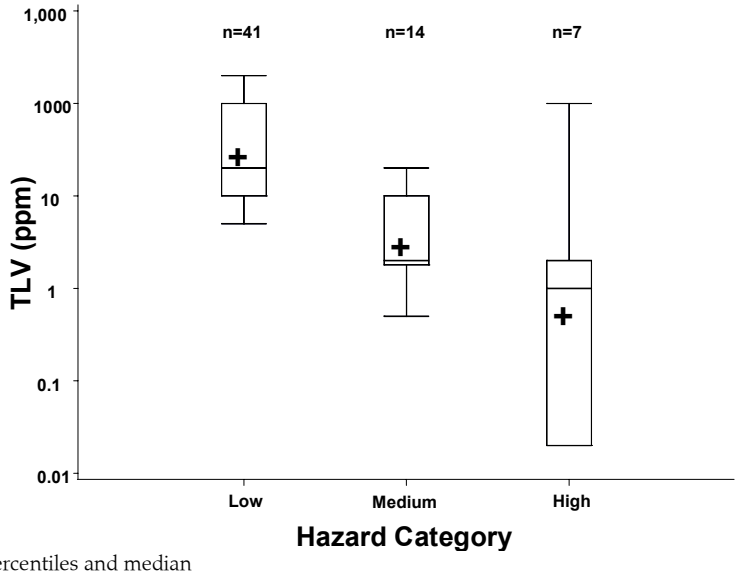
Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Figure N.5: Comparison of OEL (ppm) by hazard category



Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Figure N.6: Comparison of OEL (ppm) by hazard category



Box shows 25th and 75th percentiles and median
Plus indicates mean
Whiskers are 10th and 90th percentiles

Whilst a substantial number of OELs have been developed for volatile substances, this is not the case for solid materials. It has not therefore been possible to develop GEVs for solids from 'first principles' in the manner described above. However, a number of publications either describe or display the general relationship between OELs for volatile and non-volatile materials having similar effects (ABPI, 1995; Brooke, 1998; Guest, 1998). These general relationships have been used to identify equivalent GEVs for solids (Table N.1).

Table N.1 : Proposed workplace GEVs for volatile and non-volatile chemicals

Hazard category	Generic Exposure Value for volatiles (ppm)	Generic Exposure Value for solids (mg/m^3)
Low	10	1
Medium	1	0.1
High	0.05	0.005
SVHC	Not applicable	Not applicable

Discussion

The GEV is not meant to replicate the role of the OEL. Rather, it is designed to serve as an arbiter, in a targeted risk assessment process, for whether the use of a substance might be considered acceptable or otherwise. The method used to define the actual GEV values within the ECETOC scheme is cautionary in its very nature. It utilises the 25^{th} percentile value of the most stringent of available OELs for substances within a particular hazard category.

In the context of the desire to manage the workplace risks presented by commercial chemicals, the data contained in Figure 6 (Section 2.2.3.1) are of interest. They represent those common substances for which regulatory priorities have indicated that an OEL ought to be established. Presuming that they are representative of industrial chemicals as a whole (and there is no reason not to suppose this), then it would appear that the significant majority of substances of commercial importance have a 'low' hazard for humans. Few substances are classified as having a 'high' hazard.

APPENDIX O: THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) CONCEPT

The threshold of toxicological concern (TTC) is a concept based on the possibility of establishing an exposure threshold value for all chemicals, below which no significant risk to human health and/or the environment is expected to exist. This concept goes further than setting acceptable exposure levels as it attempts to set a *de minimis* value for any chemical or a structural class of chemicals, including those of unknown toxicity. The derivation of a TTC is different from the classical approach of setting acceptable daily intakes on the basis of substance-specific data because it uses a statistical analysis of a huge number of single data sets. The calculated distributions of effect or no-effect doses are extrapolated to a defined acceptable risk level to determine a dose that poses a negligible risk.

General threshold of no concern

The TTC concept has already been accepted in several regulations in particular in the food additives area. For example the US Food and Drug Administration (FDA) has adopted the concept of a threshold of regulation for substances used in food contact articles:

- If a substance or an impurity has not been shown to be a carcinogen in humans or animals and there is no reason, based on the chemical structure of the substance, to suspect that it is a carcinogen, a threshold of regulation is defined as a dietary concentration of 0.5 ppb (= µg/kg diet) or 1.5 µg/person/day assuming a consumption of 3 kg diet per day (FDA, 2001);
- if the substance contains an impurity that is a known carcinogen it is only allowed if the TD_{50} value (the dose that causes cancer in 50% of the animals corrected for tumours in the control animals) of the impurity based on chronic feeding studies is less than 6.25 mg/kgbw/day.

This concept is based on statistical analyses of the Gold carcinogen database (Gold *et al*, 1984, 1989; Rulis and Hattan, 1985; Munro, 1990). Munro (1990) based his analysis on a wider range of studies by including the results of NTP carcinogenicity studies. For the probabilistic analysis of the cancer studies TD_{50} values (dose leading to tumour formation in 50% of the animals) were calculated and linearly extrapolated to a cancer risk of 1:1 million).

All of those concepts came to the conclusion that there is a sound scientific basis for a general threshold of concern at 1.5 µg/person/day below which there is no significant risk to human health. This would imply that this threshold could be used for any chemical, including those of unknown toxicity. Although FDA is excluding suspected carcinogens from this evaluation it should be kept in mind that the threshold was obtained from a database on carcinogens and would, in principle, cover those as well. FDA (1995) takes that indirectly into consideration as it states that even if a substance would be identified as a carcinogen in a later stage, an unacceptable risk is not anticipated when using the TTC. Barlow *et al* (2001) reported about a

workshop on the threshold of toxicological concern in 1999. In this workshop particular attention was drawn to some potentially sensitive non-carcinogenicity endpoints such as immunotoxicity, developmental toxicity, neurotoxicity, endocrine active compounds and allergenicity as well as potentially bioacculmulative substances. Although only limited data were available on those endpoints it seemed that the thresholds for these endpoints were never below the FDA threshold of no concern. However, no firm conclusion was drawn for endpoints such as allergy for which validated test methods for quantification were not generally accepted and for which, consequently, the database is lacking to perform statistical analysis.

Other concepts have further developed the TTC approach, based either on the structure of groups of substances (Munro *et al*, 1996; Munro and Kroes, 1998), or information on certain endpoints (Cheeseman *et al*, 1999) which would allow setting higher threshold concentrations under certain conditions with a high degree of certainty to predict that a substance is safe if the concentration is not exceeded.

Threshold of toxiciological concern for certain structural classes

A meta-analysis of different databases has been performed by several authors, in particular in the context of flavouring substances with the aim to establish higher thresholds of toxicological concern for certain structural classes of substances (Munro, 1996; Munro *et al*, 1996; Munro and Kroes, 1998). Munro (1996), based on an analysis of a comprehensive database of 2,944 entries for 600 substances on chronic toxicity studies proposed human exposure thresholds for three structural classes as defined by Cramer *et al* (1978) using the 5th percentiles of the NOELs based on the lowest NOEL for each substance (see Table O.1). Subchronic studies were also used and NOELs divided by 3 to account for the shorter study duration. For studies where no effect level could be established the highest dose without effect was chosen as the NOEL for the classes. A safety factor of 100 was applied to the NOAEL. The human exposure thresholds were 1,800, 540 and 88 µg/person/day for class I, II and III respectively.

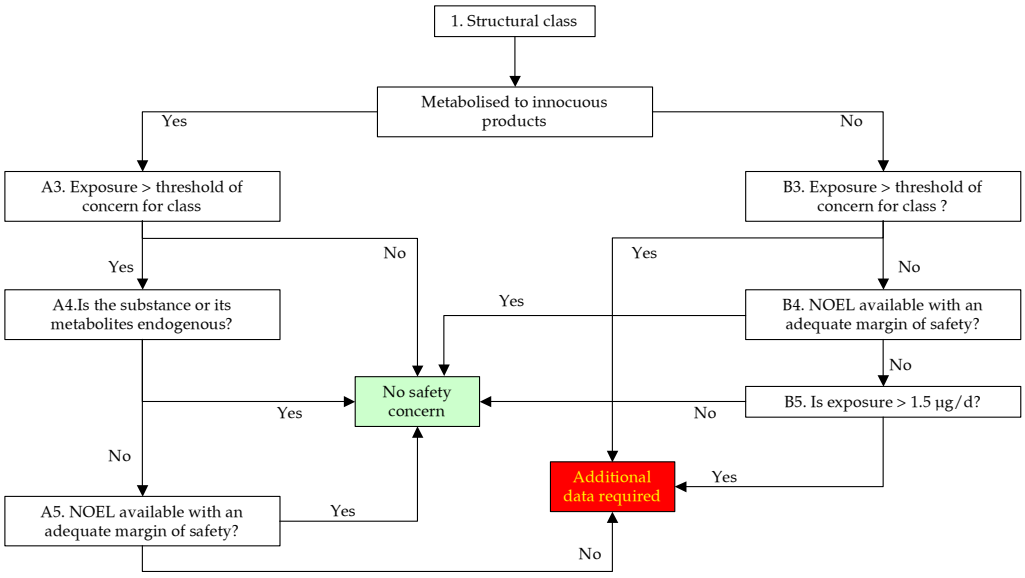
Table O.1: TTCs for structural categories

Class/TTC	Substances
I) 1,800 µg/person/day	Simple chemical structures and substances that are metabolised to non-hazardous or physiological substances (e.g. glutamic acid, mannitol, propyleneglycol).
II) 540 µg/person/day	Substances with little information on their metabolism, pharmacological or toxicological effects, but for which there are no indications for a particular toxicity. Substances with functional groups that are a bit more reactive than those in class I (e.g. beta-carotene, maltol, allyl-compounds).
III) 88 µg/person/day	Substances with an expected high toxicity because of reactive functional groups (e.g. nitrile, nitro-compounds, chlorobenzene, p-aminophenol).

The concept only applies for chemically well-defined substances with no indication of possible genotoxic effects. Developmental toxicity was included and the 5 percentile for this endpoint was in the range of the class III substances. For neurotoxic cholinesterase inhibitors the threshold was lower than class III and a threshold concentration of 18 µg/person/day was established for cholinesterase inhibitors specifically.

With regard to the evaluation of flavouring agents a decision tree has been established by the Joint FAO/WHO Expert Committee on Food Additives (WHO, 2000) based on the consideration of these different chemical classes. (See Figure O.1 from WHO, 2000 or Barlow *et al,* 2001). Up to 1999 JECFA had evaluated 610 flavours by applying the TTC concept resulting in a significant (down to 5%) reduction in the number of substances which need further evaluation.

Figure O.1: TTC approach used for the evaluation of flavouring substances by JECFA



In a further development of this concept, ILSI Europe proposes a refinement of existing TTC concepts and has put forward a decision tree approach to allocate substances with limited amount of information to different TTCs. The proposed decision tree is based on structural alerts and uses the structural classes and dose levels also applied in previous TTC concepts. The criteria proposed by ILSI for allocation of substances to the different levels of toxicological concern take into account the following structural alerts:

1. Bioaccumulation potential (limited to poly-halogenated dibenzodioxins, difurans or biphenyls and certain metals);
2. genotoxic potential (as a surrogate for a potential carcinogenicity);

3. organophosphates (as a surrogate for potential neurotoxicity);
4. structural classification (Cramer structural classes; a surrogate for potential systemic toxicity, including teratogenicity and reproduction), and
5. proteins (as a surrogate for potential food allergy).

It is important to note that the proposed TTCs would afford an adequate Margin of Safety for potential developmental and teratogenic effects (Barlow *et al*, 2001; Kroes *et al*, 2004). Similarly, several independent reviews have confirmed that the threshold for repeated dose toxicity is inclusive of the threshold for reproductive effects (for a detailed discussion see Mangelsdorf et *al,* 2003).

Threshold of toxicological concern depended on information on certain endpoints

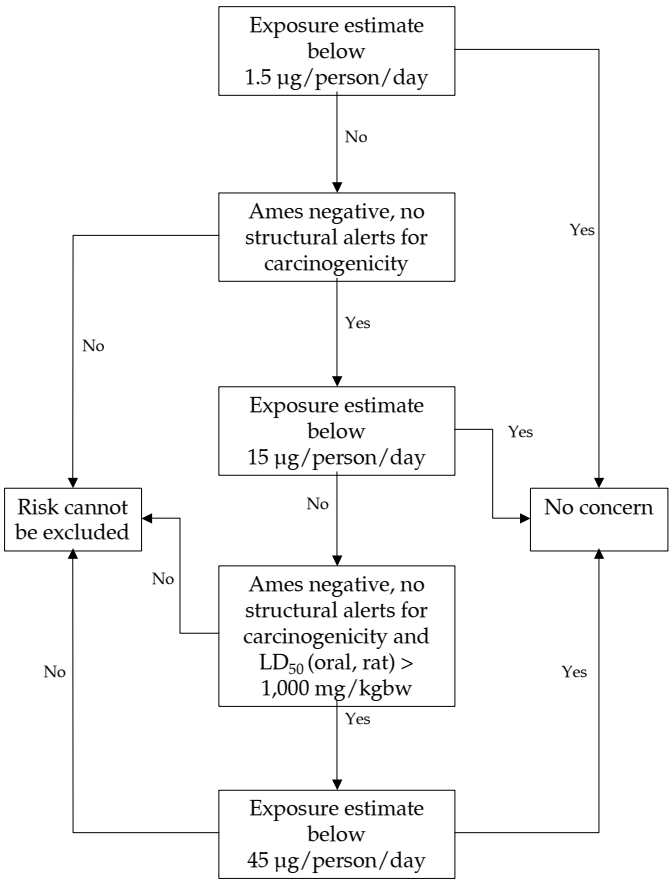
In the approach of Cheeseman *et al* (1999) the problem of specific effects that may be overlooked in the Munro (1996) and JECFA (1998) approach, such as neurotoxicity, was addressed by introducing additional parameters such as acute toxicity and Ames test.

They proposed to use short-term toxicity data, genotoxicity testing and structure activity relationships to establish more differentiated thresholds of regulation. Their analysis was based on 709 genotoxic carcinogens for which a TD_{50} with a statistical significance of at minimum $P \leq 0.01$ could be derived from oral studies. The carcinogens were divided into several subsets based on results in the Ames assay, structural alert classes for carcinogenicity and LD_{50} values. They established structural classes that would cover the most potent carcinogens (N-nitroso-compounds; endocrine disrupters (potential hormonal mechanism); strained heteronuclear rings; heavy metal compounds; alpha-nitro-furyl compounds; hydrazines, triazenes, azides, azoxy compounds; polycyclic amines; organophosphoric compounds). The likely potency of substances without those structural alerts was, according to the authors, 20 fold lower than the likely potency of structurally alerting substances. This was in particular the case when the Ames assay was negative in addition. The authors therefore proposed a threshold of regulatory concern of 5 ppb (µg/kg diet) (corresponding to about 15 µg/person/day) in the diet for Ames-negative substances without those particular structural alerts for carcinogenicity.

When analysing the relation of acute toxicity data the authors identified a major drop in potency of Ames negative carcinogens when the LD_{50} in rodents exceeds 1,000 mg/kgbw. Following their analysis they propose a threshold of no concern of 15 ppb in the diet (approximately 45 µg/person/day) for substances with absence of structural alerts for carcinogenicity, negative Ames assay and an acute toxicity (LD_{50}) in rats exceeding 1,000 mg/kgbw.

As this concept has been established in particular for food additives and the general population a first differentiation could be made by establishing a mg/kg body weight (bw) threshold based on common assumptions for body weights of workers, 70 kg; consumers, 60 kg; children, 10 kg.

Figure O.2: Concept of Cheeseman et al (1999)



The current concepts that use threshold of toxicological concern are mainly focused on dietary exposure and oral intake. However, from a scientific point of view there should be no principle difference when extending the concept to other routes of exposure other than the need for an assessment of the systemic exposure via different routes and additional extrapolation where appropriate.

These concepts are to be regarded as a toolbox to be applied as appropriate in a specific situation. They may be of particular value in situations where the exposure is well defined and an intake below the threshold of concern can be predicted with a sufficient degree of certainty. It should also be kept in mind that concepts that were based on chronic toxicity studies excluding carcinogens already used a safety factor of 100 that is traditionally used in the assessment of food additives. Concepts based on the analysis of carcinogenicity studies used very conservative assumptions, such as linear extrapolation to low doses from LT_{50} values, continuous lifetime exposure, and a life time tumour risk of 1:1 million. As the assumptions leading to a general TTC are inherently very conservative and precautionary, the concept is limited to specific scenarios and cannot serve as a general tool to define categories of exposure.

APPENDIX P: HAZARD ASSESSMENT IN TIER 1 CONSUMER RISK ASSESSMENTS

Based on the use patterns and use categories of a substance, the consumer exposure assessment at Tier 1 (see Section 2.2.3.2) will highlight the relevant exposure scenarios and identify the nature of the exposure in terms of product type, route, frequency and duration.

Systemic effects

Although some exposure situations with a low frequency (e.g. monthly) or duration (e.g. minutes) would only require an assessment of the acute exposure situation, the Tier 1 process always establishes an assessment of a continuous (24-h) and long-term situation. In terms of hazard characterisation that means that for systemic effects the generic LOAEL based on repeated exposures or actual repeated dose exposure data is used as a basis of the risk characterisation. The surrogate of hazard is thus taken from the most severe classification of the hazard category in this first worst-case approach.

Where actual data are available these should be used for the hazard assessment. Based on this information the critical toxic endpoints and the corresponding NOAELs should be determined from the appropriate toxicity data. The data to consider could include repeated dose toxicity studies and an assessment of reproduction and/or development. The relevant NOAELs or a derived value or the endpoints of concern should be used as a Reference Value in the risk assessment.

The risk assessment of a substance classified as a carcinogen of category 3 (R68), reproductive or developmental toxicant of category 3 (R62, R63), or irreversible effects (R39) should be based on the NOAEL of the endpoint from which the classification is derived.

Local effects

At Tier 0 and 1 substances without skin, eye or respiratory irritation or skin sensitisation potential are allocated to the low hazard category and are not addressed in the consumer risk assessment for these endpoints. However, substances known to cause defattening of the skin (R66) should be reviewed if there is a high frequency (daily) of the potential skin contact.

Substances classified as irritant, corrosive or sensitisers should be assessed for possible effects at the site of contact. As local effects are related to the concentration of the substance coming into contact with the site of exposure, rather than a systemic dose, a threshold concentration can be determined for those effects. The threshold concentration for skin or eye irritation should be used as the starting point for risk assessment if this information is available. Alternatively, the

boundaries for the classification of skin and eye irritants could be considered as appropriate Reference Values. Similarly, for the risk assessment of skin sensitisers, an assessment of the potential for skin contact, the elicitation threshold or the regulatory threshold to induce a response in sensitised individuals for the classification of preparations should be used (0.1%, unless specified otherwise), (see Table P.1). For a substance classified as a respiratory sensitiser, a case-by-case risk assessment is necessary.

Table P.1: Generic concentration limits for irritants based on the concentration boundaries of the preparations directive (EC, 1999b)

Classification	Target site	Risk phrase	Basis of limit	Bounding limit (%)
Irritant	Skin	R38/R68	Irritation threshold concentration	20%
Corrosive, skin	Corrosion	R34	Irritation threshold	5%
		R35	concentration	1%
Irritant	Eye	R36	Irritation threshold concentration	20%
Irritant	Eye severe	R41	Irritation threshold concentration	5%
	Skin sensitisation	R43	Elicitation threshold	0.1%

In those cases where insufficient information is available to assign the hazard category for local effects, a substance should be regarded as a potential skin sensitiser and irritant to skin, eyes and the respiratory tract.

Determination of reference margins of exposure for the Tier 1 risk assessment process

A reference MoE is used to define an adequate difference between the exposure in a particular scenario and the reference dose value describing the hazard. If the quotient of the reference dose divided by the exposure estimate exceeds the reference margin of safety there should be no concern with regard to a human health risk.

Depending on the nature of the reference dose describing the hazard, different reference margins of exposure may have to be applied. The reference MoE has to consider several extrapolation elements, described by Assessment Factors when extrapolating from animal studies to humans. The overall reference MoE can be derived by multiplying the Assessment Factors of the different extrapolation steps.

Application in the Tier 1 risk assessment for systemic effects

Workers

For workers the risk assessment is based on occupational exposure values or generic exposure values that are derived from occupational exposure values. Those values are derived under consideration of the extrapolation elements mentioned above and are already defining safe exposures for humans under the workplace conditions. Therefore application of the factors mentioned above is not appropriate in this case. In a conservative approach a reference MoE of 2 for the workers is considered adequate by the task force. This is corroborated by the validation exercise outlined in Appendix T.

Consumers

In the Tier 1 risk assessment of consumers the assessment can be either based on animal studies with repeated exposure or the generic LOAEL derived from the classification limits. Depending on the starting point different Assessment Factors are applied as outlined in Table P.2.

If animal data are used, the assumption in Tier 1 is that the NOAEL or LOAEL derived from the study is related to systemic effects. Inhalation concentrations are calculated as mg/kg body weight using the standard factors of the TGD for respiratory volume of the animal species considered (rat and mouse). It is further assumed that most of the repeated inhalation studies expose animals for 6 hours per day. As for consumers in a first worst-case approach 24-hour exposure per day is assumed, an Assessment Factor of 4 is incorporated.

In the Tier 1 risk assessment, three cases of actual repeated dose data are accounted for.

Table P.2: Assessment Factors used to determine reference MoEs for different study durations

Extrapolation elements/Assessment Factors	Study duration 28 d	Study duration 90 d	Study duration ≥ 6 months
LOAEL to NOAEL if appropriate	3	3	3
Duration: (for inhalation additional factor of 4)	6	2	1
Interspecies (for inhalation:1)	rat: 4	rat: 4	rat: 4
	mouse: 7	mouse: 7	mouse: 7
Intraspecies	5	5	5
Reference MoE from a LOAEL	rat: 360	rat: 120	rat: 60
	mouse: 630	mouse: 210	mouse: 105
Reference MoE from a NOAEL	rat: 120	rat: 40	rat: 20
	mouse: 210	mouse: 70	mouse: 35

In the case of inhalation exposure the interspecies factor will become 1 as the allometric scaling factor is based on the metabolic rate that is proportional to the respiration rate and thus automatically accounted for in inhalation studies. On the other hand an additional duration factor of 4 is introduced for inhalation exposure to account for the 6-hour inhalation duration in the animal experiment versus 24-hour consumer exposure. This leads to the same overall reference MoE for inhalation and oral or dermal exposure.

If the generic LOAEL is used it is to be considered that the cut off in the classification directive is referred to as a clear adverse effect and the generic level will mostly be used only in the absence of information on repeated dose studies. For the LOAEL to NOAEL extrapolation it is therefore considered appropriate to choose a factor of 6 that is close to the highest factor observed in the literature surveyed by ECETOC (2003a). As the generic value is based on rat data, the interspecies factor for the rat is used in the calculation (Table P.3).

Table P.3: Assessment Factors used to derive a reference MoE for a generic LOAEL

Extrapolation element	**Assesment Factor**
LOAEL to NOAEL	6
Duration (inhalation: additional factor of 4)	2
Interspecies (inhalation:1)	4
Intraspecies	5
Reference MoE	240

APPENDIX Q: DETERMINATION OF DERMAL RISKS IN THE WORKPLACE

The risks from dermal exposures are only specifically evaluated at the Tier 1 stage of the ECETOC approach. At Tier 0, the conditions under which inhalation exposure to low hazard substances are considered to be insignificant, are also considered to present a low risk from any dermal contact with such (low hazard) substances.

The rationale for the approach at Tier 0 is based upon the fact that the 'low' hazard category does not include any materials that might be expected to have any substantive effect from skin contact (e.g. dermal sensitisers; substances that are toxic by dermal administration). These substances are placed in either the moderate or high hazard categories. Where incidental dermal exposure to irritants or corrosives may occur, then it is considered that the use of gloves and other protection (as required to be advised within the safety data sheet [SDS] for the substance) offers an adequate basis for concluding that the risks from skin contact does not constitute a concern (and which is consistent with normal proven practice with such materials). However, where substantive exposures may arise (as would be the case for the medium and high exposure potential categories), then such risks are further evaluated within Tier 1. This philosophy to the tiering of dermal risks is consistent with that used to identify substances that present risks from inhalation exposure.

At the Tier 1 level, the following process for evaluating potential risks is followed within the scheme:

1. Dermal risks are only evaluated in those scenarios that might be expected to be associated with significant dermal contact with the substance. Such an assessment is made for each scenario on the basis of experiences from across industry and historical regulatory consensus. No evaluation of dermal risk is undertaken in those scenarios (indicated in Tables Q.1 - Q.3) that are excluded.
2. Substances which are unlikely to constitute any risk from dermal contact, due to their physico-chemical properties, are not considered. Such cases are when the substance has either high hydrophobicity (log $P > 5$), high hydrophilicity (log $P < -1$) or a high molecular weight (>1,000). These conditions are consistent with the advice contained within the revised TGD (EC, 2003a).
3. An estimate of the dermal exposure loading is then determined for each scenario that might be expected to be associated with significant dermal contact with the substance. This is achieved by linking the descriptors of the scenario to the inputs of the dermal portion of the EASE model. Where dermal exposure can be presumed to represent a potentially significant source of exposure, then the workplace characteristics that serve as inputs for this element of EASE (e.g. whether there is expected to be direct contact with the substance and the likely nature of the contact) are related to the specific characteristics of the exposure scenario. The

estimated dermal applied dose for each scenario is determined by multiplying the EASE output (in mg/cm^2/day), by the assumed dermal contact area (which varies according to the scenario and ranges from 420 - 1,500 cm^2), accounting for a mean bodyweight of 70 kg. It has been demonstrated (ECETOC, 1997; Schneider *et al*, 1999) that the dermal portion of EASE is conservative in its estimation of industrial dermal exposures. In line with the approach adopted for EASE predictions of inhalation exposure (Appendix U), minor modifications to the predicted dermal outputs from EASE have been made for some scenarios where the output is inconsistent with experience (see Tables Q.1 - Q.3).

4. Subsequent to estimating the exposures, it is necessary to compare these with a suitable 'marker of concern' for the respective hazard categories. For each category of hazard potential, a dermal equivalent of the GEV (termed the Generic Dermal Exposure Value or 'GDEV') was derived by extrapolating the GEV to an equivalent internal dose value, calculated by (firstly converting the GEV into mg/m^3 if it is given in ppm and then) multiplying the GEV by 10 (10 m^3 being inhaled over a working shift by a person under light/moderate workload) and dividing by 70 (consistent with the 70 kg standard default for a male) and assuming 100% absorption via inhalation.
5. The estimated applied dose for each scenario where dermal exposure is considered to present a realistic possibility is then compared to the GDEV to derive the worker Margin of Exposure (MoE_w) for the scenario. When the MoE_w is less than 2, then a more detailed evaluation of the risk is considered warranted at the Tier 2 level.

Workers are assumed not to be wearing gloves or other forms of personal protection at either the Tier 0 or Tier 1 levels. The role (and effectiveness) of personal protection is a consideration for Tier 2 assessments. This is consistent with the EU TGD.

For substances where a Tier 2 assessment is indicated, then, in addition to consideration of the role of PPE, factors such as any physico-chemical factors that may mitigate against dermal absorption (e.g. (Q)SAR predictions of dermal permeation rates) and the incorporation of actual monitoring data can all be taken due account of.

For volatile substances and gases, the conversion from GEV (ppm) to the GDEV (mg/m^3) is undertaken according to the standard formula:

GDEV [mg/m^3] = (molecular weight/molecular volume in litres at 20ºC and 1,013 hPa) x GEV [ppm].

Risks from dermal sensitisers

The risks from dermal sensitisation can also be addressed using a similar approach. Because substances classified as dermal sensitisers (R43) are categorised as having a moderate hazard potential, then only those with a minimal exposure potential will fall out of the ECETOC scheme at the Tier 0 level. All other emission situations will progress to Tier 1. The Tier 1 assessment for dermal sensitisers is intended to evaluate the risk from the *induction* of sensitisation. The consequences of exposures eliciting any existing allergic responses are not considered within the ECETOC scheme.

Where a substance is classified as R43 and it is present at levels in excess of 0.1%, then the risk of induction can be assessed at the Tier 1 level as follows:

i. Determine the dermal exposure loading (in mg/cm^2) associated with the identified exposure scenarios as described in #2 and #3 above. The predicted loading arises from an assumption that exposure is to the 'pure' (100%) material.

ii. The human induction thresholds for a number of dermal sensitisers have now been identified and ranked (Gerberick *et al*, 2001). Using the information available on moderate sensitisers (which represent substances that might typically be encountered in non-dispersive uses of chemicals such as formaldehyde and glutaraldehyde), an operational human NOEL for this class can be identified at c.100 $\mu g/cm^2$.

    In the EU, a dermal sensitiser is required to be labelled as a sensitiser when its content in a preparation exceeds 1%. It is also required to be declared within the SDS at concentrations above 0.1%, in order, in part, to assist with the management of any existing cases of dermal allergy. Many of the more ubiquitous and better characterised groups of skin sensitisers, are known *not* to *induce* sensitisation at concentrations below 0.1% (ECETOC, 2003b). Thus substances that are classified as skin sensitisers, but which are present in preparations at less than 0.1% are not addressed within the ECETOC approach. This approach ensures that all materials that would be viewed as weak, moderate or strong sensitisers are adequately addressed, but not the few materials that are considered to be extreme sensitisers (and which in several instances are already required to be labelled when present in preparations at levels less than 0.1%).

    Compare the estimated exposure (#4) with the generic sensitisation value (#5) to derive the MoE for the scenario. Based upon the MoE, establish whether a Tier 2 assessment is required.

iii. For substances where a Tier 2 assessment is indicated, then additional factors such as accounting for the actual percentage of the sensitising substance within the preparation;

information on the induction thresholds for sensitisers of similar potency to the substance; or any physico-chemical factors that may mitigate against sensitisation (e.g. extreme hydrophobicity or hydrophilicity that would serve to substantially reduce epidermal loading) can be taken due account of.

Table Q.1: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - On-site uses

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Uses as Raw Materials, Feedstocks or Intermediates	**Yes**	**No**										
Use in a **closed** continuous process		n/a	no	n/a								
Use in a continuous process			no	n/a								
Use in a **closed** batch process i.e. where **no** opportunity for breaching arises, including product transfers and sampling		n/a	no	n/a								
Use in a batch or other process (including related process stages, e.g. filtration, drying) where opportunities for exposure arise, e.g. sampling, dis/charging of materials		✓	yes	10	480	yes	0.07	EASE predicts (contained system, signif breaching, no direct handling) very low. Assumes 2 hands face only	831	83	6	10
	✓		yes	100		no	0.69	EASE predicts (signif breaching, no direct handling, intermittent exposure). Assumes 2 hands face only	83	8	1	1

Table Q.2: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Non-dispersive uses

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Non-dispersive uses	**Yes**	**No**										
Use in a **closed continuous process**			no	n/a								
Use in a **continuous process**			no	n/a								
Use in a **closed** batch process i.e. where no opportunity for breaching arises, including product transfers and sampling			no	n/a								
Use in a batch process including chemical reactions and/or the formulation by **mixing, blending or calendering** of liquid and solid-based products	✓		yes	10	480	yes	0.07	EASE predicts (non-dispersive, mobile dust, no direct handling) very low. Assumes 2 hands face only	831	83	6	10.00
		✓	yes	1,000		no	6.86	EASE predicts (no-dispersive, direct handling, intermittent exposure). Assumes 2 hands face only	8	1	0	0.10

Table Q.2: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Non-dispersive uses (cont'd)

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Non-dispersive uses	**Yes**	**No**										
Spraying of the substance or preparations containing the substance in industrial applications e.g. coatings	✓		no	100	1,500	yes	2.14	EASE predicts very low (non-dispersive, non-direct handling). 0.1mg/cm² a realistic worst case. Assumes 2 hands and forearms	27	3	0	1.00
		✓	yes	1,000		no	21.43	EASE predicts (signif breaching, direct handling, intermittent exposure). Assumes 2 hands and forearms	3	0	0	0.10
Dis/charging the substance (or preparations containing the substance) to/from vessels	✓		yes	10	480	yes	0.07	EASE predicts (non-dispersive, mobile dust, no direct handling) very low. Assumes 2 hands face only	831	83	6	10.00
		✓	yes	1,000		no	6.86	EASE predicts (non-dispersive, direct handling, intermittent exposure). Assumes 2 hands and forearms	8	1	0	0.10

Table Q.2: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Non-dispersive uses (cont'd)

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Non-dispersive uses	**Yes**	**No**										
Filling containers with the substance or its preparations	✓		yes	100	480	yes	1.43	EASE predicts very low (non-dispersive, non-direct handling). 0.1mg/cm² a realistic worst case. Assumes 2 hands face only	40	4	0	1.00
		✓	yes	1,000		no	6.86	EASE predicts (signif breaching, direct handling, intermittent exposure). Assumes 2 hands face only	8	1	0	0.10
Roller application or brushing of adhesives and other surface coatings	✓		yes	100	960	yes	1.37	EASE predicts (non-dispersive, mobile dust, direct handling, incidental contact). Assumes 2 hands only	42	4	0	1.00
		✓	yes	1,000		no	13.71	EASE predicts (non-dispersive, mobile dust, direct handling, intermittent contact). Assumes 2 hands only	4	0	0	0.10
Use as a **blowing** agent in the manufacture of foams, etc			no	n/a								
Use for coating/treatment of articles, etc (including cleaning) by **dipping or pouring**	✓		yes	10	480	yes	0.07	EASE predicts (non-dispersive, mobile dust, no direct handling) very low. Assumes 2 hands face only	831	83	6	10.00

Table Q.2: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Non-dispersive uses (cont'd)

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Non-dispersive uses	**Yes**	**No**										
		✓	yes	1,000		no	6.86	EASE predicts (non-dispersive, mobile dust, direct handling, intermittent contact). Assumes 2 hands face only	8	1	0	0.10
Production of products or articles from substance by **compression, tabletting or pelletisation**	✓		yes	10	480	yes	0.07	EASE predicts (non-dispersive, mobile dust, no direct handling) very low. Assumes 2 hands face only,	831	83	6	10.00
		✓	yes	1,000		no	6.86	EASE predicts (non-dispersive, mobile dust, direct handling, intermittent contact). Assumes 2 hands face only	8	1	0	0.10
Use as a **laboratory reagent**			no	n/a								
Use as a **fuel**			no	n/a								
Use as a **lubricant** (including metal working fluids)	✓		yes	100	960	yes	1.37	EASE predicts (non-dispersive, mobile dust, direct handling, incidental contact). Assumes 2 hands only	42	4	0	1.00
		✓		2,000		no	27.43	EASE predicts 5 mg/cm² (signif breaching, direct handling, extensive exposure). 2 mg/cm² a more realistic worst case. Assumes 2 hands	2	0	0	0.05

Table Q.3: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Wide dispersive uses

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Wide dispersive uses	**Yes**	**No**										
Use for the formulation of liquid and solid-based products by **mixing, blending or calendering**	✓		yes	10	480	yes	0.07	EASE predicts (wide-dispersive, mobile dust, no direct handling) very low. Assumes 2 hands face only	831	83	6	10.00
		✓	yes	2,000		no	13.71	EASE predicts 5 mg/cm² (wide-dispersive, mobile dust, direct handling, intermittent). 2 mg/cm² a more realistic worst case. Assumes 2 hands face only	4	0	0	0.05
Spraying of the substance or preparations containing the substance e.g. paints and coatings	✓		yes	100	1,500	yes	2.14	EASE predicts (wide-dispersive, mobile dust, direct handling, incidental). Assumes 2 hands and forearms	27	3	0	1.00
		✓	yes	5,000		no	107.14	EASE predicts (wide-dispersive, mobile dust, no direct handling) very low. Assumes 2 hands and forearms	1	0	0	0.02
Discharging the substance (or preparations containing the substance) to/from vessels	✓		yes	10	960	yes	0.14	EASE predicts (wide dispersive, direct handling, intermittent exposure). Assumes 2 hands	416	42	3	10.00
		✓	yes	2,000		no	27.43	EASE predicts 5 mg/cm² (wide dispersive, direct handling, intermittent exposure). 2 mg/cm² a more realistic worst case. Assumes 2 hands	2	0	0	0.05

Table Q.3: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Wide dispersive uses (cont'd)

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Wide dispersive uses	**Yes**	**No**										
Filling containers with the substance or its preparations	✓		yes	100	480	yes	2.86	EASE predicts very low (non-dispersive, non-direct handling). 0.1mg/cm² a realistic worst case. Assumes 2 hands face only	20	2	0	1.00
		✓	yes	1,000		no	6.86	EASE predicts (signif breaching, direct handling, intermittent exposure). Assumes 2 hands face only	8	1	0	0.10
Roller application or brushing of adhesives and other surface coatings	✓		yes	100	960	yes	1.37	EASE predicts (wide dispersive, mobile dust, direct handling, incidental). Assumes 2 hands	42	4	0	1.00
		✓	yes	2,000		no	27.43	EASE predicts 5 mg/cm² (wide dispersive, mobile dust, direct handling, intermittent). 2 mg/cm² a more realistic worst case. Assumes 2 hands	2	0	0	0.05
Use for coating/treatment of articles, etc (including cleaning) by **dipping or pouring**	✓		yes	100	480	yes	0.69	EASE predicts very low (wide-dispersive, mobile dust, no direct handling) 0.1mg/cm² a realistic worst case. Assumes 2 hands face only	83	8	1	1.00
		✓	yes	2,000		no	13.71	EASE predicts 5 mg/cm² (wide-dispersive, mobile dust, direct handling, intermittent). 2 mg/cm² a more realistic worst case. Assumes 2 hands face only	4	0	0	0.05

Table Q.3: Calculation of dermal exposure and uptake for ECETOC exposure scenarios - Wide dispersive uses (cont'd)

Generic scenarios for assessment of dermal exposure at Tier 1	LEV present?		Does dermal exposure occur?	Predicted EASE dermal exposure (µg/cm²/day)	Exposed skin surface (cm²)	LEV present?	Predicted dermal exposure (mg/kg/day)	Comments	Dermal risks (MoE vs GDEV)			Dermal risk (R43 MoE)
									Low	Medium	High	
Wide dispersive uses	**Yes**	**No**										
Production of products or articles from substance by **compression, tabletting, extrusion or pelletisation**			no	n/a								
Use as a **laboratory reagent**			no	n/a								
Use as a **fuel**			no	n/a								
Use as a **lubricant** (including metal working fluids)	✓		yes	100	960	yes	1.37	EASE predicts (dispersive, mobile dust, direct handling, incidental contact). Assumes 2 hands	42	4	0	1.00
		✓		2,000		no	27.43	EASE predicts (dispersive, mobile dust, direct handling, intermittent contact). Assumes 2 hands	2	0	0	0.05

APPENDIX R: CHOICE AND USE OF ASSESSMENT FACTORS

ECETOC (2003a) has presented a proposal for scientifically derived Assessment Factors that could reasonably be used in the framework of a tiered risk assessment process to establish reasonable 'reference margins of exposure'. It has focused on proposing, where possible, plausible numerical values as appropriate default Assessment Factors to account for the uncertainty and the variability in the available databases. The approach may be particularly useful for general industrial chemicals where detailed toxicity studies may not always be available. The default Assessment Factors recommended in this report should be used in risk assessment where more appropriate substance-specific information is lacking or cannot be readily obtained. The values for the defaults are considered to be justifiable, since their choice is based on current science and transparent assumptions. They should be seen as useful 'interim guides' in the risk assessment process.

Wherever possible, the physico-chemical properties of the substance being assessed should be taken into account; these are often available or can be estimated. Any additional data on biological properties (e.g. reactivity, bioaccumulation, toxicokinetics and toxicodynamics) should also be considered to allow more specific modification of the proposed default values.

The minimum MoE approach would combine the following elements that were addressed by ECETOC (2003a):

- Extrapolation from a LOAEL to a NOAEL;
- duration extrapolation;
- interspecies differences;
- intraspecies differences.

Another element would be route-to-route extrapolation, i.e. extrapolation from an experimental route to a route that is relevant for the actual exposure situation. This has to be done using specific data of the study and cannot be addressed by a default factor. Guidance is given by ECETOC (2003a).

There are a number of preconditions for using the default Assessment Factors provided by ECETOC (2003a). The defaults should be modified if substance-specific data are available. Before applying the default approach it should be checked in particular if the substance is likely to have a prolonged half-life (i.e tendency to accumulate), is likely to have toxic or persistent metabolites or if a specific MOA is known. Locally acting (irritant) substances have to be assessed in a different way from those with systemic toxicity.

The rationale and limitations for the different default factors and also possible alternatives are discussed by ECETOC (2003a). Guidance is also given in which cases somewhat higher or lower factors may be more appropriate to use.

Table R.1: Recommended default Assessment Factors (ECETOC, 2003a)

Elements of extrapolation	Default AF
Establishment of NOAEL	
- LOAEL to NOAEL	3
Duration of Exposure	
- subacute/chronic NOAEL	6
- subchronic/chronic NOAEL	2
- local effects by inhalation	1
Interspecies and intraspecies	
- interspecies (systemic effects $bw^{0.75}$)	
- mouse (scaling)	7
- rat (scaling)	4
- intraspecies (systemic effects)	5 (general population) 3 (workers)
- interspecies (local and systemic effects by inhalation)	1
- intraspecies (local effects)	5 (general population) 3 (workers)

A multiplication of the appropriate Assessment Factors would then give a 'reference margin of safety' that could be used for comparison with the exposure concentration. For example if a standard rat 28-day study is considered the appropriate study that addresses the appropriate endpoint and an adequate NOAEL has been established in this study, the use of the default Assessment Factors would result in a reference MoE of 6x4x3 = 72 for workers and 6x4x5 = 120 for consumers. An additional adjustment may be needed based on the frequency (i.e. 5 or 7 d/wk) and/or duration (i.e. 6-h inhalation) of the dosing in the study in comparison with the exposure scenario that is considered.

APPENDIX S: VERIFICATION OF THE GENERIC LOWEST EFFECT LEVELS

The ECETOC concept of the Generic Lowest Effect Value (GLEV) was verified using the information contained in two databases:

1. The (draft) existing chemicals risk assessment documents as available on the public ECB website (http://ecb.jrc.it)
2. Effects data-base of Industrial Chemicals, Fraunhofer Institute of Toxicology and Experimental Medicine (Bitsch et al, 2003)

In the first step of this verification the appropriate hazard category was assigned to each of the substances listed in the database according to Annex 1 of Directive 67/548/EEC. To ensure inclusion of the most up-to-date hazard information the classifications listed on the current draft of the 29th ATP were also taken into account. Substances of very high concern (CMRs) were excluded from this verification procedure, as they require a higher tier risk assessment; substances not listed in Annex 1 and those with an outdated hazard classification were also excluded in this exercise. In the next step, the LOAEL and/or NOAEL for the critical endpoint(s) were identified for each of the selected substances in the Existing Chemical Risk Assessment documents. Where available, the LOAEL of the critical endpoints were compared to the appropriate GLEV. In some of the risk assessment documents the LOAEL for the critical endpoint was not clearly identified; in these cases the NOAEL for the critical effect was compared to the GLEV/6. The value 6 is the default Assessment Factor used in the ECETOC process to extrapolate from a LOAEL to a NOAEL (see Appendix P; ECETOC, 2003a). The results of this comparison are presented below.

Table S.1: Comparison of GLEV with identified critical effect for EU risk assessment substances

	Hazard Category			
	Low	**Medium**	**High**	**Other[a]**
No. of substances	**10**	**14**	**3**	**21**
LOAEL > GLEV or NOAEL > GLEV/6	10	14	1	-
LOAEL < GLEV	0	0	2	-
Class. R34/35/41			2/2	

[a] Substances of very high concern (CMRs) or without up-to-date hazard classification.

The comparison of the LOAEL or NOAEL with the GLEV indicates that the GLEV represents a conservative estimate of the Reference Value for the risk assessment for the medium and low hazard category. Of the three substances allocated to the high hazard category two were very

strong local irritants (acrylaldehyde and hydrogen fluoride, classified R34 and R35, respectively), with LOAELs for local (irritant) effects below the generic values for the high hazard category.

A similar approach was used for the information collated in the Fraunhofer database (Bitsch *et al*, 2003). This database comprises a comprehensive list of repeated dose toxicity studies; information on a total of 1,230 endpoints have been collated in this database. For each study the following details are available: species, duration, exposure route, data reliability and overall NOAEL and LOAEL; for each endpoint the corresponding LOAEL and NOAEL are also listed.

For this verification the hazard classification for each of the substances was obtained and the corresponding hazard category assigned. Substances of very high concern or those outside the scope of the ECETOC approach were not included in the evaluation. A comparison of the LOAEL or NOAEL for each of the studies was compared to the appropriate GLEV or GLEV/6, respectively. No effort was made to identify the critical endpoint because the structure of this database does not lend itself to reliably establish the most critical effect for each study. The results of this comparison are shown in the table below.

Table S.2: Comparison of GLEV with identified critical effect (Fraunhofer database)

	Hazard Category			
	Low	**Medium**	**High**	**Other[a]**
No. of studies	64	171	21	84
LOAEL > GLEV or NOAEL > GLEV/6	61	152	18	-
LOAEL < GLEV	3	19	3	-
Class. R34/35/41	0	12/19	3/3	
Non-critical study [b]	2/3	3/19	-	
LOAEL > GLEV	93%	88%	86%	-
LOAEL > GLEV, excl. corrosives, non-critical study	98%	97%	100%	
LOAEL < GLEV	2% (1/62)	3% (4/156)	0	

[a] Other includes substances classified as CMRs; not listed in Annex 1 or outside the scope of the ECETOC approach

[b] Other studies available of longer duration/higher reliability and LOAEL > GLEV

The results of the evaluation demonstrate that the GLEV is a reliable parameter for a conservative estimate for the LOAEL for repeated dose toxicity studies for *ca*. 90% of the cases. Corrosive substances (i.e. those classified R34, 35, 41) cause local irritative effects at the site of first contact in repeated dose toxicity studies, often without evidence of systemic toxicity. Excluding these corrosives from the generic approach, the number of cases where the GLEV is lower than the true LOAEL is 96 and 100% for the medium and high hazard category

respectively. A few cases were identified showing a LOAEL below that of a similar experiment of longer exposure duration. Assigning a higher weight to the experiment with the longest duration, the concordance of the GLEV is >97%.

For those cases where the LOAEL is below the GLEV (n=1 and 4 for the low and medium hazard category, respectively) these were associated with toxic endpoints related to local irritation response at the site of first contact, without evidence of systemic effects.

Overall, this evaluation has shown that the GLEV provides a conservative estimate of a surrogate Reference Value suitable for the risk assessment of repeated consumer exposure.

Comparison with other risk assessment tools

The Threshold of Toxicological Concern (TTC) is a method for risk assessment of substances present in food without an adequate toxicological database (see Appendix O for a more detailed description; Munro *et al*, 1996; Cheeseman *et al*, 1999; Kroes *et al*, 2000).

Table S.3 lists the 3 highest TTCs proposed by ILSI.

Table S.3: TTCs proposed by Kroes et al (2004)

Category	TTC (mg/person/day)	NOAEL (mg/kg/day) [a]
I	1.8	3
II	0.54	0.9
III	0.09	0.15 [b]
		≥1.0 [c]

[a] NOAEL = TTC x 100/60 kg (100 is the safety factor applied to derive the human safe dose)

[b] TTC criteria exclude substances with concerns for bioaccumulation, genotoxicity and organophosphates

[c] Lowest NOAEL for substances within the ECETOC criteria (see text)

ECETOC has proposed a Generic No Adverse Effect Level of 0.8 mg/kg/day for chemicals of the medium hazard category; this value is derived from the GLEV of the medium hazard category (5 mg/kg/day – see Table 10) by applying a default Assessment Factor of 6 (see Table P.3). This generic NOAEL is below that of TTC categories I and II proposed by ILSI; these categories consist of substances with a low concern for toxicity and/or a lack of structural concerns.

The ECETOC approach has confined the applicability of the GLEV concept only to those substances not exhibiting the following properties or structural alerts:

- Corrosion (not fully excluded but requiring a separate assessment for local effects);

- mutagenic potential (category 2 and 3) not fully excluded, but requiring further assessment;
- bioconcentration potential (not fully excluded, but modified assessment needed (see Section 2.2.3);
- potent pharmacological activity (see applicability domain 2.3).

Application of the criteria developed by ECETOC for its GLEV concept to the 448 substances allocated to structural class III within the TTC concept demonstrates that all substances within the ECETOC criteria had a NOAEL for repeated dose toxicity of ≥ 1 mg/kg/day and a LOAEL of > 5 mg/kg/day. Substances assigned to a high hazard category in the ECETOC concept are allocated a GLEV of 0.5 mg/kg per day for the oral route, which would correspond to a generic NOAEL of 0.08 mg/kg per day, which is fully in line with the proposed value of 0.15 of the TTC concept for substances with expected high hazard.

The verification discussed above was conducted based on the hazard classification according to Annex 1 of Directive 67/548 and included only substances with a toxicology database including, as a minimum, information on acute toxicity, irritation, sensitisation, mutagenicity and a repeated dose toxicity. The minimum information required to conduct an assessment specified for the ECETOC TRA approach does not include information on repeated dose toxicity and substances without such information are likely to be assessed. For this reason, the verification with the Fraunhofer database was repeated but without taking into account information related to repeated exposures (Bitsch *et al*, 2003). The hazard category of each substance was assigned using the classification based on acute toxicity, irritation, and sensitisation. A concern regarding potential DNA reactivity was assigned on the basis of the risk phrases R40, R68, R46, R45 and R49. The distribution of the hazard classes using the two approaches is shown in Table S.4.

Table S.4: Allocation to hazard category using full and minimum hazard data set [a]

Hazard category	**Basis for hazard category**		
	Full hazard classification	**Re-allocated based on minimum information[a]**	**Minimum information[a]**
Low	33	-	43
Medium	60	Low 3	35
		Str. Alert 22	
High (non CMR)	10	Str. Alert 4	6
High (CMR)	47	Low 7	-
		Str. alert 40	
Structural alert	-		66

[a] Data present the number of substances

Table S.4 demonstrates that by relying on a minimum hazard information set a total of 66 substances have a structural concern, using the classification R40, R68, R46, R45 and R49 as a trigger. A total of 10 substances are 're-allocated' from the medium and high hazard category to the low hazard category. For the high hazard category, substances classified R60 or R61 were re-allocated. For the medium hazard category, the reclassification was based on repeated dose toxicity, fertility or developmental endpoints (R48, 62 or 63).

To determine the impact of the reclassification associated with the reduced information, the NOAEL and/or LOAEL of the repeated dose toxicity were compared with the GLEV values for the low hazard category. This comparison indicates that for 3 of 10 substances the GLEV value for the low hazard category exceeds the observed NOAEL/LOAEL and might result in a false negative outcome at Tier 1 when relying on the GLEV in a risk assessment of consumer applications. For 7 of 10 substances the NAOEL/LOAEL exceeded the GLEV and the presence or absence of data beyond the minimum information requirements would not have impacted the potential outcome of a consumer risk assessment at Tier 1.

This verification has shown that the absence of information on repeated dose toxicity can lead to an incorrect allocation of hazard category. For example, examination of the Fraunhofer database indicates that 10 of 43 substances (ca. 25%) would be incorrectly allocated to the low hazard category. The consequences of this 'misclassification' are not so severe as the raw statistics suggest, however, because of the conservative manner in which data are transformed within the approach. Thus, although c.25% of substances were ' misclassified', when these substances were subject to a consumer risk assessment at Tier 1, then an incorrect outcome (i.e. a failure to identify a risk when one is present) occurred for only 3 of the 10 misallocated substances. Such a rate of false negatives is sufficiently high to justify a default allocation to the medium hazard category in the absence of information on repeated dose toxicity. A similar default downgrading of the medium to high hazard category is not justified though (see discussion below).

Substances may be allocated to the medium hazard category on the basis of acute toxicity classification, irritation/corrosivity or skin sensitisation potential, absence of concerns for genotoxicity and alerts for potential respiratory sensitisation (N.B. reliable screening assays for respiratory sensitisers are not yet available). Based on the minimum information requirements, a clear discrimination between the medium and high hazard category can be achieved. With regards to repeated dose toxicity, an evaluation of the Munro database has shown that the lowest NOAELs observed for the substances within the ECETOC applicability domain have a NOAEL and LOAEL for repeated dose toxicity (including effects for fertility and development) >1 and >5 mg/kg/day, respectively, and meet the criteria for the GLEV value for the medium hazard category (see Table S.3). It is therefore concluded that, based on the minimum information requirements and applicability limits of the ECETOC approach, allocation to the medium hazard category in the absence of information on repeated dose toxicity can be justified.

APPENDIX T: VALIDATION OF WORKPLACE RISKS AT TIER 1

Background and process followed

To evaluate the validity of the proposed ECETOC approach for the Tier 1 assessment of workplace health risks, exposure scenarios were developed for a range of situations that describe working conditions typical of those associated with the use of chemicals throughout industry (Appendix V). These situations include several that have been agreed by the EU (for example at the Technical Meetings) as being 'of concern', as well as others that clearly represent the responsible and safe use of chemicals. The case studies are intended to be representative of the range of workplace exposure situations that are prevalent across Europe and which any risk assessment scheme might be expected to address. As such, they do not include extreme conditions of use, but do include a majority that relate to activities expected to be encountered amongst downstream users of chemicals.

A total of 66 case studies were identified and described (n=34 for volatiles and n=32 for solids). Appendix V describes the scenario, together with an indication of whether it is considered to be 'a concern' (and which would hence warrant a detailed targeted risk assessment of the scenario at the Tier 2 level). For each scenario, a quantified estimate of the exposure was generated utilising either the EASE (EC, 2003a) or COSHH Essentials (Maidment, 1998) regulatory models.

In addition to evaluating the validity of the approach, the exercise also sought to establish the boundaries/limits that might be applicable for the process. In other words, to identify any circumstances where, at the Tier 1 level, it may not be fully valid and/or where further refinements of the approach would be warranted. This phase of the validation also aimed to explore the effect that different worker Margins of Exposure (MoE_w) might have on the overall accuracy and sensitivity of the proposed process.

By comparing the predicted exposure, obtained from either the EASE or COSHH Essentials (CE) models with the Occupational Exposure Limit (OEL) or Generic Exposure Value (GEV) for the substance, it is possible to derive an MoE_w for each scenario. An OEL already incorporates some safety factor, dependent upon the nature and severity of the health effect that it is intended to protect against. The process for deriving the GEV (see Section 2.2.3.1), because it is based upon a pooling and statistical evaluation of available OELs, ensures that some generic margin of safety is also integrated within the GEV. Based upon the ability of the ECETOC process to identify accurately those instances where risks are considered of concern (true positives) from those where risks are acceptable (true negatives), it is possible to explore the overall validity of the Tier 1.

Results

For each scenario, a MoE_w was derived for both the EASE and CE exposure estimates and utilising both the OEL and GEV (i.e. within each scenario, a total of 4 possible MoE_ws for volatile materials and 2 for solids). Tables T.1 – T.4 summarise the results for volatile substances for different combinations of exposure prediction model (EASE and CE) and OELs/GEVs. Tables T.5 and T.6 contain the results for non-volatile (solid) substances, where only GEVs were available for comparison purposes.

Table T.1: COSHH essentials exposure prediction versus EU OELs

EU risk outcome	Outcome of ECETOC Tier 1 screening for volatiles	
	Concern	No concern
Concern (9)	9 (True positive)	0 (False negative)
No concern (25)	12 (False positive)	13 (True negative)

Accuracy = 65% Sensitivity = 100% n = 34

Assuming a MoE of 2 and taking the 100th % of the predicted exposure range

Table T.2: COSHH essentials exposure prediction versus ECETOC GEVs

EU risk outcome	Outcome of ECETOC Tier 1 screening for volatiles	
	Concern	No concern
Concern (8)	8 (True positive)	0 (False negative)
No concern (26)	15 (False positive)	11 (True negative)

Accuracy = 56% Sensitivity = 100% n = 34

Assuming a MoE of 2 and taking the 100th % of the predicted exposure range

Table T.3: EASE exposure prediction versus EU OELs

EU risk outcome	Outcome of ECETOC Tier 1 screening for volatiles	
	Concern	No concern
Concern (9)	9 (True positive)	0 (False negative)
No concern (25)	14 (False positive)	11 (True negative)

Accuracy = 68% Sensitivity = 100% n = 34

Assuming a MoE of 2 and taking the 100th % of the predicted exposure range

Table T.4: EASE exposure prediction versus ECETOC GEVs

EU risk outcome	Outcome of ECETOC Tier 1 screening for volatiles	
	Concern	**No concern**
Concern (9)	9 (True positive)	0 (False negative)
No concern (25)	14 (False positive)	11 (True negative)

Accuracy = 59% Sensitivity = 100% n = 34

Assuming a MoE of 2 and taking the 100th % of the predicted exposure range

Table T.5: COSHH Essentials exposure prediction versus ECETOC GEV (solids)

EU risk outcome	Outcome of ECETOC Tier 1 screening for solids	
	Concern	**No concern**
Concern (15)	15 (True positive)	0 (False negative)
No concern (17)	10 (False positive)	7 (True negative)

Accuracy = 65% Sensitivity = 100% n = 32

Assuming a MoE of 2 and taking the 100th % of the predicted exposure range

Table T.6: EASE exposure prediction versus GEVs (solids)

EU risk outcome	Outcome of ECETOC Tier 1 screening for solids	
	Concern	**No concern**
Concern (15)	15 (True positive)	0 (False negative)
No concern (17)	7 (False positive)	10 (True negative)

Accuracy = 73% Sensitivity = 100% n = 32

Assuming a MoE of 2 and taking the 100th % of the predicted exposure range

Discussion

The results clearly demonstrate that the proposed scheme offers a simple, workable and suitably cautionary mechanism for use in a tiered approach to the assessment of workplace risks. Utilising a MoE_w of 2 results in the advocated Tier 1 process having a sensitivity of 100% (that is, in no case did a real risk fail to be identified i.e. no false positives). Its accuracy (measured as a sum of true positives and true negatives, compared with the sum of all scenarios), on the other hand, varies depending on the combination of exposure estimation model and OEL/GEV. The most accurate approach combines the EASE model and published EU OELs. However, as established OELs are unavailable for most of the substances that will be dealt with under REACH, it is proposed that the GEV serves as the immediate default. The combination of EASE and the GEV offers an accuracy of 59% and 73% for volatile substances and solids respectively.

In contrast, the false positive frequency (defined as the total false positives divided by the sum of the true negatives and false positives) finding is around 60%. Clearly, any screening approach needs to incorporate a degree of conservatism. How high this conservatism ought to be, though, is a matter for discussion. Approaches that are too conservative have the potential to lose their practical value over time, simply because of a workplace equivalent of the 'cry wolf' syndrome. There is thus a need to balance conservatism with usability.

The cautionary nature of Tier 1 results might, perhaps, be expected. The derived MoE_ws are inherently conservative in nature by virtue of the fact that the top end of the predicted exposure is used (equivalent to the 95th percentile of likely exposures for that scenario) as the denominator. Moreover, the GEV represents the 25th percentile of the comparable OEL range, where the OEL already incorporates safety factors. Hence the combination of the two might be expected to yield a significant proportion of false positives.

The validation exercise also sought to establish the boundaries/limits that might be applicable for the process. In other words, to identify any circumstances where, at the Tier 1 level, it may not be fully applicable. The following (limited) conditions, which are mainly determined by the known limitations of the available exposure prediction models (ECETOC, 1997), are those where the ECETOC scheme appears unsuitable for the assessment of workplace risks:

- Mists (liquid aerosols);
- fumes arising from the use of a material within a process;
- working situations not described within the suite of generic scenarios, e.g. confined spaces;
- abnormal exposure situations, e.g. spills.

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th %)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Use in a continuous process (with no process sampling)						
Solids (mg/m^3)	yes	High	1	0.01	Assumes respirable, low dust technique, non-fibrous and readily aggregating dust	EASE prediction is plainly wrong for a totally enclosed system.Revision consistent with EASE range
	no		1	0.01		
	yes	Moderate	1	0.01	Assumes inhalable, low dust technique, non-fibrous readily aggregating dust	
	no		1	0.01		
	yes	Low	0.1	0.01	EASE predicts zero based on granular	
	no		0.1	0.01		
Volatiles (ppm)	yes	High	0.1	0.01	Assumes no aerosols, 50 KPa vapour pressure and full containment	EASE prediction is plainly wrong for a totally enclosed system. Zero exposure foreseen which should equate to not >0.01 ppm
	no		0.1	0.01		
	yes	Moderate	0.1	0.01	Ditto, 15 KPa vapour pressure	
	no		0.1	0.01		
	yes	Low	0.1	0.01	1 KPa vapour pressure	
	no		0.1	0.01		
Use in a continuous process (with process sampling)						
Solids (mg/m^3)	yes	High	1	1	Assumes respirable, low dust technique, non-fibrous non-readily aggregating dust	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made accordingly. Consistent with EASE range
	no		5	5		
	yes	Moderate	1	0.1	Assumes inhalable, low dust technique, non-fibrous non-readily aggregating dust	
	no		5	0.5		
	yes	Low	0.01	0.01	Granular dust. EASE predicts zero. Zero shown as 0.01 mg/m^3	
	no		0.01	0.01		
Volatiles (ppm)	yes	High	200	20	Assumes no aerosols, 50 KPa vapour pressure, significant breaching, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made accordingly (and equating to c. EASE/10)
	no		500	50		
	yes	Moderate	50	5	Ditto, 15 KPa vapour pressure	
	no		100	10		
	yes	Low	3	0.5	1 KPa vapour pressure	
	no		10	1		
Use in a batch or other process (including related process stages e.g. filtration, drying) where opportunities for exposure arise e.g. sampling, dis/charging of materials						
Solids (mg/m^3)	yes	High	5	5	Assumes respirable, dry manipulation, non-fibrous non-readily aggregating dust	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made accordingly
	no		50	25		
	yes	Moderate	0.5	0.5	Assumes inhalable, dry manipulation, non-fibrous readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3	EASE appears to underpredict for non-LEV situation
	no		0.1	0.5		

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION (CONT'D)

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th %)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Volatiles (ppm)	yes	High	200	100	Asssumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made (prediction/2) to account for fact that opportunity for exposure is limited
	no		500	250		
	yes	Moderate	50	25	Ditto, 15 KPa vapour pressure	
	no		100	50		
	yes	Low	3	1	Ditto, 1 KPa vapour pressure	
	no		10	5		
Dis/charging the substance (or preparations containing the substance) to/from vessels						
Solids (mg/m^3)	yes	High	5	5	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		50	50		
	yes	Moderate	0.5	0.5	Assumes inhalable, dry manipulation, non-fibrous readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3	EASE appears to underpredict for non-LEV situation
	no		0.1	0.5		
Volatiles (ppm)	yes	High	200	100	Assumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by emitting task and not overall (8hr) activity. Revisions made (prediction/2) to account for fact that opportunity for exposure is limited
	no		500	250		
	yes	Moderate	50	25	Ditto, 15 KPa vapour pressure	
	no		100	50		
	yes	Low	3	3	Ditto, 1 KPa vapour pressure	
	no		10	10		
Roller application or brushing of adhesives and other surface coatings						
Solids (mg/m^3)	yes	High	5	1	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	EASE prediction driven by dry manipulation. Is essentially task based exposure and not 8hr activity. Revisions made (prediction/5) to account for fact that opportunity for exposure is limited
	no		50	10		
	yes	Moderate	0.5	0.5	Assumes inhalable, dry manipulation, non-fibrous readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	EASE appears to underpredict for non-LEV situation
	no		0.1	0.5		

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION (CONT'D)

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th%)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Volatiles (ppm)	yes	High	500	100	Assumes no aerosols in lieu of LEV presence, 50 KPa, wide dispersive use. Where no LEV then aerosols and segregation assumed	EASE prediction does not appear to adequately account for LEV effectiveness. Revisions made (prediction/5-20) to account for fact that opportunity for exposure is limited
	no		500	500		
	yes	Moderate	100	20	Ditto, 15 KPa vapour pressure	
	no		500	100		
	yes	Low	50	10	Ditto, 1 KPa vapour pressure	
	no		500	100		
Filling containers with the substance or its preparations						
Solids (mg/m^3)	yes	High	5	1	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made accordingly
	no		50	20		
	yes	Moderate	0.5	0.5	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3	EASE appears to underpredict for non-LEV situation
	no		0.1	0.5		
Volatiles (ppm)	yes	High	200	50	Assumes no aerosol formation, 50 KPa, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by emitting task and not overall (8hr) activity. Revisions made (prediction/4) to account for fact that opportunity for exposure is limited
	no		500	250		
	yes	Moderate	50	13	Ditto, 15 KPa vapour pressure	
	no		100	100		
	yes	Low	3	1	Ditto, 1 KPa vapour pressure	
	no		10	10		
Spraying of the substance or preparations containing the substance e.g. paints and coatings						
Solids (mg/m^3)	yes	High	10	10	Assumes respirable, dry crushing/grinding, non-fibrous, non-readily aggregating dust	
	no		200	200		
	yes	Moderate	1	1	Assumes inhalable, dry crushing/manipulation, non-fibrous, readily aggregating dust	
	no		20	20		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 or 1 mg/m^3 due to physical energy	
	no		1	1		
Volatiles (ppm)	yes	High	500	100	Assumes aerosol formation, 50 KPa vapour pressure, wide dispersive use. Where no LEV then direct handling with GV assumed	EASE does not appear to account for effectiveness of LEV. Revisions made (prediction/5-10) to account for fact that predictions significantly overestimate actual data
	no		1,000	1,000		
	yes	Moderate	200	50	Assumes aerosol formation, 15 KPa, non-dispersive use. Where no LEV then segregation assumed	
	no		500	500		
	yes	Low	200	20	Assumes aerosol formation, 1 KPa, non-dispersive use. Where no LEV then segregation assumed	
	no		500	100		

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION (CONT'D)

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th%)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Use for the formulation of liquid and solid-based products by mixing, blending or calendaring						
Solids (mg/m^3)	yes	High	5	5	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		50	50		
	yes	Moderate	0.5	0.5	Assumes inhalable, dry manipulation, non-fibrous readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	EASE appears to underpredict for non-LEV situation
	no		0.1	1		
Volatiles (ppm)	yes	High	200	100	Assumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by emissions task and not overall (8hr) activity. Revisions made (prediction/5 - 10) to account for fact that opportunity for exposure is limited in such activities
	no		500	500		
	yes	Moderate	50	20	Ditto, 15 KPa vapour pressure	
	no		100	100		
	yes	Low	3	3	Ditto, 1 KPa vapour pressure	
	no		10	10		
Use as a laboratory reagent						
Solids (mg/m^3)	yes	High	1	0.5	Assumes respirable, low dust technique, non-fibrous, non-readily aggregating dust	EASE prediction clearly inappropriate for laboratory situation. Effectiveness of LEV (fume cupboard) not adequately addressed
	no		5	5		
	yes	Moderate	1	0.1	Assumes inhalable, low dust technique, non-fibrous non-readily aggregating dust	
	no		5	0.5		
	yes	Low	0.1	0.01	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	Zero exposure foreseen which equates to 0.01 mg/m^3
	no		0.1	0.1		
Volatiles (ppm)	yes	High	200	10	Assumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by emissions task and not overall (8hr) activity. Revisions made (prediction/5 - 20) to account for fact that opportunity for exposure is limited in such activities and fume cupboards effective
	no		500	50		
	yes	Moderate	50	1	Ditto, 15 KPa vapour pressure	
	no		100	10		
	yes	Low	3	0.1	Ditto, 1 KPa vapour pressure	
	no		10	5		
Use as a lubricant (incl metalworking fluids) and machining of solids						
Solids (mg/m^3)	yes	High	10	10	Assumes respirable, mobile, dry grinding and crushing, non-fibrous, non-readily aggregating dust	EASE not intended to address use of solid materials within solutions, but exposure estimates appear reasonable when compared to published data (total matter)
	no		200	200		
	yes	Moderate	10	5	Assumes inhalable, dry grinding and crushing, non-fibrous, non-readily aggregating dust	
	no		200	50		
	yes	Low	0.1	1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	Zero exposure does not adequately account for kinetic energy of activity
	no		0.1	10		

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION (CONT'D)

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th%)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Volatiles (ppm)	yes	High	200	200	Assumes aerosols, 50 KPa vapour pressure, no - dispersive use. Where no LEV then segregation assumed	EASE prediction driven by tasks and open use of product. Revisions made (prediction/2-5) to account for fact that opportunity for exposure is limited in such activities
	no		500	500		
	yes	Moderate	200	100	Ditto, 15 KPa vapour pressure	
	no		500	500		
	yes	Low	200	50	Ditto, 1 KPa vapour pressure	
	no		500	100		
Production of products or articles from substance by compression, tabletting, extrusion or pelletisation						
Solids (mg/m^3)	yes	High	5	5	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		50	50		
	yes	Moderate	0.5	0.5	Assumes inhalable, dry manipulation, non-fibrous readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	EASE appears to underpredict for non-LEV situation
	no		0.1	1		
Volatiles (ppm)	yes	High	200	100	Assumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	Revisions made (prediction/2) to account for fact that typical effectiveness of LEV for such activities underestimated
	no		500	500		
	yes	Moderate	50	25	Ditto, 15 KPa vapour pressure	
	no		100	100		
	yes	Low	3	3	Ditto, 1 KPa vapour pressure	
	no		10	10		
Use in a closed batch process i.e. only opportunity for breaching via sampling						
Solids (mg/m^3)	yes	High	1	0.1	Assumes respirable, low dust technique, non-fibrous, non-readily aggregating dust	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made accordingly
	no		5	1		
	yes	Moderate	1	0.1	Asumes inhalable, low dust technique, non-fibrous, non-readily aggregating dust	
	no		5	1		
	yes	Low	0.1	0.01	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	Zero exposure foreseen which equates to 0.01 mg/m^3
	no		0.1	0.1		
Volatiles (ppm)	yes	High	0.1	0.1	Assumes no aerosols, 50 KPa vapour pressure, no breaching where 'LEV' indicated and use of LEV where 'no LEV' shown	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made (prediction/10) to account for fact that opportunity for exposure is limited in such activities
	no		200	20		
	yes	Moderate	0.1	0.1	Ditto, 15 KPa vapour pressure	
	no		50	5		
	yes	Low	0.1	0.01	Ditto, 1 KPa vapour pressure	
	no		3	3		

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION (CONT'D)

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th%)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Use as a blowing agent						
Solids (mg/m^3)	yes	High	N/a	N/a		
	no		N/a	N/a		
	yes	Moderate	N/a	N/a	Soid substances assumed not to be used for such applications	
	no		N/a	N/a		
	yes	Low	N/a	N/a		
	no		N/a	N/a		
Volatiles (ppm)	yes	High	200	40	Assumes gas, non-dispersive use and breached closed system	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made (prediction/5) to account for fact that opportunity for exposure is limited in such activities
	no		500	100		
	yes	Moderate	50	10	Assumes no aerosols, 15 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	
	no		100	20		
	yes	Low	3	0.5	Ditto, 1 KPa vapour pressure	
	no		10	2		
Use for coating/treatment of articles, etc (including cleaning). by dipping or pouring						
Solids (mg/m^3)	yes	High	1	1	Assumes respirable, low dust technique, non-fibrous, readily aggregating dust	
	no		5	5		
	yes	Moderate	1	1	Assumes inhalable, low dust technique, non-fibrous, readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	EASE appears to underpredict for non-LEV situation
	no		0.1	0.5		
Volatiles (ppm)	yes	High	200	200	Assumes no aerosols, 50 KPa vapour pressure, wide dispersive use. Where no LEV then segregation assumed	
	no		500	500		
	yes	Moderate	50	50	Ditto, 15 KPa vapour pressure	
	no		100	100		
	yes	Low	3	3	Ditto, 1 KPa vapour pressure	
	no		10	10		
Use as a fuel						
Solids (mg/m^3)	yes	High	5	5	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		50	50		
	yes	Moderate	5	5	Assumes inhalable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		50	50		
	yes	Low	0.1	1	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	EASE appears to underpredict for typical uses e.g. coal
	no		0.1	5		

APPENDIX U: BASIS FOR THE EASE ESTIMATES OF EXPOSURE AND MODIFICATIONS TO THE INHALATION EASE PREDICTION (CONT'D)

Exposure scenario	LEV	Fugacity	Predicted EASE exposure (95 th%)	Exposure prediction adopted by ECETOC	Comments	Rationale for deviation from EASE prediction
Volatiles (ppm)	yes	High	200	20	Assumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by assumption that fuel is not consumed. Relevant to distribution but not use. Revisions made (prediction/10) to account for fact that opportunity for exposure is limited in such activities
	no		500	50		
	yes	Moderate	50	5	Ditto, 15 KPa vapour pressure	
	no		100	10		
	yes	Low	3	0.1	Ditto, 1 KPa vapour pressure	
	no		10	1		
Use as a fuel						
Solids (mg/m^3)	yes	High	5	5	Assumes respirable, dry manipulation, non-fibrous, non-readily aggregating dust	
	no		50	50		
	yes	Moderate	0.5	0.5	Assumes inhalable, dry manipulation, non-fibrous readily aggregating dust	
	no		5	5		
	yes	Low	0.1	0.01	Granular dust. EASE predicts zero. Zero shown as 0.1 mg/m^3 due to physical energy	Zero exposure foreseen which equates to 0.01 mg/m^3
	no		0.1	0.01		
Volatiles (ppm)	yes	High	200	40	Assumes no aerosols, 50 KPa vapour pressure, non-dispersive use. Where no LEV then segregation assumed	EASE prediction driven by sampling task and not overall (8hr) activity. Revisions made (prediction/5) to account for fact that opportunity for exposure is limited in such activities
	no		500	100		
	yes	Moderate	50	10	Ditto, 15 KPa vapour pressure	
	no		100	20		
	yes	Low	3	0.5	Ditto, 1 KPa vapour pressure	
	no		10	2		

APPENDIX V: WORKPLACE SCENARIOS USED AS THE PRELIMINARY BASIS FOR THE VALIDATION AT TIER 1

Exposure scenario	Acceptable risk?
Volatile substances	
Use of acetone as a large volume raw material (RM) in a closed continuous plant. 500 tpd.	Yes
Spray application of acetone as a solvent-based lacquer in a factory (spray booth). 10 litres per day.	Yes
Spray application of amyl acetate as a solvent-based lacquer in a factory (no LEV). 1 litre per day.	No
Use of amyl acetate as a solvent in the batch manufacture of a product. 10 tpd. LEV to reaction vessel.	Yes
Use of cyclohexane as an on-site RM in a closed continuous plant. 1,000 tpd.	Yes
Use of cyclohexane as a solvent in floor varnishes. 1 kg applied. General ventilation only.	No
Use of 1,4-dichlorobenzene as a medium volume RM in a closed batch plant. 10 tpd.	Yes
Use of 1,4-dichlorobenzene as a medium volume RM in a batch plant with LEV. 10 tpd.	Yes
Batch manufacture of a specialty coating using ethylamylketone as the solvent. 500 litres batch size, 2 batches per day. LEV system.	Yes
Brush application of an ethylamylketone-based coating (no LEV but GV). 0.5 litres per day.	Yes
Loading road tankers with n-hexane. No LEV.	No
Use of n-hexane as an RM in a batch plant plant. 10 tpd. LEV to reaction vessel.	Yes
Use of monochlorobenzene as an solvent adhesive for hand lay-up in the rubber industry. General ventilation only. 1 kg/d.	No
Production of monochlorobenzene-based adhesive. Batch process. LEV. 0.5 tonnes per batch. 2 batches/day.	Yes
Use of pentane as a blowing agent in the manufacture of foams. 100 kg/d in a semi-enclosed system.	Yes
Use of pentane as propellant in a cosmetic aerosol. Filling line. Contained system. 300 kg/d.	Yes
Application of toluene-based paint on door/window trims. GV only.	Yes
Batch manufacture of a specialty ink using toluene as the solvent. 50 litres batch size, 2 batches per day. No LEV system.	No
Batch manufacture of a specialty paint using xylene as the solvent. 5,000 litres batch size, 6 batches per day. LEV available.	Yes
Batch manufacture of a specialty ink using xylene as the solvent. 100 litres batch size. LEV provided.	Yes
Batch manufacture of an ammonia-based cleaning product. 100 litres batch size, 4 batches per day. LEV system.	Yes
Batch manufacture of a butyl acrylate-based varnish. 500 litres batch size, 10 batches per day. LEV available.	Yes
Application of butyl acrylate-based varnish on floor. Windows closed (no LEV).	No
Use of hydrogen fluoride as a large volume RM in a closed system continuous plant. 1,000 tpd.	Yes
Use of nitric acid as a RM in a closed system plant. 10 tpd.	Yes
Use of nitric acid as a laboratory reagent. LEV (fume cupboard). 250 mls used per application (6/day).	Yes
Formulation of a phenol-based industrial disinfectant by batch. 1 tpd. No LEV to process.	No
Use of acrolein as an RM in a closed system plant. 20 tpd.	Yes
Use of acrolein as an RM in a batch chemical plant. 50 kg pumped from drums. 2 batch per day. LEV to vessel.	No
Use of carbon tetrachloride as a spot cleaner. 5 mls per application. No LEV. 10 applications per day.	No
Use of chloroform as a histopathology solvent. No LEV but good GV. 5 mls used per applicant (20/day).	Yes
Use of fluorine as an RM in a closed system plant. 1 tpd. High integrity sytem due to acute effects.	Yes
Use of monochloroethane as a process chemical in a batch plant. 100 kg/d. LEV available.	
Use of phosgene within a process stage in a closed batch plant. 0.1 tpd. High integrity sytem due to acute effects.	Yes

APPENDIX V: WORKPLACE SCENARIOS USED AS THE PRELIMINARY BASIS FOR THE VALIDATION AT TIER 1 (CONT'D)

Exposure scenario	Acceptable risk?
Solid substances	
Use of titanium dioxide in the m/f of a specialty paint. Charge from sacks and some ventilation. 1 tpd.	Yes
Use of TiOx as a pigment in bulk paint production. Closed system. 50 tpd.	Yes
Use of a reactive dye in industrial dyeing of fabric. Closed system. 10 kg/d.	Yes
Weighing bulk de-dusted reactive dye to form batch recipe in dye kitchen. No LEV. 2 kg per batch.	No
Use of zinc stearate as release agent in general rubber industry. Waxed form. LEV to moulds. 50 kg/d.	Yes
Discharge to sacks from Zn sterate manufacture. LEV. 500 tpd.	No
Use of carbon black in manufacture of synthetic rubber for tyres. Carbon black supplied to rubber mills from bulk. 500 kg/d.	No
Manufacture of photocopier toners using carbon black. Enclosed process. 0.1 tpd.	Yes
Use of zinc oxide as filler in batch manufacture of antiseptic cream.100 kg per batch. No LEV.	No
Hand application of ZnO powder in manufacture of enamels. 50 g/day. No LEV.	Yes
Hand batch manufacture of cement at building site. No LEV. Open air. 150 kg per batch. Ready aggregation.	No
Machine manufacture of concrete. No LEV. Semi-enclosed system. 200 kg per batch.	Yes
Use of calcium hydroxide as effluent treatment additive. GV only. 500 kg/d.	No
Use of calcium hydroxide as agrochemical. Tractor application from sacks. No LEV. 200 kg/d.	No
Use of trimelletic anhydride as an RM for manufacture of a plasticiser. Addition from IBC. 500 kg per batch. Contained system.	Yes
Filling of TMA into sacks at production facility. LEV. 5 tpd.	Yes
Manufacture of bread in a small bakers. Flour exposure. 50 kg per batch. No LEV.	No
Large scale rolling and cutting of pastry in pie factory. Flour exposure. 250 kg per batch. No LEV.	No
Use of tungsten carbide in batch manufacture of grinding wheels. Addition to blender from sacks. No LEV. 150 kg/d.	Yes
Spray application of tungsten carbide for descaling of metal structure. Open air. No LEV. 100 kg/d.	No
Batch formulation of agrochemical. 150 kg per batch of endosulfan from drums, 4 batches per day. LEV.	Yes
Filling of agrochemical (5% endosulfan a.i.) into 500 g boxes. 300 kg/d. No LEV.	No
Use of lead chromate in batch manufacture of a specialty coating. 150 kg per batch, 10 batches per day. LEV available.	No
Use of lead chromate in ceramics by hand application of powder. No LEV. 50g/d.	No
Use in pearl form for creation of NaOH solution. No LEV. 5 kg per batch.	Yes
Use of NaOH in crystal form for industrial liquid cleaner. No LEV. 20 kg/d.	Yes
Use of NaCN as a medium volume RM. LEV. NaCN in egg form. 200 kg/d.	Yes
Use of NaCN as a metal finishing chemical (addition to solution). No LEV. NaCN in egg form. 2 kg/d.	No
Use of sulphur as an RM in the chemical industry. 10 tpd. No LEV.	No
Use of sulphur as an agrochemical by dusting. 3 kg/d. No LEV.	No
Bulk use of NaCl in chemical industry to precipitate reaction salts. Closed system. 1 tpd.	Yes
Use of NaCl in textiles industry to fix dyes. Charging to vats. No LEV. 50 kg per batch.	Yes

APPENDIX W: HERA INFORMATION USED IN VERIFICATION OF THE ECETOC TIER 1 CONSUMER ASSESSMENT

Table W.1: HERA information used in verification of the ECETOC Tier 1 consumer assessment

Chemical name	CAS number[a]	Tonnage	Main use cat.	Log K_{ow}	VP (hPa)	Mol weight	EU hazard class	Consumer use category	Fraction in product	NOAEL	HERA aggregate exposure (mg/kg/day)
AHTN (6-Acetyl-1,1,2,4,4,7 -hexamethyltetraline)	1506-02-1 and 21145-77-7	1,000 - 5,000	WDU [b]	5.7	0.000682	258.41	Xn; R22	Soap and detergents	0.005	5 mg/kg/day rat, oral, 90 day daily dose	0.000033
HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta-gamma-2-benzopyran)	1222-05-5	1,000 - 5,000	WDU [b]	5.9	0.000727	258.41	Unclassified	Soap and detergents	0.009	150 mg/kg/day rat, oral 90 day daily dose	0.00007
FWA-5 (benzenesulphonic acid, 2,2'-([1,1'-biphenyl]-4,4'-diyldi-2, 1-ethenediyl)bis-, disodium salt)	27344-41-8	~1,000	WDU [b]	-2.32	7×10^{-18}	562.58	Xi; R36	Soap and detergents	0.001	190 mg/kg/day rat, oral, lifetime daily dose	0.00103
Fatty acid salts	143-07-7, 85711-09-3	71,000	WDU [b]	0.2 - 6.1	1.1×10^{-9} - 4.5×10^{-14}	210.36 -378.69	Unclassified	Soap and detergents	0.2	7500 mg/kg/day (LOAEL) rat, oral,16 week daily dose	0.0029
Zeolite A	1318-02-1, 1344-00-9	650,000	WDU [b]	Crystalline solid (NA)	Crystalline solid (NA)	284 and 2,190	Unclassified	Soap and detergents	0.34	60 mg/kg/day rat, oral, 2 year daily dose	0.0127
Sodium tripolyphosphate	7758-29-4	300,000	WDU [b]	Inorg solid (NA)	Negligible (solid)	367.86	Unclassified	Soap and detergents	0.63	225 mg/kg/day rat, oral, 2 year daily dose	0.033

Table W.1: HERA information used in verification of the ECETOC Tier 1 consumer assessment (cont'd)

Chemical name	CAS number [a]	Tonnage	Main use cat.	Log K_{ow}	VP (hPa)	Mol weight	EU hazard class	Consumer use category	Fraction in product	NOAEL	HERA aggregate exposure (mg/kg/day)
Alcohol ethoxysulphates	102783-14-2, 96130-61-9	260,000	WDU [b]	Liquid unknown	Liquid negligible	305-699	Xi; R38,41	Soap and detergents	0.27	75 mg/kg/day rat, oral 2 year daily dose	0.029
TAED (tetraacetylethylenediamine)	10543-57-4	61,000	WDU [b]	-0.1	4.8×10^{-8}	228.25	Unclassified	Soap and detergents	0.13	90 mg/kg/day rat, oral, 90 day daily dose	0.000013
Alkyl sulphate	1120-01-0, 96690-75-4	102,000	WDU [b]	1.6 - 4.6	6.3×10^{-13} 3.7×10^{-15}	288.4-372.54	Xn; R22,38, 41	Soap and detergents	0.2	61 mg/kg/day rat, oral, 90 day daily dose	0.0059
Perboric acid, sodium salt (monohydrate: PB1) (tetrahydrate: PB4)	10332-33-9 10486-00-7	280,000	WDU [b]	Inorg solid (NA)	Negligible	99.8 153.9	Xn; R22,36/38 Xi; R36	Soap an detergents	0.31	100 mg/kg/day rat, oral, dev study (~ 28 day, dose 4d/wk)	< 0.0008
Linear alkylbenzene sulphonate (LAS)	1322-98-1, 85117-50-6	400,000	WDU [b]	3.3	3.2×10^{-15}	342.4	Xn; R22,38, 41	Soap and detergents	0.37	85 mg/kg/day rat, oral, 9 month daily dose	0.004

[a] Many substances are described by multiple CAS numbers. In the table a maximum of 2 CAS numbers per substance are shown.

[b] WDU = Wide dispersive use

The key parameters for the Tier 1 consumer assessment are those listed in the columns EU Hazard Classification, Fraction in product, and NOAEL.

The last column of the table gives the value of the aggregate systemic exposure obtained by the HERA assessment as a reference.

Table W.2: Comparison of HERA consumer risk assessment outcomes with ECETOC conclusions

Chemical name	Consumer use category	Fraction in product	HERA aggregate	ECETOC total surrogate	Ratio	ECETOC tier at which 'no concern' is identified
			Exposure (HAE) (mg/kg/day)	Exposure (ETSE) (mg/kg/day)	ETSE/HAE	
AHTN (6-Acetyl-1,1,2,4,4,7-hexamethyltetraline)	Soap and detergents	0.005	0.000033	0.006	182	Tier 0
HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran)	Soap and detergents	0.009	0.00007	0.01	143	Tier 0
FWA-5 (benzenesulphonic acid, 2,2'-([1,1'-biphenyl]- 4,4'-diyldi-2,1-ethenediyl)bis-, disodium salt)	Soap and detergents	0.001	0.00103	0.0012	1.2	Tier 0
Fatty acid salts	Soap and detergents	0.2	0.0029	0.24	83	Tier 0
Zeolite A	Soap and detergents	0.34	0.0127	0.41	32	Tier 1
Sodium tripolyphosphate	Soap and detergents	0.63	0.033	0.77	23	Tier 1
Alcohol ethoxysulphates	Soap and detergents	0.27	0.029	0.33	11	Tier 1
TAED (tetraacetylethylenediamine)	Soap and detergents	0.13	0.000013	0.16	12,300	Tier 0
Alkyl sulphate	Soap and detergents	0.2	0.0059	0.23	39	Tier 1
Perboric acid, sodium salt (monohydrate: PB1) (tetrahydrate: PB4)	Soap and detergents	0.31	< 0.0008	0.37	462.5	Tier 1
Linear alkylbenzene sulphonate (LAS)	Soap and detergents	0.37	0.004	0.45	112.5	Tier 1

Table W.3: Comparison of ECETOC and EU existing chemicals risk assessments for consumer uses

Chemical name	CAS number	Critical use	Consumer use category	Conclusion EU consumer risk assessment (use specific)[a]	Conclusion ECETOC Tier 1 consumer risk assessment
Acrylic acid	79-10-7	Wide dispersive	C02 Adhesives	*(ii)*	NFRR [b]
			C11 Paper products	*(ii)*	NFRR [b]
Methyl methacrylate	80-62-6	Wide dispersive	C12 Paints	*(ii)*	FRR [c]
			C02 Adhesives	*(ii)*	NFRR [b]
Methyl acetate	79-20-9	Wide dispersive	C02 Adhesives	*(ii)*	NFRR [b]
			C01 Artists' supplies	*(ii)*	NFRR [b]
Naphthalene	91-20-3	Wide dispersive	C19 Construction materials	*(ii)* *[the overall conclusion is (iii) due to insecticide consumer use]*	FRR [c]
1,4-Dichlorobenzene	106-46-7	Wide dispersive	C16 Soaps and detergents	*(ii)*	FRR [c]
Toluene	108-88-3	Wide dispersive	C02 Adhesives	*(iii) [due to acute irritation]*	NFRR [b] (irritation warning)
			C03 Automotive care	*(ii)*	NFRR [b]
			C12 Paints	*(iii)*	FRR [c]
Cyclohexane	110-82-7	Wide dispersive	C02 Adhesives	*(iii)*	NFRR [b]
Ethyl acetoacetate	141-97-9	Wide dispersive	C12 Paints	*(ii)*	NFRR [b]
			C16 Soaps and detergents	*(ii)*	FRR [c]
Methyl tert-butyl ether	1634-04-4	Wide dispersive	C03 Automotive care	*(ii)*	NFRR [b]
Hydrogen peroxide	7722-84-1	Wide dispersive	C14 Polishes	*(iii)*	FRR [c]
			C16 Soaps and detergents	*(iii)*	FRR [c]

[a] *(ii)*: 'There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.'

(iii): 'There is a need for limiting the risks; risk reduction measures which are being applied shall be taken into account.'

[b] NFRR: No Further Risk Assessment Required.

[c] FRR: Further Risk Assessment Required

APPENDIX AA: DEVELOPMENT OF EUSES LOOK-UP TABLE

The fundamental principles and methodology of the EU TGD for risk assessment of new and existing substances (EC, 1996c, 2003b) are implemented in the computer program EUSES (European Union System for the Evaluation of Substances). This was designed as a decision-support system for the evaluation of the risks of substances to man and the environment. The documentation and program can be obtained from the European Chemicals Bureau, Ispra, Italy (http://ecb.jrc.it/Euses/).

The main outputs of EUSES are local and regional risk characterisation ratios (RCRs) for several environmental compartments (air, surface water, sediment, soil, biota). An RCR is the ratio of the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC). A substance is potentially of concern when the RCR is greater than 1. The core EUSES model (without the embedded models Simple Treat, Simple Box and the effect and risk characterisation) requires 466 input parameters, 961 connections between parameters and 132 defaults (Berding *et al*, 1999). In addition, the number of emission scenarios is large because an emission scenario is determined by a combination of one of the 4 main categories (MC), one of the 15 industry categories (IC) and one of the 55 use categories (UC). The MCs were intended originally to provide a general impression of the relevance of the exposure during the whole life-cycle. In the context of environmental risk assessment, MCs are often used to characterise release scenarios for the estimation of emissions to the environment at individual stages of the life-cycle, i.e. at production, formulation and industrial/professional use. They can therefore be allocated to release fractions, which are used as default values where specific information is lacking. The four MCs are (I) 'use in closed systems', (II) 'use resulting in inclusion into or onto a matrix', (III) 'non-dispersive use' and (IV) 'wide dispersive use' (EC, 1996c, 2003a). The IC specifies the branch of industry (including personal and domestic use, and use in the public domain) where considerable emissions occur by application of the substance as such, or by the application and use of preparations and products containing the substance. The use category (UC) specifies the specific function of the substance.

It can be concluded that EUSES is a complex model. Running this model requires a significant amount of substance-specific data together with a thorough understanding of release and emissions scenarios. As such, in practice the EUSES model is only useable for priority substances (for which a comprehensive data set is available), and can only be handled by experienced risk assessors.

Key drivers of EUSES model

Some input parameters in EUSES have a more important contribution to the RCRs than others. Thus in attempting to simplify the exposure assessment these key drivers need to be identified.

Some sensitivity analyses on EUSES have already been performed to identify these key parameters. Jager *et al* (1997, 1998, 2000) identified tonnage and the release fraction (based on the release scenario) as important input parameters for the exposure assessment of the aquatic compartment (water and sediment), the sewage treatment plant and the atmosphere. Biodegradability can be important for almost every compartment. The organic carbon-water partition coefficient (K_{oc}) and the bioconcentration factor (BCF) are important in respectively the terrestrial compartment and the fish and worm eating predators. Both K_{oc} and BCF are highly correlated with the octanol-water partitioning coefficient (K_{ow}) (Schrap and Opperhuizen, 1990).

Berding (2000) carried out a local sensitivity analysis on the estimation of regional background concentrations for a number of substances. It was not possible to link classes of substances with particular physico-chemical and biodegradation properties to sensitivities of input parameters. Nevertheless, some correlations between model parameters and sensitivities could be established. The lower the degradation rate in a compartment, the higher the sensitivity to the physico-chemical data. The sewage treatment plant model plays only a minor part in calculating regional background concentrations. A sensitivity analysis on the local PEC, which is always higher and therefore more relevant than the regional PEC, was not performed.

Further, volatility is a critical parameter for the exposure assessment of highly volatile substances (as these substances will eventually end up in the atmospheric compartment rather than the aquatic or terrestrial).

Consequently, the key parameters for an environmental risk assessment are: on the exposure side: tonnage, release scenario, biodegradability, lipophilicity (octanol/water partitioning) and volatility; and on the effects side: ecotoxicity. Release scenario and biodegradability are specified in EUSES as categorical (respectively nominal and ordinal) parameters. All other key parameters are continuous variables.

Effect of key parameters on EUSES output

Release scenarios

In EUSES (and the TGD), a large number of release scenarios are defined (A/B Tables in the TGD, dealing with emissions at different life-cycle stages, depending on a chemical's industry and use category). Essentially, these scenarios can be reduced to two distinct release options: point source and wide dispersive release. All release scenarios are effectively linear combinations of these two basic options, with a different weighting of the two (EC, 1996c, 2003a).

In this exercise, the two options for release were production (point source emission assuming 100% release) and wide dispersive use (private use, based on the TGD detergent scenario IC5/UC9). The parameters of the two scenarios are shown in Table AA.1.

Table AA.1: Parameters of the production and wide dispersive use scenario

Local	Point source or production scenario	Wide dispersive or private use scenario	Unit
Local direct emission to air	6.85	0	kg/d
Local emission to wastewater	266.8	0.542	kg/d
Number of days for emission	365	365	d
Fraction to air	0.025	0	-
Fraction to wastewater	0.974	0.99	-
Fraction to industrial soil	0.001	0.01	-
Fraction main source	1	0.002	-
Number of days	365	365	d

The release fractions presented in Table AA.1 can be overly conservative especially for particular uses such as intermediate chemicals for which emissions are extremely low. The release scenarios could therefore be further refined based on the MC. In order to determine a conservative and representative release fraction for each MC, a quantification of all possible release fractions (defined in the A tables of the TGD) is needed. Verdonck *et al* (2003) attempted to characterise the probability distribution of release fractions per MC. However, no information about the frequency of occurrence of specific scenarios (industry and use categories, tonnage, classes of physico-chemical properties) in the overall chemical universe was available. It was concluded that an extensive database of chemicals and their use scenarios would be needed to conduct this analysis successfully.

Parameters with linear effect

The effect of tonnage and ecotoxicity on RCR is more easy to predict because the tonnage and ecotoxicity are linearly related to the RCR. If, for example, tonnage is doubled, RCR is also doubled. Similarly, if the PNEC is decreased twofold, the RCR will be doubled. As the effects of these parameters were highly transparent, they were not assessed further in this work.

Parameters with non-linear effect

The lipophilicity (expressed in the octanol/water partitioning coefficient K_{ow}) is a continuous variable, ranging for the log transformed value from less than 0 (highly hydrophilic) to greater than 6-7 (highly hydrophobic). Log K_{ow} has a continuous effect on the RCR except for a step-increase in the RCR where log K_{ow} equals 5 due to specific correction factors in the EUSES model that are activated if log K_{ow} is greater than or equal to 5 (EC, 1996c, 2003a).

Volatility (expressed as the air/water partition coefficient K_{aw} or dimensionless Henry's Law Constant (H)) is a continuous variable that ranges from very low (close to 0) to very high (order of magnitude 10E+6) value. The effect of H on the RCR is especially meaningful when the environmental compartment of concern is changed due to H. Henry´s Law Constant is equal to the ratio of the vapour pressure and the water solubility (SOL). In the EUSES model the vapour pressure (VP) is used instead of the Henry´s Law Constant.

The dependence of the water solubility (SOL) on log K_{ow} was taken into account using the QSAR of Hansch *et al* (1968) to calculate solubility from K_{ow}:

$$\text{Log (SOL)} = -1.214 \times \log K_{ow} + 0.85$$

where SOL is the water solubility in mol/l

This way, unrealistic combinations of log K_{ow} and SOL were avoided.

For biodegradability, four standard options are available in EUSES: non-biodegradable, inherently biodegradable, readily biodegradable failing the 10-day window, and readily biodegradable. The effect of these four options was examined, and a first screening indicated that only two options really needed to be considered: readily biodegradable and non-biodegradable. The other two options are intermediates of these two extremes, with results closest to the 'non-biodegradable' option.

Other (fixed) EUSES input parameters

The properties of the hypothetical substance 'hypotheticum' (as described in the publications on the SimpleTreat model, Struijs *et al*, 1991) were used. The EUSES default parameters were used as much as possible. The physico-chemical properties of hypotheticum are shown in Table AA.2. The emission related parameters are shown in Table AA.3.

Table AA.2: Physico-chemical properties for hypotheticum

Physico-chemical properties	Value	Unit
Melting point	-35	°C
Molecular weight	200	g/mol
Octanol-water (log K_{ow})	variable	-
Water solubility	dependant on K_{ow}	mg/l
Vapour pressure	variable	Pa
Predicted No-Effect Concentration	0.00001	kg/m^3

Table AA.3: Emission data for hypotheticum

Emissions	Tonnes/year	Value	Unit
Production volume EU	1,000	2,739	kg/d
Volume imported in EU	0	0	kg/d
Volume exported from EU	0	0	kg/d
Tonnage EU	1,000	2,739	kg/d
Production volume region	1,000	273.9	kg/d
Tonnage region	1,000	273.9	kg/d
Connection fraction to STP		0.8	

Response analysis

Response plots

Based on the identification of the EUSES key parameters, the effect of two release scenarios (wide dispersive use and point source), two biodegradation options (readily and non-biodegradable), the continuum of log K_{ow} and the continuum of log VP on the RCR_{max} was investigated. The RCR_{max} is the maximum local RCR found for either the aquatic, the terrestrial or the sediment compartment, i.e. the compartment of most concern.

Response plots are three-dimensional displays of a response variable (RCR_{max} in this case) on the regular grids of the explanatory variables (log K_{ow} and VP in this case). A Monte Carlo type of analysis was used to create response plots. Uniform distributions were assumed for log K_{ow} and log VP with their respective ranges 0 to 7 and – 2 to 6. Independent random samples were then taken from each distribution in several runs (using the efficient sampling algorithm Latin Hypercube (McKay, 1988)). In each run, RCR_{max} was calculated using the EUSES model. The water solubility was also varied based on log K_{ow} as described above. After many runs, enough data were gathered to construct the response plots.

The results from these four scenarios are represented as a series of three-dimensional plots, representing the RCR_{max} (for a given tonnage, ecotoxicity, release scenario and biodegradability) in one axis as a function of log K_{ow} and log VP in the remaining axis in so-called response plots.

Next, based on the shape of the response plots, the continuum of combinations of log K_{ow} and VP was then divided into a limited number of fields in the parameter space, within which distinctive groups of the RCR_{max} occur. This division was the basis for the creation of the RCR_{max} look-up table.

The EUSES program is a so-called 'closed software', making it impossible to perform an automatic Monte Carlo or sensitivity analysis (Berding, 2000) as the EUSES software needs to be controlled to assign automatically different values for log K_{ow} and log VP. For this research, an unofficial spreadsheet version of EUSES was made available by RIVM (RIVM, 2003)[a]. This EUSES spreadsheet was benchmarked against the official EUSES program, and was found to be a sufficiently accurate surrogate. The @RISK package (Palisade, 2003) was used for the Monte Carlo analysis in Microsoft Excel. The sampled inputs together with the simulated output (RCR_{max}) were stored and after the simulations were introduced in Tecplot (Dundas Software, 2001) to obtain a three-dimensional view of the results. The number of Monte Carlo simulations was set at 1,000. Figure AA.1 shows 1,000 combinations of log K_{ow} and log VP are 'large' enough to be randomly distributed over the parameter space of log K_{ow} and log VP while covering the range totally for all scenarios.

Figure AA.2 illustrates the effect of log K_{ow} and log VP on the RCR_{max}. On the basis of these figures a division was made into 4 distinct groups of the RCR_{max}. For log K_{ow}, two distinct groups can clearly be discriminated: log K_{ow} greater and less than 5. For log VP, two groups can also be distinguished: log VP greater and less than 0, as for log VP greater than 0, the RCR_{max} decreases significantly.

[a] RIVM does not take responsibility on the performance of the unofficial EUSES spreadsheet.

Figure AA.1: Thousand sampled points in the log K_{ow} – log VP space

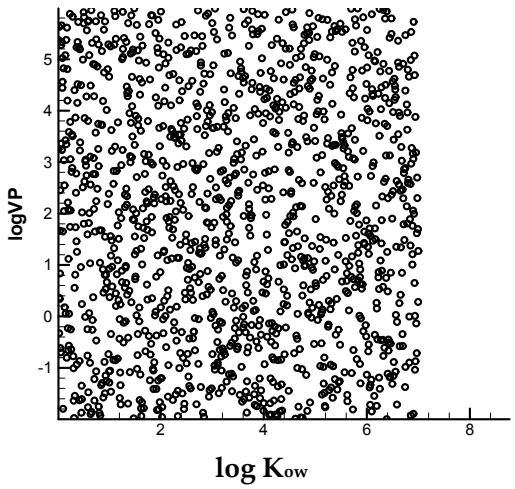
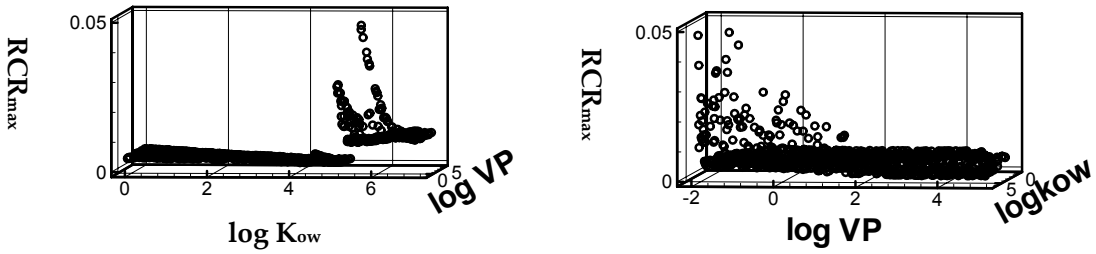
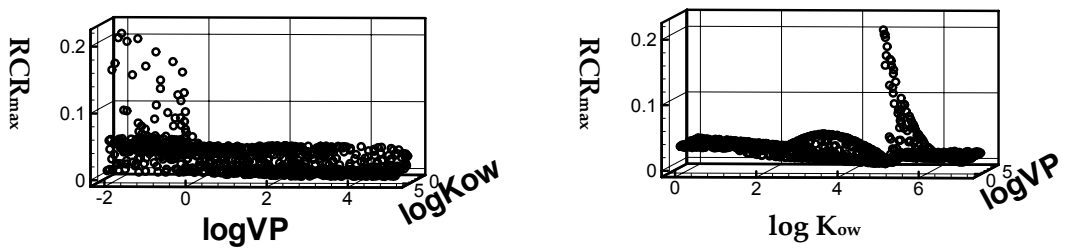


Figure AA.2: Three-dimensional view of log K_{ow}, log VP and RCR_{max}

Private use, readily biodegradable



Private use, non-biodegradable



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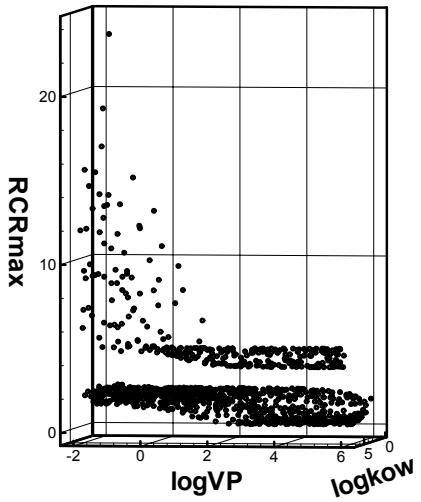
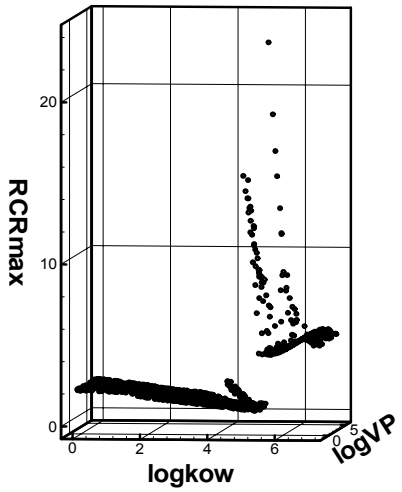
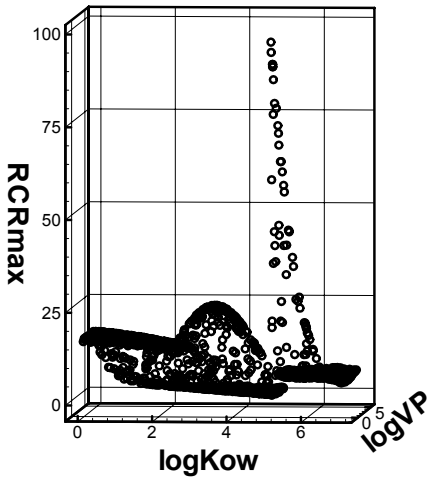
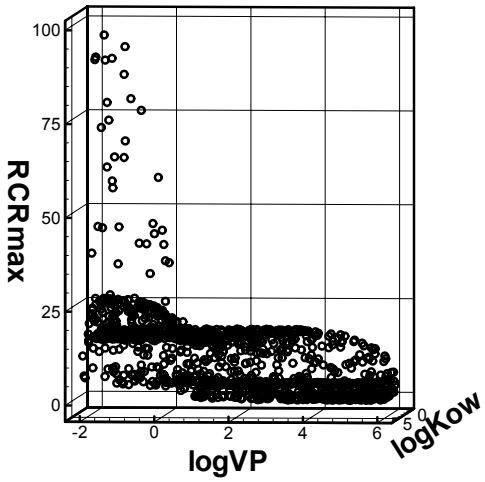




Production use, non-biodegradable





RCR look-up table

A distribution of RCR_{max} values was found for each defined class of log K_{ow}, log VP, release scenario and biodegradability. The maximum, 95th percentile and median were calculated for each class. The RCR_{max} summary statistics for two release scenarios (production and private use), two biodegradability classes (readily and non-biodegradable), two classes of log VP and two classes of log K_{ow} are shown in Table AA.4.

Table AA.4: RCR_{max} look-up table (95^{th} percentile, based on 1,000 iterations)

		Production scenario		Private use scenario	
Log (K_{ow})	**Log VP**	**Readily biodegradable**	**Non-biodegradable**	**Readily biodegradable**	**Non-biodegradable**
0 → 5	-2 → 0	2.24	26.04	0.0043	0.052
	0 → 6	2.12	16.82	0.0043	0.034
5 → 7	-2 → 0	15.46	91.14	0.0384	0.181
	0 → 6	5.61	7.71	0.0150	0.017

Key assumptions: tonnage = 1 tonne/year
PNEC = 1 µg/l

The RCR_{max}s in the look-up table were determined using a tonnage of 1 tonne/year (Table AA.4 indicates tonnes/year) and a PNEC of 10 µg/l. Since the RCR is linearly related to tonnage and ecotoxicity, the RCR_{max}s from the look-up table can easily be adjusted to other tonnages and PNECs by using following, simple transformation rule:

$$RCR_{max,tonnage,PNEC} = \frac{RCR_{max,lookuptable} \cdot Tonnage(tonne/year)}{PNEC(mg/l)}$$

Preliminary validation

A preliminary validation was performed to explore the conservativeness of the developed look-up table. The approach was applied to 41 chemicals that were identified by the authorities as priorities for detailed and comprehensive risk assessments. The data used were extracted either from the current draft or finished EU Risk Assessment Reports (RAR) on these chemicals (downloaded from EC, 2003a). The outcome was then compared with the risk assessment outcome based on the full EUSES assessment. The RARs indicated that all chemicals had a RCR_{max} greater than one. The screener, based on the proposed look-up table (95^{th} percentiles were used) indicated a potential concern for all chemicals and further assessment for all chemicals was therefore required.

The preliminary validation exercise demonstrated that the substances selected as priority chemicals within the EU existing substances work, would also trigger further risk assessments when applying the look-up table approach. This indicates there may be a low risk of false negatives.

Clearly, a more extended validation study is needed based on a more diverse database of chemicals (with representatives from all main, industry and use categories and with different

physico-chemical and biodegradation properties) to further assess both the absence of false negatives and the limited occurrence of false positives. In particular, the database should also contain chemicals of no concern, with RCR_{max} less than one, to check whether the look-up table is overly conservative (and identifies a need for further assessment for essentially all chemicals) or not. The availability of such a database would also enable the determination of conservative and representative release fractions for each main category to further refine the look-up table.

Conclusions

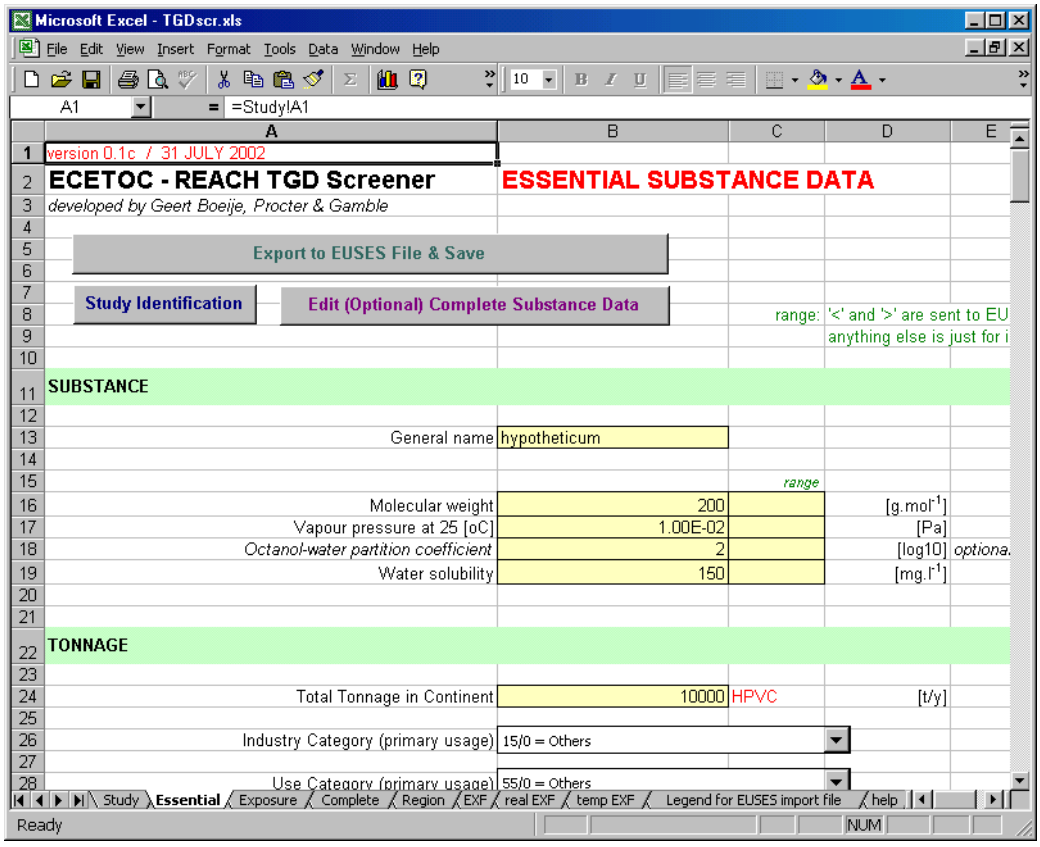
An easy-to-use, pragmatic and conservative rule-based approach for the de-selection of substances of very low or no immediate concern at an early stage was developed based on the principles and basic concepts from the EU TGD and EUSES. A simple look-up table gives RCRs for two groups of standardised chemical release scenarios, two biodegradability groups and two octanol-water partition coefficient and two vapour pressure groups. A simple transformation rule can then be used to calculate the RCR for specific tonnages and ecotoxicities (predicted no-effect concentrations). The development of the rule-based screener and a preliminary validation, demonstrating its objectives, also indicated the need for an extensive and representative list of chemicals to further improve and validate the tool.

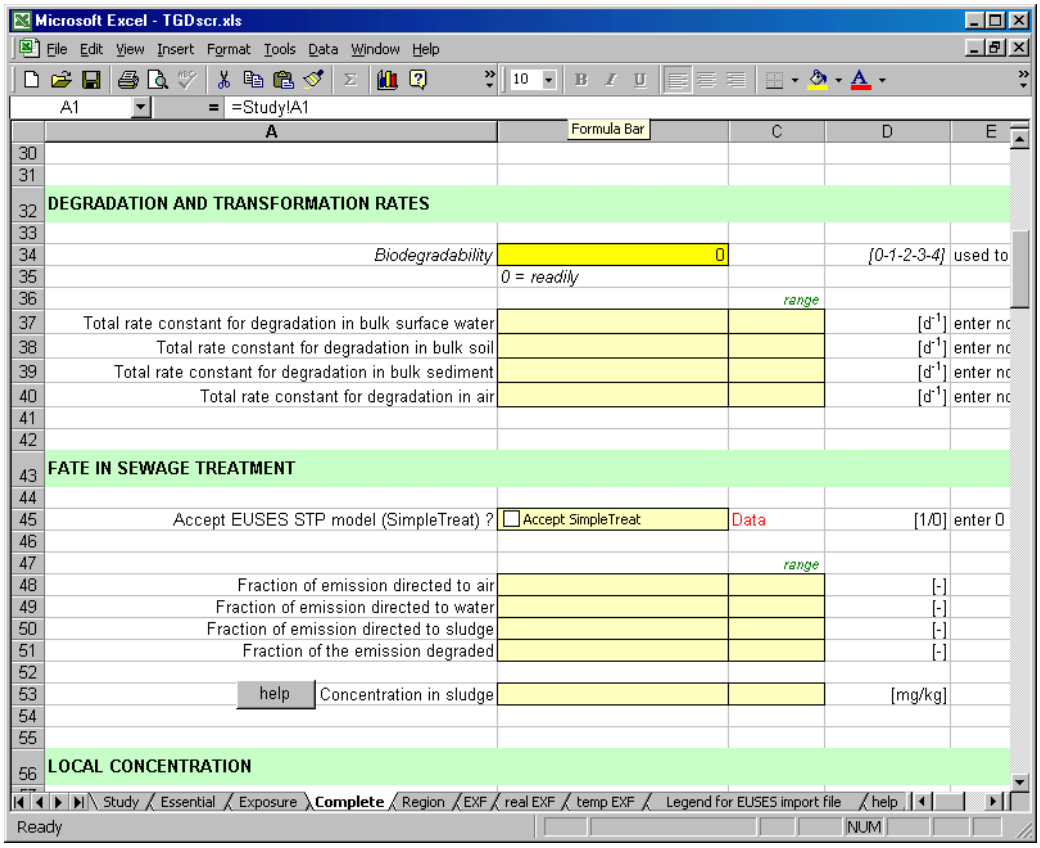
APPENDIX BB: EUSES INTERFACE

A spreadsheet has been developed to facilitate the input of relevant parameters into the EUSES program, and to ensure consistency of the modifications to the default EUSES parameter set. All parameters relevant to the ECETOC TRA can be entered into the spreadsheet in a user-friendly way. Comments can be included next to the actual numbers. Subsequently, the spreadsheet converts the user's input into an EUSES Export File (.exf). The Export File can then be imported into the EUSES program, and the EUSES model calculations can be run.

This spreadsheet is not used for any model calculations. All equations in EUSES are maintained unaltered. However, some specific models in EUSES may be by-passed by over writing the model result with user-specified values. For example, EUSES normally predicts chemical removal in a waste-water treatment plant by means of the SimpleTreat model. *Via* the spreadsheet, the user can replace these default predictions with measured values, which override the EUSES estimations.

The ECETOC input spreadsheet is compatible with EUSES 2.0 (http://ecb.jrc.it/Euses/).

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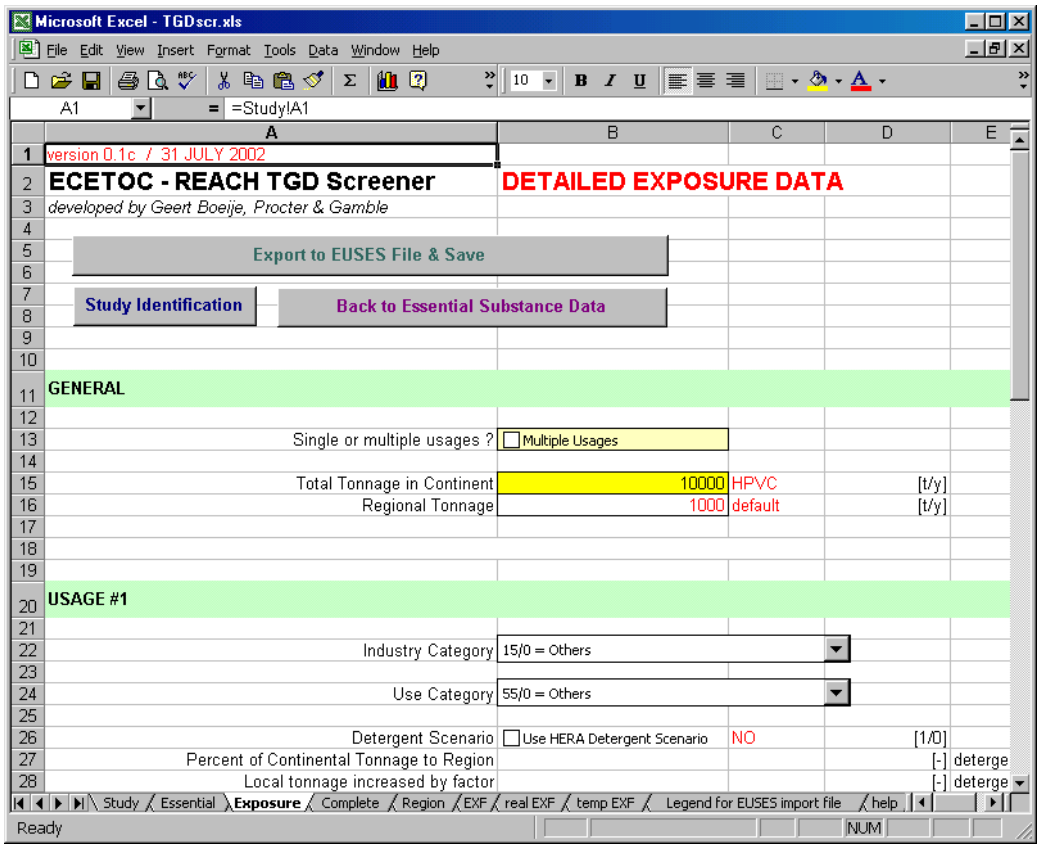
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APPENDIX CC: GUIDANCE ON HOW TO SELECT THE APPROPRIATE ENVIRONMENTAL RELEASE AT TIER 0

Environmental release estimation is a crucial part of the environmental risk assessment as it influences strongly the result. Ideally, measured data should be used but normally are not available. Therefore the EU TGD (EC, 2003a) provides a release estimation scheme based on so called main, industry and use categories. This scheme takes into account the full life-cycle of a substance like production, formulation, industrial use, service life, and private use as well as recovery and the different uses in different industries. In addition release is correlated to several other parameters like physico-chemical data (e.g. vapour pressure, water solubility, use type) in order to account for the different releases to the environmental compartment air, water and soil. To make it even more complicated, production or use days are derived from production tonnage and assumed number of release sites. This complex system can be simplified using drop down lists within an exposure modelling system like EUSES but this gives the user the feeling of working with a black box.

The approach presented here is based on the EU TGD for Risk Assessment (EC, 2003a) approach as described briefly before but tries to reduce the complexity. It uses the 16 so called industry categories of the EU TGD and the most relevant life-cycle steps (e.g. production, industrial use) and assigns for each Industry Category (IC) possible life-cycle steps and makes proposals on which main release category might be associated (see Table CC.1 below). The five different main release categories ('used in closed system' (isolated and non-isolated), 'included into/onto a matrix', 'non-dispersive use' and 'wide dispersive use') are marked in different colours accounting for the release percentages of 0.1, 1, 10, 20 and 100 % of the total tonnage. Only the coloured main release categories for a life-cycle step need to be considered but there might be more than one possibility. In such a case the user needs to decide which category is more appropriate and needs to select the higher release if not certain. If for a substance more than one life-cycle step needs to be considered the release estimation should be based normally on the highest release. For example, when production of isolated intermediates (1% release) and non-dispersive use (20% release) are being considered then the assessment should be based on non-dispersive use. If more than one IC has to be taken into account the highest release from all life-cycle steps for all uses could be used and applied to the total tonnage. This will often be overly conservative requiring further refinement at Tier 1.

Guidance on how to select the main release category for use in the Environment Tier 0 Tool:

1. Use the following TabIe CC.1 and identify the IC concerned (a brief description of the use of the substances which fall under an IC is given in Table CC.1 as well to make selection easier); substances not falling under IC 1 to 15 are handled under IC 16 (other) where guidance is limited;

2. mark all relevant life-cycle steps of the IC and select the most appropriate main release categories (if unclear take the higher release); only the coloured sections need to be considered for selection;
3. check from all selected main release categories of an IC the highest release and use it in the Tier 0 calculation;
4. if more than ONE IC has to be taken into account apply the procedure described under 1) to 3) to all industry categories. Select afterwards the highest main release category and apply it to the total tonnage for all ICs to be considered. Be aware that this procedure is conservative and will, most likely, need to be replaced by a more specific Tier 1 approach.

Table CC.1: Industry categories and corresponding substance life-cylce steps and main release categories

IC	Industry concerned	Industry description	Life-cycle step	Closed system (1% release assumed)	On/in a matrix (10 % release assumed)	Non-dispersive use (20 % release assumed)	Wide-dispersive use (100 % release assumed)
1	Agricultural industry	Substances for pest control (pesticides, veterinary medicines) and manuring. Processing (= application) of pesticides is out of scope as it is regulated by 91/414/EEC.	Production				
			Formulation				
			Processing				
2	Chemcial industry Basic chemicals	Basic chemicals are substances used generally throughout all branches of (chemical) industry and usually in considerable amounts e.g. solvents and pH regulating agents (acids and alkalis)	Production				
			Formulation				
			Processing				
3	Chemical industry Chemicals used in Synthesis	Substances used in synthesis are substances either regulating the chemical reaction process (e.g. catalyst) or being used as an intermediate in a chemical reaction to form a new substance	Production				
			Formulation				
			Processing				
4	Electrical/electronic industry	Substances used in electroplating, polymer processing and paint application to allow the production of resistors, transistors, capacitors, diodes, lamps, etc.	Production				
			Formulation				
			Processing				

Table CC.1: Industry categories and corresponding substance life-cylce steps and main release categories (cont'd)

IC	Industry concerned	Industry description	Life-cycle step	Closed system (1% release assumed)	On/in a matrix (10 % release assumed)	Non-dispersive use (20 % release assumed)	Wide-dispersive use (100 % release assumed)
5	Personal/ domestic use	Substances for use in household (for maintenance, care, furniture, kitchenware, garden and personal care, cleaners, washing powders, for leather, textiles, cars, etc.)	Production				
			Formulation				
			Private use				
6	Public domain	Substances for use by skilled workers at places like offices, public buildings, waiting rooms, garages for professional cleaning and maintenance	Production				
			Formulation				
			Processing				
7	Leather processing industry	Substances to be used for leather manufacturing out of raw hides including tanning and dyeing, making fast to dry-cleaning and rain	Production				
			Formulation				
			Processing				
8	Metal extraction, refining and processing industry	Substances for extraction of metals from ores (e.g. flotation agents), manufacturing of steel and other metals; includes substances for metal working processes (cutting, drilling, rolling, etc)	Production				
			Formulation				
			Processing				
9	Mineral oil and fuel industry	Substances from processing crude oil by physico-chemical processes (distillation, cracking, platforming)	Production				
			Formulation				
			Processing				
			Private use				
10	Photographic industry	Substances used in photographic processes	Production				
			Formulation				
			Processing				
			Private use				
11	Polymers industry	Substances used in manufacturing of polymers (e.g. process aids like radical starters, modifiers, etc.)	Production				
			Formulation				
			Processing				
12	Pulp, paper and board industry	Substances used in the production, formulation, processing and recovery of pulp, paper and board (e.g. fillers, impregnations, colourants, etc.)	Production				
			Formulation				
			Processing				
			Recovery				

Table CC.1: Industry categories and corresponding substance life-cylce steps and main release categories (cont'd)

IC	Industry concerned	Industry description	Life-cycle step	Closed system (1% release assumed)	On/in a matrix (10 % release assumed)	Non-dispersive use (20 % release assumed)	Wide-dispersive use (100 % release assumed)
13	Textile processing industry	Substances for treatment of fibres for cleaning, spinning, dyeing, impregnation, weaving, finishing, coating, etc.	Production				
			Formulation				
			Processing				
			Private use				
14	Paints, lacquers and varnishes industry	Substances used for the production of paints, lacquers and varnishes (e.g. antioxidants, rheological modifiers, thickeners, etc.)	Production				
			Formulation				
			Processing				
			Private use				
15	Engineering industries: civil and mechanical	Substances used e.g. in wood processing industries (e.g. for manufacturing of wooden furniture), motor car manufacture, building industry, etc.	Production				
			Formulation				
			Processing				
			Private use				
16	Other industries	Substances which cannot be associated with the industries given above are placed in 'Other Industries' No clear guidance can be given but at least exclusions can be proposed	Production				
			Formulation				
			Processing				
			Private use				

APPENDIX DD: ENVIRONMENTAL EFFECTS ASSESSMENT AND APPLICATION FACTORS

In the derivation of safe levels or prediction of no-effect concentration for the aquatic ecosystem, a number of uncertainties must be addressed to extrapolate from single-species laboratory data to a multi-species ecosystem. These areas have been adequately discussed in other papers (e.g. ECETOC, 1993b; EC, 1996c, 2003a), and can be summarised as:

- Intra- and interspecies variations;
- extrapolation from short-term to long-term toxicity;
- extrapolation from laboratory data to field.

Data on a given substance are rarely sufficient to derive a 'safe' level without the application of a factor to compensate for uncertainties in the predictive power of the data or to provide an extra measure of safety. In this document these factors are termed Application Factors as adopted and discussed by ECETOC (1993b; 1995) and later reports based on the aquatic hazard database (ECETOC, 1993c, 2003c).

The size of an application factor depends on two aspects of the data:

i. Ecological relevance: Data from short-term studies in the laboratory generally need large Application Factors; data from long-term laboratory studies or ecosystem field studies need smaller Application Factors.
ii. Data value (i.e. number and quality of studies): As more high quality data become available, the uncertainty in a substance's toxicity is reduced and the lower the Application Factor needs be to account for this reduced uncertainty. Generally, a full data set at the acute or chronic level contains three quality-controlled studies on at least two taxonomic groups; at the ecosystem level one carefully conducted study on appropriate species or communities should be sufficient. The Application Factors are therefore not necessarily fixed and lower factors may be justified if more high quality data become available.

The PNEC for the aquatic compartment is estimated from acute or chronic data originating in laboratory or field (ecosystem) studies. The three Application Factors necessary for this estimation are:

Application Factor 1 - derives the PNEC from acute laboratory studies.
Application Factor 2 - derives the PNEC from chronic laboratory studies.
Application Factor 3 - derives the PNEC from ecosystem studies.

In reality, Application Factors 1-3 are built up from smaller elements (F):

F_1 - acute : chronic ratio (ACR)

F_2 - chronic : ecosystem ratio
F_3 - ecosystem : PNEC ratio

These three ratios are multiplied together to give Application Factor 1-3. Thus:

Application Factor 1 = $F_1 \times F_2 \times F_3$
Application Factor 2 = $F_2 \times F_3$
Application Factor 3 = F_3

The PNEC is derived by extrapolation, using Application Factors, from acute and/or chronic single-species laboratory data to ecosystems which contain populations of different species. The choice of the size of these factors (1,000, 100, 10, 3, 1) as discussed above depends on the confidence with which a PNEC can be derived from the available data. This confidence increases if data are available on the toxicity to organisms at a number of trophic levels, in different taxonomic groups and with lifestyles representing various feeding strategies. Thus, lower Application Factors can be used when more relevant data sets are available.

Ecotoxicological data collected in the laboratory can be difficult to translate into accurate predictions of effects that might occur in the field. Some features will tend to make laboratory tests overestimate effects in the field; with others the reverse may be the case.

Recently, Forbes and Calow (2002) critically reviewed the extrapolation methodology as a pragmatic way to develop an assessment of effects on ecological systems with the minimum amount of empirical information. Forbes and Calow (2002) argue that 'Individual level responses (as measured in laboratory tests) often provide protective estimates of population-level effects, and changes in ecosystem structure are likely to provide protective estimates of change in ecosystem processes. Sometimes these estimates may be very overprotective, but until further improvements in our understanding of intra- and interspecies differences in chemicals occur focusing testing on individual level responses and changes in species composition rather than ecosystem structure is not likely to lead to gross underestimates of chemical effects in natural ecosystems.'

Forbes *et al* (2001) had already demonstrated both analytically and by simulation, that for populations with multiplication rates close to one, effects of toxicants at the population level are likely to be less than or equal to effects on individual life-cycle traits, suggesting that risk assessments based on the latter should be protective of population-level impacts. Their analyses suggest that current extrapolation approaches appear to be protective, and may often be very overprotective, but they identified conditions in which this may not be the case. For instance, not taking into account the proportions of the different life-cycles in a community can lead to either

under- or over-conservative protection levels, depending on the relative sensitivity and abundance of the different life-cycle types.

Forbes and Calow (2002) also argue: 'Within species the acute-to-chronic ratios are variable. It may be possible to reduce uncertainty by using more precise ACRs for specific classes of chemicals. However, since interspecies differences may be at least as important a contributor to variation in ACR as is chemical class, applying standard chemical-specific factors for all species may not improve the precision of the extrapolation markedly.' In contrast, they tentatively concluded, based on a limited data set, that the factor of 10 generally used to allow for interspecies differences may be underprotective for a substantial fraction of chemicals. The authors suggest their analysis could provide an argument for increasing the extrapolation factor, when only acute data are available, by an order of magnitude.

Application Factors

For environmental risk assessment of new or existing substances in Europe, PNECs are estimated from limited acute or chronic data through the use of conservative default Application Factors (EC, 1996c, 2003a). The default Application Factor chosen depends upon the number of organism classes (e.g. vertebrates, invertebrates, plants) and endpoint types (acute versus chronic) that are available in the ecotoxicity database for the substance. As a consequence, Application Factors implicitly take into consideration differences in species sensitivity and acute to chronic extrapolation.

Table DD.1: Mean and standard deviation of the Acute to Chronic Ratio (ACR) by MOA class (Roex et al, 2000)

Class	ACR
MOA 1 (Nonpolar narcotics (inert))	2.6 ± 1.6 (n = 11)
MOA 2 (Polar narcotics (less inert))	9.8 ± 11.8 (n = 12)
MOA 3 (Reactive)	Not determined
MOA 4 (Specific acting)	17.3 ± 26.6 (n = 45)
Metals	15.3 ± 28.8 (n = 34)

The critical review of the extrapolation methodology by Forbes and Calow (2002) was based on a limited data set and concluded that the factor 10 generally used to allow for interspecies differences may be underprotective for a substantial number of chemicals.

Based on a detailed literature review, Roex *et al* (2000) examined the relationship between acute to chronic ratios (ACRs) in aquatic organisms to MOA. These authors found that both the magnitude and variability of the ACR varied between classes (Table DD.1). Substances designated as inert were found to exhibit the lowest and least variable ACRs while specific acting chemicals and metals demonstrated higher more variable ACRs with polar narcotics showing an intermediate behaviour. These authors concluded that given the consistent ACR observed for inert chemicals, acute toxicity tests could be used to provide reliable estimates of chronic effect endpoints. The above research indicates that MOA-based SARs may be a promising tool for refining default Application Factors used in PNEC derivation.

Roelofs *et al* (2003) examined the differences in sensitivity among species exposed to a chemical as a function of MOA and they derived Application $Factor_{interspecies}$ for MOA 1, 2 and a combination of MOA 3 and 4. They showed that increasing the minimum number of toxicity data to derive an Application $Factor_{interspecies}$ tends to result in narrower uncertainty distributions. Furthermore, the median values of the Application $Factor_{interspecies}$ of narcotic chemicals are lower than the median values of the group with MOA 3 and 4 (Table DD.2). Also, the distributions of the Application $Factor_{interspecies}$ for narcotic chemicals is narrower.

Table DD.2: Mean and 90% confidence interval (in brackets) for the application factor$_{interspecies}$ by toxic MOA as determined by Roelofs* et al *(2003) for substances with toxicity data for more than 3 species

Class	Application Factor$_{interspecies}$
MOA 1 (Nonpolar narcotics (inert))	8.7 (2.3 – 170)
MOA 2 (Polar narcotics (less inert))	6.3 (2.1 – 37)
MOA 3 (Reactive) + MOA 4 (Specific acting)	27 (2.5 – 1,905)

The above research suggests that MOA-based SARs may be a promising tool for refining default Application Factors used in PNEC derivation.

The use of a factor of 1,000 on short-term toxicity data is a conservative and protective factor and is designed to ensure that substances with the potential to cause adverse effects are identified in the effects assessment. It assumes that each of the uncertainties identified above makes a significant contribution to the overall uncertainty. The narrow species sensitivity distribution, and the small ACRs justify the reduction of the Application Factors for lethal narcosis type materials with a factor 10 when only short-term toxicity data are available, as the uncertainty in PNEC derivation is considerably less when compared to other MOAs.

In general, the EU TGD (EC, 2003a) suggests for long-term toxicity data to use an Application Factor of 100 for a single long-term NOEC (fish or daphnia) if this NOEC was generated for the trophic level showing the lowest $L(E)C_{50}$ in the short-term tests. An Application Factor of 50 applies to the lowest of two NOECs covering two trophic levels when such NOECs have been generated covering that level showing the lowest $L(E)C_{50}$ in the short-term tests. In case of narcosis-type compounds the practices to require inclusion of the trophic level showing the lowest $L(E)C_{50}$ introduces a non-justifiable conservatism given the low ACRs for this class. Here, a factor of 100 or 50 is applied, irrespective whether the NOEC was generated for the trophic level showing the lowest $L(E)C_{50}$.

For compounds with a high log K_{ow} no short-term toxicity may be found. This may also be the case even in long-term tests where steady state may still not have been reached. In fish tests for non-polar narcotics, the latter can be substantiated by the use of long-term QSARs (ECETOC, 1998; 2003d). Use of a higher Application Factor can be considered in such cases where steady state does not seem to have been reached. A long-term test may be carried out for such substances. The NOEC from this test can then be used with an Application Factor of 100. If, in addition, a NOEC is determined from an algal test of the base-set, an Application Factor of 50 is applied.

An Application Factor of 10 will normally only be applied when long-term toxicity NOECs are available from at least three species across three trophic levels (e.g. fish, daphnia, and algae or a non-standard organism instead of a standard organism). When examining the results of long-term toxicity studies, the PNEC should be calculated from the lowest available NOEC.

For effects assessment, application factors are used as described in the EU TGD (EC, 1996c, 2003a). If data are available on three trophic levels the factor is reduced from 1,000 to 100; and if data are available on two trophic levels then a value of 500 is recommended.

Conclusion

The need to proceed in a test programme from screening to more investigative research studies relies on a logic and risk-based hierarchy for decision-making. This is based on a stepwise risk assessment scheme that, according to the value of environmental risk quotient, will trigger the need to develop additional data.

This stepwise approach allows systematic collection of data and addresses both immediate (acute) effects of chemicals and their potential effects after repeated exposure and possible accumulation within the organism. The stepwise approach for the evaluation of both exposure and effect - which has been adopted in both environmental and human health risk assessments - realises the most efficient use of data and resources, allowing decisions at the earliest possible

stage whilst maintaining ample margins of safety so that protection of man and environment can be ensured. This approach also enables the allocation of resources to the highest priority compounds, i.e. those of most concern in terms of risk.

APPENDIX EE: MODE OF ACTION AND AQUATIC EXPOSURE THRESHOLDS OF NO CONCERN

Introduction

In the mid-nineteen seventies, a task group from the American Institute of Biological Sciences chaired by H. Ward was charged by US-EPA to derive criteria and a rationale for decision making in aquatic hazard evaluation (Dickson *et al*, 1978). From comparison of a set of basic test data with (estimated) exposure concentrations, they derived criteria and specified type and sequence of conditional tests to be performed. Their approach required test data as a start in order to set aside chemicals for further extensive toxicity testing. Their initial work has evolved among others into Technical Guidance Documents that are used by the European Union for risk assessment of industrial chemicals (EC, 1996c, 2003a).

The Threshold of Toxicological Concern (TTC) is a concept based on the possibility of establishing an exposure threshold value for all chemicals, below which there is no significant risk to human health and/or the environment. This concept goes further than setting acceptable exposure levels for individual chemicals as it attempts to set a *de minimis* value for any chemical or a structural class of chemicals, including those of unknown toxicity. Kroes *et al* (2000) defined TTC as 'a level of exposure to chemicals below which no significant risk is expected to exist'.

The new draft Chemicals Legislation recently proposed by the European Commission may require environmental fate and effects information for an estimated 30,000 substances manufactured or imported into the EU (EC, 2003b). The further acceptance of threshold concepts would be beneficial for both industry and regulators in avoiding extensive toxicity testing and safety evaluations when human intake or environmental exposure are below such a threshold (EU-SSC, 2000). Hence, in contrast to using a set of basic test data as the initial starting point of a screening risk assessment, use of Threshold Concepts would contribute to a reduction in the use of animals and focus limited resources of time, cost and expertise on the testing and evaluation of substances with greater potential to pose risks to human health and the environment.

The TTC, as applied in human health risk assessment, has been reapplied to pharmaceuticals in the environmental (Straub, 2002), but not yet for general organic chemicals. Derivation of a data-based environmental exposure threshold of no concern (ETNC) is currently limited to the freshwater environment due to the general lack of quality data for the effect of industrial chemicals on sediment, marine or soil species. Hence, the use of a subscript function is introduced to indicate specifically the environmental compartment for which the ETNC concept is considered applicable e.g. the Aquatic Exposure Threshold of No Concern ($ETNC_{aquatic}$).

The Verhaar categorisation system for the prediction of the toxic effect concentrations of organic environmental pollutants to fish (Verhaar *et al*, 1992) separates organic chemicals into four

distinct classes that can be assigned a Mode of Action (MOA). These four classes are: (1) inert chemicals (baseline toxicity), (2) less inert chemicals, (3) reactive chemicals, and (4) specifically acting chemicals:

1. Inert chemicals are chemicals that are not reactive when considering overall acute effects, and that do not interact with specific receptors in an organism. The MOA of such compounds in acute aquatic toxicity is called (lethal) narcosis. Effect concentrations for a number of endpoints can be predicted using QSARs that were developed for these endpoints (see e.g. EC, 2003a).
2. Less inert chemicals are slightly more toxic than predicted by baseline toxicity estimations. These chemicals are often characterised as compounds acting by a so-called 'polar narcosis' mechanism, and can commonly be identified as possessing hydrogen bond donor acidity, e.g. phenols and anilines (Escher and Hermens, 2002).
3. Reactive chemicals display an enhanced toxicity that is related to the phenomenon that these chemicals can react unselectively with certain chemical structures commonly found in biomolecules or are metabolised into more toxic species.
4. Specifically acting chemicals exhibit toxicity due to (specific) interactions with certain receptor molecules (specific or receptor toxicity).

The Verhaar categorisation scheme does not include metals, inorganics and ionisable organic chemicals.

A comparable application of a chemical categorisation approach is incorporated in the Assessment Tools for The Evaluation of Risk (ASTER). This is an expert system developed by the US EPA which selects QSARs based on the predicted mode of action of chemicals (Russom *et al*, 1991; Russom *et al*, 1997).

Straub (2002) applied the $ETNC_{aquatic}$ concept to pharmaceuticals (classed as MOA 4 type substances) and proposed that a value of 0.01 µg/l would be appropriate for aquatic organisms. Chemicals classed with other modes of action (types 1-3) do not specifically interact with biota and thus it can be assumed that the $ETNC_{aquatic}$ will be greater than 0.01 µg/l. This paper gives details of analysis of existing quality assured aquatic toxicity databases and substance hazard assessments designed to derive an $ETNC_{aquatic}$ for general organic chemicals with MOA 1, 2 or 3 ($ETNC_{aquatic,MOA1-3}$).

Methods

Existing environmental toxicological databases and substance hazard assessments for organisms in the freshwater environment were analysed. Only data(bases) that have undergone a quality

assessment, and are categorised as high quality data were used. For organic chemicals EURATS-online and the ECETOC Aquatic Toxicity (EAT 3) database were used. Supportive evidence was gathered through the use of acute toxicity databases e.g. the US EPA Duluth fathead minnow database, and the Utrecht University, the Netherlands, guppy database.

Where possible the cumulative frequency distribution was determined to estimate the 95-percentile coverage limit value (expressed as the lower limit of the 50% confidence interval). Such a value provides a description of the coverage of available toxicity values in the database into one number, which is termed the Database Coverage Concentration (DCC), and is expressed as the DCC (95,50). These analyses were done with the probability graphing functions of Minitab Statistical Software package (release 13.32), with a maximum likelihood estimation method assuming a normal or lognormal distribution.

Existing substances risk assessments

In 1993 the European Union Council adopted Council Regulation EEC/793/93 (EC, 1993a), or the Existing Substances Regulation (ESR), thereby introducing a comprehensive framework for the evaluation and control of 'existing' chemical substances. The Regulation was intended to complement the already existing rules governed by Council Directive 67/548/EEC for 'new' chemical substances. An 'Existing' chemical substance in the EU is defined as any chemical substance listed in the European INventory of Existing Commercial Substances (EINECS), an inventory containing 100,195 substances. Any chemical substance introduced into the EU market for the first time after 18 September 1981 is referred to as a new chemical. The Regulation EEC/793/93 (EC, 1993a) foresees that the evaluation and control of the risks posed by existing chemicals will be carried out in four steps: data collection, priority setting, risk assessment and risk management.

The risk assessment is performed by one of the EU Member States (MS) on behalf of all, with discussions with other MS-experts in Technical Meetings held in Ispra, Italy and coordinated by the European Chemicals Bureau (ECB). ECB is responsible for maintaining the online EUropean Risk Assessment Tracking System (EURATS). For the four EU priority list chemicals (n=141) it provides a possibility to find information where in the assessment process a substance has reached, and an overview of conclusions reached, statistics and testing requirements.

ECETOC Aquatic Hazard Assessment database

The EAT 3 database (ECETOC, 2003c) was used as it contains only high quality measured data on the toxicity of chemicals to aquatic organisms. The ECETOC database consists only of those aquatic toxicity data from the open literature that could pass a set of rigorous quality criteria. Its

preparation was commissioned by the European Centre for the Ecotoxicology and Toxicology of Chemicals (ECETOC) and contains aquatic toxicity data for many aquatic species and combinations of species, ranging from bacteria to algae to arthropods to fish to microcosms. Both acute and chronic data on effect concentrations (e.g. log LC_{50}s) and No-Effect Concentrations (NOECs; n>600) on a number of separate endpoints (e.g. lethality, growth inhibition) are included in the database.

Acute toxicity databases

Fathead minnow database

This US EPA Duluth database consists of 753 flow-through bioassays conducted with juvenile fathead minnows on 617 chemicals selected from a cross section of the Toxic Substances Control Act Inventory of industrial organic chemicals. All studies employ 28 to 36 day old animals, are 96 h in duration, and consist of multiple treatment levels (typically five effect concentrations and a control) and a single dilution water source. All aqueous chemical exposure concentrations are quantified and meet a minimum set of well-defined quality assurance measures. The 96-h mortality responses are analysed with the trimmed Spearman–Karber method to obtain an LC_{50} and 95% confidence interval, where possible. For a more complete description of the database, see Russom *et al* (1997).

Guppy database

The University of Utrecht (the Netherlands) has a database of acute toxicity results for 180 organic chemicals tested in static renewal bioassays with two to three month old guppies (Verhaar *et al*, 1992). Bioassay durations range from 7 to 14 d and incorporate a range of chemical concentrations. To quantify lethal potency as LC_{50}s, methods described by Litchfield and Wilcoxon are employed. A more complete description of the methods used to generate this toxicity database are presented in Könemann (1981).

Application Factors used for derivation of the $ETNC_{aquatic}$

For environmental risk assessment of new or existing substances in Europe, PNECs are estimated from limited acute or chronic data through the use of conservative default Application Factors (EC, 1996c, 2003a). The default Application Factor chosen depends upon the number of organism classes (e.g. vertebrates, invertebrates, plants) and endpoint types (acute versus chronic) that are available in the ecotoxicity database for the substance. As a consequence, Application Factors implicitly take into consideration differences in species sensitivity, acute to

chronic extrapolation and lab to field extrapolation. Thus, for derivation of the $ETNC_{aquatic}$ from PNECs an additional Application Factor is not considered to be applicable.

Recently, Forbes and Calow (2002) critically reviewed the extrapolation methodology as a pragmatic way to develop an assessment of effects on ecological systems with the minimum amount of empirical information. They tentatively concluded, based on a limited data set, that the factor of 10 generally used to allow for interspecies differences may be underprotective for a substantial fraction of chemicals. The authors suggest their analysis could provide an argument for increasing the extrapolation factor, when only acute data are available, by an order of magnitude.

Based on a detailed literature review, Roex *et al* (2000) examined the relationship between acute to chronic ratios (ACRs) in aquatic organisms as a function of mode of action. These authors found that both the magnitude and variability of the ACR differed between classes. Substances designated as inert were found to exhibit the lowest and least variable ACRs while specific acting chemicals and metals demonstrated higher, more variable ACRs. Polar narcotics showed an intermediate behaviour. They concluded that given the consistent ACR observed for inert chemicals, acute toxicity tests could be used to provide reliable estimates of chronic effect endpoints.

Roelofs *et al* (2003) examined the differences in sensitivity among species exposed to a chemical as a function of mode of action and they derived Application $Factor_{interspecies}$ for MOA 1, 2 and a combination of MOA 3 and 4. They showed that increasing the minimum number of toxicity data to derive an Application $Factor_{interspecies}$ tends to result in narrower uncertainty distributions. Furthermore, the median values of the Application $Factor_{interspecies}$ of narcotic chemicals are lower than the median values of the group with MOA 3 and 4. Also, the distributions of the Application $Factor_{interspecies}$ for narcotic chemicals is narrower.

When deriving a PNEC for the freshwater environment, using data from long-term toxicity tests, an application factor of 100 is used for a single long-term NOEC (fish or daphnia) if this NOEC was generated for the trophic level showing the lowest $L(E)C_{50}$ in the short-term tests (EC, 2003a). An application factor of 10 will normally only be applied when long-term toxicity NOECs are available from at least three species across three trophic levels (e.g. fish, daphnia, and algae or a non-standard organism instead of a standard organism) (EC, 2003a). In deriving the $ETNC_{aquatic}$ from the ECETOC EAT 3 database it is assumed that the latter is the case.

When deriving a PNEC for the freshwater environment, using data from short-term toxicity tests, a factor of 1,000 is used. This approach is designed to be conservative and to ensure that substances with the potential to cause adverse effects are identified in the effects assessment (EC, 2003a). It assumes that each of the uncertainties identified above makes a significant contribution

to the overall uncertainty. The narrow species sensitivity distribution, and the small ACRs justify the reduction of the Application Factors for lethal narcosis type materials when only short-term toxicity data are available, as the uncertainty in PNEC derivation is considerably less when compared to other MOAs. For derivation of the $ETNC_{aquatic}$ it is suggested that an application factor of 100 is applied to the LC_{50} datapoints for the substances with MOA 1 and 2. In their risk assessments, also the US EPA uses a factor of 100 as originally suggested by Dickson *et al* (1978). For derivation of the $ETNC_{aquatic}$ from substances with MOA 3 an application factor of 1,000 is applied. In case of use of multiple MOAs for $ETNC_{aquatic}$ derivation the highest Application Factor has been applied. This builds in some additional conservatism.

Results

Existing substances risk assessments

PNECs derived for the aquatic environment in draft or completed EU Risk Assessments for EU Priority Lists chemicals were extracted from the risk assessment reports (RARs) available on EURATS-Online (status November 2003). From a total of 141 substances that are on the four EU Priority Lists, 59 RARs are posted for organic chemicals with MOA 1, 2 or 3. Thirty-nine of these are final and officially published RARs, four are final draft reports and sixteen reports are in draft form (Table EE1). In six of these reports no PNEC was derived for the aquatic environment due to absence of chronic toxicity at the substance's water solubility reducing the number of substances for this analysis to 53.

Table EE.1: Lowest PNEC value derived from draft or completed EU risk assessments for each of the three MOAs investigated

Substance	CAS number	PNEC (µg/l)	MOA[a]
Alkanes, C10-13, chloro	85535-84-8	0.5	1
4,4'-isopropylidenediphenol	80-05-7	1.6	2
Acrolein (acrylaldehyde)	107-02-8	0.1	3

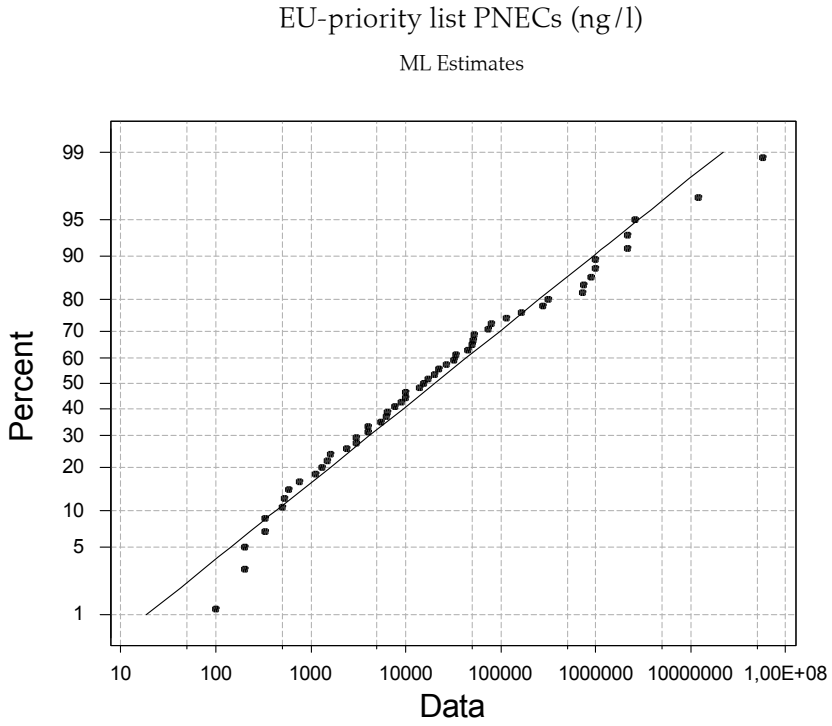
[a] 1 = non-polar narcosis; 2 = polar-narcosis; 3 = electrophiles or pro-electrophiles

Furthermore, in the case of nonylphenol (linear and branched form) the RAR mentions that the PNEC derived from general chronic toxicity data should also be protective for estrogenic effects (a specific mechanism of toxic action). In contrast, the RAR of 4,4'-isopropylidenediphenol (bisphenol A) discusses that the PNEC value might need to be lowered to 0.1 µg/l to include this specific mechanism of toxic action. As this analysis focuses on MOA 1, 2, or 3 a PNEC of 1.6 µg/l is used.

The lowest PNEC value from the EU Priority List substances is for Acrolein, a substance with a reactive Mode of Action (MOA 3) which has a nominal value of 0.1 µg/l (Table EE1). The cumulative frequency distribution of the available PNEC data points is presented in Figure EE1. For the combined MOAs the DCC(95,50) is 0.09 µg/l (n=53).

Given that no Application Factor applies to PNECs, it is evident that both the lowest number and the DCC(95,50) approach suggest that the $ETNC_{aquatic,MOA1-3}$ value is 0.1 µg/l.

Figure EE.1: Cumulative frequency distribution based on PNECs from draft or completed EU risk assessments for general organic chemicals with MOAs 1, 2 and 3



ECETOC EAT 3 database

Lowest NOEC values for all four of the MOAs were taken from the ECETOC EAT 3 database. The number of quality assured datapoints for MOAs 1, 2, 3 and 4 are 137, 122, 105 and 239, respectively. The lowest NOEC values are given in Table EE.2.

Table EE.2: Lowest NOEC value derived from ECETOC EAT 3 database for each of the 4 MOAs investigated

Substance	CAS number	NOEC (µg/l)	MOA
Pentachlorobenzene	608-93-5	5[a]	1
3,4-dichloroaniline	95-76-1	1[b]	2
2,4-dinitro-6-sec-butylphenol	88-85-7	4.9[c]	3
Fenthion	98-82-8	0.0006[d]	4

[a] Chaisuksant *et al*, 1998; [b] Guilhermino *et al*, 1999; [c] Woodward, 1976; [d] Roux, 1995

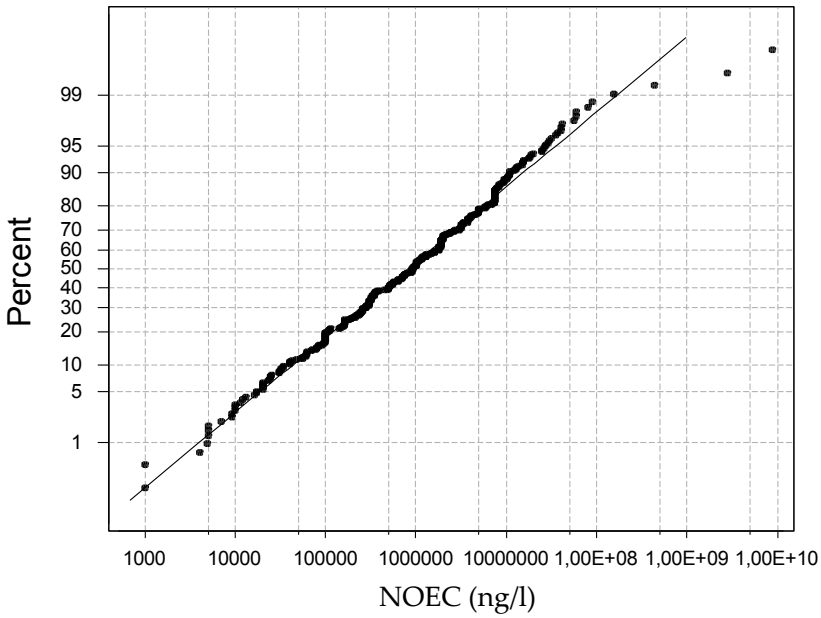
The cumulative frequency distribution of the available data in the ECETOC EAT 3 database is presented in Figure EE.2a when data are combined for MOA 1, 2 and 3, and in Figure EE.2b in function of their MOA. The DCC (95,50) for the combined and separated MOAs are presented in Table EE.3, with the Application Factor for chronic values used (10-100), and the resulting ETNC values.

Table EE.3: Summary table with the derived $ETNC_{aquatic}$ for the MOA (separate or in combination) from the different data sources indicating the number of datapoints, the 95th percentile value (with 50% confidence limits) for the Database Coverage Concentration, and Application Factor used.

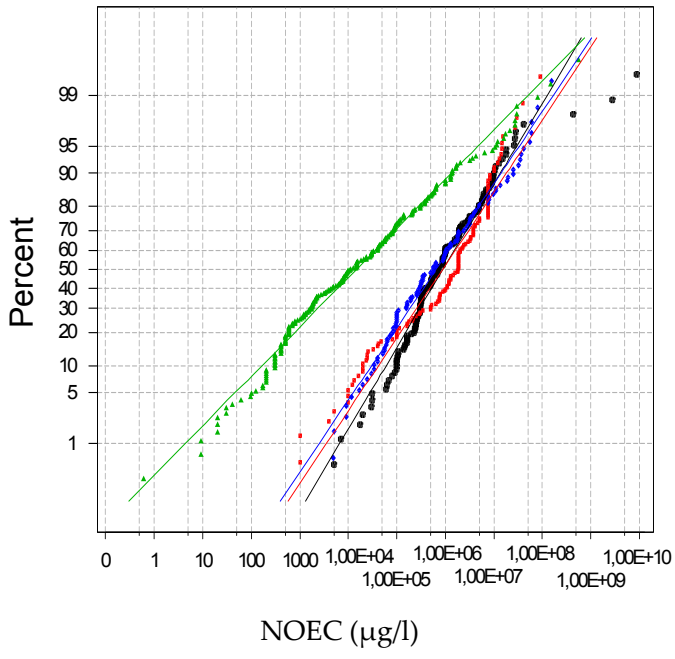
Main data source	MOA	Number of chemicals	DCC (95,50) (µg/l)	Application Factor	$ETNC_{aquatic}$ (µg/l)
Existing substances risk assessments	**All (1-3)**	**53**	**0.09**	**1**	**0.09**
Chronic toxicity data source					
ECETOC EAT 3 database	1	137	22	10	2.2
	2	122	14	10	1.4
	3	105	9	100	0.09
	All (1-3)	**364**	**17**	**100**	**0.17**
	4	239	0.04	100	0.0004
Acute toxicity data source					
Fathead minnow	1	241	500	100	5
	2	76	1,199	100	12
	3	95	71	1,000	0.07
	All (1-3)	**412**	**278**	**1,000**	**0.28**
	4	50	6	1,000	0.006
Guppy	1	42	153	100	1.5
	2	56	1,210	100	12
	3	40	108	1,000	0.11
	All (1-3)	**138**	**170**	**1,000**	**0.17**
	4	36	4.6	1,000	0.005

Figure EE.2: Cumulative frequency distribution based on NOEC values derived from ECETOC EAT 3 database for the combined MOA 1,2 and 3 (a) or as a function of their mode of action (b)

a) NOEC MOA 1-3 (ng/l)
ML Estimates



b) Lognormal base 10 Probability Plot for NOEC (µg/l) by MOA
ML Estimates

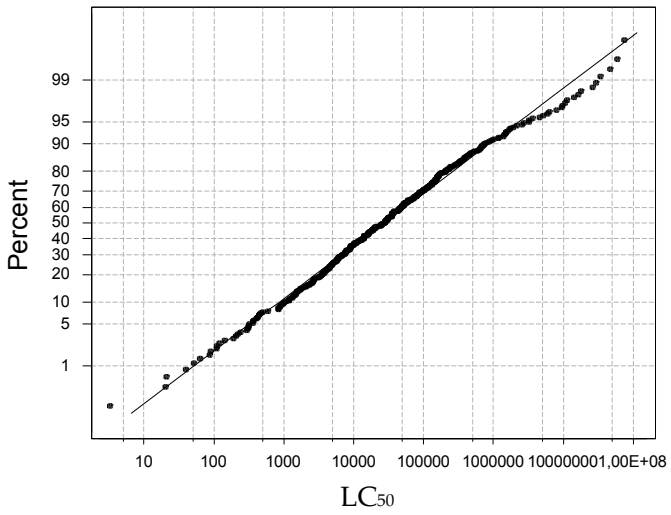


Fathead minnow database

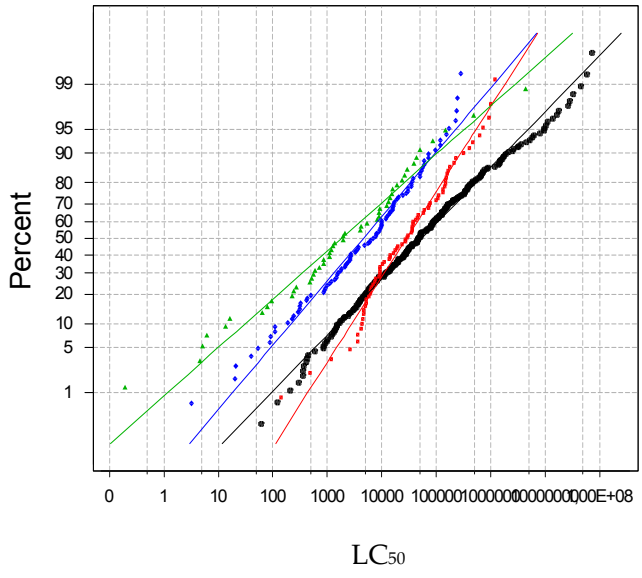
The cumulative frequency distribution of the available data in the fathead minnow database is presented in Figure EE.3a when data are combined for MOA 1, 2 and 3, and in Figure EE.3b in function of their MOA. The DCC (95,50) for the combined and separated MOAs are presented in Table EE.3, together with the Application Factor for acute values used (100-1,000) and the resulting ETNC values.

Figure EE.3: Cumulative frequency distribution based on LC_{50} values derived from US EPA Duluth fathead minnow database for the combined MOA 1, 2 and 3 (a) or as a function of their MOA (b)

a) Lognormal base 10 Probability Plot for LC50 (µg/l)
ML Estimates



b) Lognormal base 10 Probability Plot for LC50 (µg/l) by MOA (Verhaar et al, 1992)
ML Estimates

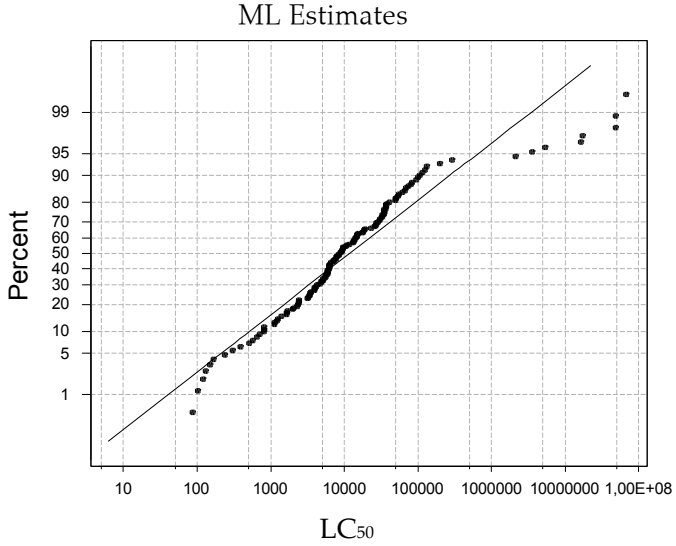


Guppy database

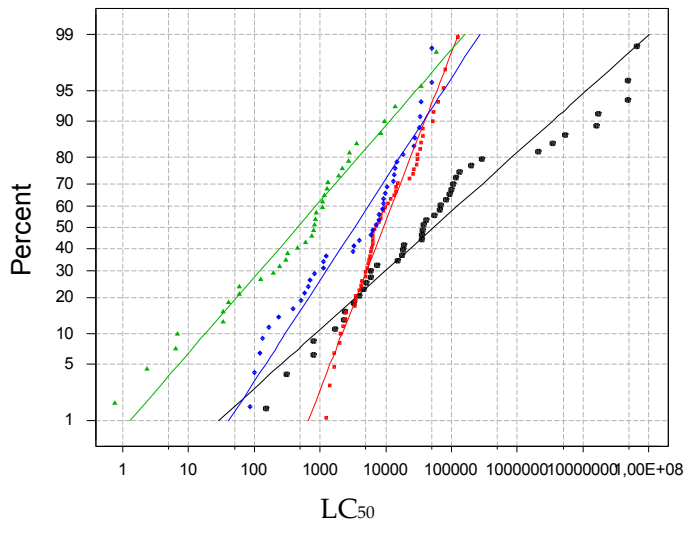
The cumulative frequency distribution of the available data in the guppy database is presented in Figure EE.4a when data are combined for MOA 1, 2 and 3, and in Figure EE.4b in function of their MOA. The DCC (95,50) for the combined and separated MOAs are presented in Table EE.3, together with the Application Factor for acute values used (100-1,000) and the resulting ETNC values.

Figure EE4: Cumulative frequency distribution based on LC_{50} values derived from Utrecht University guppy database for the combined MOA 1, 2 and 3 (a) or as a function of their MOA (b)

a) Guppy 14d-LC50 in µg/l; MOA1-3



b) Guppy 14d-LC50 in µg/l



Discussion

It was expected that the $ETNC_{aquatic}$ for general industrial chemicals with MOA 1, 2 or 3 should be above the one derived for pharmaceuticals (MOA 4), i.e. 0.01 µg/l, due to the absence of a MOA designed to interact with biota. As shown in Table EE.3, the $ETNC_{aquatic,MOA1-3}$ is about 0.1 µg/l, irrespective of the data source (EURATS or ECETOC) and approach (lowest value or 95th percentile) used. This is also supported by the analysis of the fish acute toxicity databases.

Based on the data presented, the PNEC value derived for the EU priority list substance acrolein is the lowest number available. To date, acrolein appears to be the 'reasonable worst-case' chemical for substances, including reactive materials, that are covered by the EU existing chemicals legislation. In the (near) future, other PNEC information may become available and it cannot be excluded that the EU Risk Assessment activities give some additional lower values in due time since reports were not available for all organic chemicals in the set of 141 priority list chemicals. For example, it appears that the Netherlands will propose a $PNEC_{water}$ for hexachlorocyclopentadiene, a precursor of the pesticide endosulfan, of 0.03 µg/l. Notably this material appeared to uncouple oxidative phosphorylation (Sinhaseni *et al*, 1983), a specific MOA (MOA 4).

The preliminary proposal from Greece for the $PNEC_{water}$ for anthracene is 0.012 µg/l. In laboratory tests, PAHs remain relatively nontoxic until internal concentrations are sufficient to achieve lethal narcosis. Of greater concern from an environmental standpoint is toxicity resulting from photoactivation. Certain PAHs, including anthracene, absorb radiant energy in the presence of solar ultraviolet radiation (UV), thereby inducing redox cycling through the formation of free oxygen radicals, which results in an increase in toxicity by an order of magnitude or more (reviewed by Arfsten *et al*, 1996). There is currently not enough information available from the EU risk assessment process to confirm or deny that the $PNEC_{water}$ as derived for anthracene is based on this specific MOA (MOA 4).

The New Chemicals Database, which includes information on new notified substances in the European Union (EEC, 1967) was screened by Sokull-Kluettgen and Vollmer (personal communication, 2003) for information on acute toxicity to fish, daphnia and algae and long-term toxicity data for fish and daphnia. They reported that based on their analysis, which did not make a distinction between MOA, there is no evidence to suggest that an $ETNC_{aquatic,MOA1-3}$ of 0.1 µg/l is an un-acceptable value.

Complete MOA stratification in the analysis of the databases shows that in the case of MOA 1 or 2 the $ETNC_{aquatic}$ value could be even higher than 0.1 µg/l (Table EE.3). It is noted that this has to be looked upon as a preliminary analysis because the number of chemicals in the EURATS databases is too limited to support a robust data analysis for this case. MOA information is not available from the EU New Chemicals database precluding further supportive evidence from

this source. When more information from the EU risk assessment process becomes available a complete MOA stratification analysis may be feasible.

The EU TGD uses 'Mode of Action'-specific-QSARs to estimate toxicity for MOA 1 and 2 substances (EC, 1996c, 2003a). In combination with the appropriate Application Factor, this approach may provide an alternative data point for use in the screening risk assessment.

Many chemicals designed to have a specific MOA, such as pharmaceuticals or pesticides, are not included in the new EU Chemicals legislation as specific legislation applies. Hence, this MOA may not have been considered in depth, and given they are more toxic than the above substances it is recognised that for a broad application of the $ETNC_{aquatic}$ concept covering also such types of chemistry the $ETNC_{aquatic}$ value will probably have to be much lower. This is substantiated by the significantly lower $ETNC_{aquatic,MOA4}$ derived on the basis of the information in the ECETOC EAT 3 database (Table EE.3).

For pharmaceuticals, which are a sub-group of the MOA 4 class, a draft guideline/discussion paper for an Environmental Risk Assessment for non-GMO-containing drugs was published by the European Medicines Evaluation Agency (EMEA) (Straub, 2002). The draft guideline describes a step-wise, tiered procedure for the ERA. The first tier consists of deriving a crude predicted environmental concentration (PEC) in the aquatic compartment for the pharmaceutical ingredient or its major metabolites. If this crude PEC is < 0.01 µg/l, and no environmental concerns are apparent, no further assessment is deemed necessary. Therefore, this screening level risk assessment approach utilised the $ETNC_{aquatic}$ concept and implicitly established an $ETNC_{aquatic,MOA4}$ of 0.01 µg/l for pharmaceutical ingredients or its major metabolites (Straub, 2002). However, the EU CSTEE opinion on the EMEA draft guideline did not consider that the proposed number is scientifically valid as examples of pharmaceuticals are available that show higher aquatic toxicities (EU-CSTEE, 2001).

Nouwen *et al* (1997) classified a set of chemicals according to the Verhaar-system based on the structural information present in fragments of these chemicals. Using a PLS discriminant analysis method they observed that the inert (Class 1) and less inert chemicals (Class 2) are concentrated in a relatively small region, whereas the reactive (Class 3) and specifically acting chemicals (Class 4) were more spread out. The reactive chemicals showed some diffuse border with the inert chemicals, and distinction between reactive and specifically acting chemicals was not straightforward. Prediction of class membership for a set of high production volume chemicals (HPVCs), not formerly classified, was reasonably good.

In a further validation of the Verhaar-system, all available fish acute toxicity data were retrieved from the ECETOC EAT database (ECETOC, 1993c), the original database of quality-evaluated aquatic toxicity measurements prepared by the European Centre for the Ecotoxicology and

Toxicology of Chemicals (Verhaar *et al*, 2000). The individual chemicals for which fish data were available were classified according to the original rule-base and predictions of effect concentrations or ranges of possible effect concentrations were generated. These predictions were compared to the actual toxicity data retrieved from the database. The results of this comparison show that, generally, the classification system provides adequate predictions of either the aquatic toxicity (Class 1) or the possible range of toxicity (other classes) of organic compounds. A slight underestimation of effect concentrations occurs for some highly water soluble, reactive chemicals with low log K_{ow} values. At the other end of the scale, some compounds that are classified as belonging to a relatively toxic class appear to belong to the so-called baseline toxicity compounds. For some of these, additional classification rules were proposed (Verhaar *et al*, 2000). Furthermore, some groups of compounds cannot be classified, although they should be amenable to predictions. For these compounds additional research as to class membership and associated prediction rules was proposed.

Application areas for the concept

Application of the ETNC concept may occur in several areas. For instance, a chemical producer has access to the chemical's structure so they can assess the MOA with the Verhaar *et al* (1992) categorisation approach. In the absence of further information on its toxicity, the $ETNC_{aquatic,MOA1-3}$ of 0.1 µg/l can be used as a first approximation for comparison with estimated exposure levels in screening level environmental risk assessments. In the case of low volume chemicals or substances used in process oriented research and development there may not yet be any toxicity information available due to the relative early stages of (commercial) development. In the absence of further information on (greater) market acceptability there will probably be limited resources available to invest in safety information. The $ETNC_{aquatic,MOA1-3}$ provides an initial tool for screening and prioritisation based on environmental risk considerations.

When the chemical producer has access to acute toxicity information they can apply an appropriate Application Factor (e.g. 100 or 1,000) to derive a PNEC and subsequently compare this with the $ETNC_{aquatic,MOA1-3}$. When the $ETNC_{aquatic,MOA1-3}$ is higher, they will have to use expert judgement to decide whether the $ETNC_{aquatic,MOA1-3}$ may be used in the environmental risk assessment.

Downstream users may not have specific information on chemical structure or environmental toxicity. They may have access to some ecotoxicological information on Safety Data Sheets (SDS) (EEC, 1991). However, an SDS may not always indicate the actual LC_{50} or NOEC value, or the number of species tested. For such cases, it may be difficult to derive a PNEC value. Instead, they could apply the $ETNC_{aquatic}$ value and compare this with the environmental exposures originating from their specific uses. This allows them to assess the need for a request for further information from their supplier.

Environmental analytical experts are another group of potential users of the ETNC concept. Due to the nature of their research they do have access to the chemical structures for those materials that they include in their environmental monitoring exercise, but may not have access to quality toxicity information. As this is similar to the first example for application of the concept by chemical producers, environmental analytical experts, with necessary changes, could use the $ETNC_{aquatic,MOA1-3}$ to put their monitoring data into a risk assessment perspective.

In summary, application of the $ETNC_{aquatic}$ in a tiered risk assessment scheme will help chemical producers and importers to set data generation priorities and thus refine or reduce animal use. This will be of particular value for low volume chemicals and those used in process oriented research and development. It may also help to inform downstream users on the relative risk associated with their specific uses, and can be of value to put environmental monitoring data in a risk assessment perspective.

APPENDIX FF: USE OF QSARS TO CHARACTERISE EFFECTS AND THEIR LINK TO TOXIC MODE OF ACTION

One of the essential input parameters used in the environmental risk assessment of chemicals is the knowledge of the aquatic toxicity of these chemicals, such as, but not limited to, lethality to a certain species, or inhibition of growth or reproduction of a species. Normally this toxicity is expressed as the LC_{50}, the aqueous concentration associated with 50% individual survival of a test population within a specified period, or as the NOEC (No-Observed-Effect Concentration) for sublethal toxicity.

Much research has been and is being devoted to developing reliable estimation procedures for the toxicity of environmental pollutants, and so-called QSARs are the predominant tools for this (Escher and Hermens, 2002). Initial research assumed that chemicals from the same chemical class should behave in a toxicologically similar manner. Consequently, homologous series of chemicals were used and toxic effects were assumed to be imparted by common structural components used in chemical class assignments. Further, potency was assumed to vary with chemical uptake, which correlated with the hydrophobicity of substituent moieties within the chemical class (Bradbury *et al*, 2003).

Research completed over the past several years addressing the joint toxic action of chemicals and toxicodynamic responses observed in fish challenges the notion that QSARs are reliably based on typical chemical classification schemes. An evaluation of the US EPA fathead minnow database (Russom *et al*, 1997) illustrated that toxicological classifications based on typically used chemical classes can be problematic. Therefore, the use of MOA-based QSARs requires an appreciation of both toxic mechanisms and the critical structural characteristics and properties of a chemical that govern its action by a specific mechanism.

A primary uncertainty in the use of QSARs is the selection of appropriate models for the chemicals of interest. QSAR support systems started to convert from a chemical class perspective, e.g. the US EPA ECOSAR system, to one that is more consistent with assumptions regarding modes of toxic action (Verhaar *et al*, 1992; Verhaar *et al*, 1996; Russom *et al*, 1997; Nouwen *et al*, 1997; Verhaar *et al*, 2000). For example, assessment tools for the evaluation of risk (ASTER) is an expert system developed by the US EPA that selects QSARs based on the predicted MOA of chemicals (Russom *et al*, 1991; Russom *et al*, 1997). Similar rule-based systems have been developed by the University of Utrecht (Verhaar *et al*, 1992) (see Appendix EE for further description). Both these systems identify substructures for each chemical activity and QSARs can be subsequently assigned based on this categorisation method.

APPENDIX GG: TIER 0 AND 1 ENVIRONMENTAL RISK ASSESSMENT CASE STUDIES WITH LOW PRODUCTION VOLUME CHEMICALS

Objective, approach and limitations

The following evaluation was carried out using spreadsheet version 0.4.

Objective

- Check applicability of the environmental screening tool (Tier 0 and Tier 1) to the Environmental Risk Assessment (ERA) of low production volume (LPV) chemicals;
- compare the results from the Tier 0 Screening and Tier 1 Rule-based risk assessments with the results from Tier 1 EUSES Environmental Risk Assessment;
- identify the advantages and limitations of the ERA Screener and what needs to be improved.

Approach

- Eight substances with publicly available peer-reviewed data (German BUA Reports on LPV chemicals) were used (see Figures GG.1a and b);
- all relevant data and results were compiled in an Excel sheet for transparency.

Limitations

- Most of the LPV BUA substances are intermediates which are very ecotoxic and in most cases are not biodegradable but have low releases;
- substances from other use categories with other properties are currently missing.

Data availability and restrictions

Physico-chemical data and fate data (vapour pressure, K_{ow}, biodegradability)

- Fully available for all eight LPV substances (measurements or QSAR predictions).

Effect data (aquatic compartment)

- Sufficient aquatic effect data as well as data on bacterial toxicity were available.

Release data

Production/use volume

Exact figures were available for only one substance. For the others only ranges were given; in most cases the average values were used.

Release fractions

For all assessments the Emission Category 'used in closed system - isolated with 0.1% release' was used.

Use information

Sufficiently described for production and use (four substances); incomplete or not at all described for the use (three substances); use out of scope of the exercise (one substance - biocide). Figure GG.1:

Figure GG.1a: Substances and life-cycle step(s) assessed

CAS No.	Name	Life cycle steps assessed		Tonnage Tonnes/y	Biodeg	Ecotox	Tier 0 Screening	Tier 1 Rule based	Tier 1 EUSES
		Production	Use						
60-09-3	4-aminoazobenzene			200					
78-94-4	Methyl vinyl ketone			500					
78-95-5	Monochloroacetone			200					
79-07-2	2-chloroacetamide			999					
88-18-6	2-tert-butylphenol			999 150					
107-19-7	Propargyl alcohol			750					
130-15-4	1,4-naphthoquinone			630				Data missing	Data missing
636-30-6	2,4,5-trichloroaniline			750 450					

Figure GG.1b: Colour codes

Life cycle step	Biodegradation	Ecotoxicity	Results Tier 0 and 1
Covered	Ready		No further assessment
-	Inherent	LC/EC_{50} 1-10mg/l	-
Not covered	None	LC/EC_{50} <1mg/l	Further assessment needed

Advantages, disadvantages and limitations of the ERA screener

Advantages

- An easy-to-use tool;
- the amount of data needed for running the screener is relatively small;
- data input is supported by drop down lists;
- result is clear (no or further assessment needed).

Disadvantages

- Easy-to-use can mean that the tool can be misused because the user lacks of basic understanding of the matter (e.g. picking the emission scenario by chance without understanding the background or combining different uses in one run without understanding the implications).

Limitations

- Emission scenarios are not fully developed yet and will be updated soon by a statistical analysis of the emission tables in the EU TGD;
- handling of different uses in one run is not possible;
- guidance document on how to use the ERA Screener is not available yet.

Data refinement used for these case studies

The data refinement applied should be seen as one of several possible. It makes best use of the data available in the BUA reports.

For the Tier 0 environmental risk assessment

The default settings (release fraction, dilution factor, etc.) have resulted in 'further risk assessment required' for most cases (Figure GG.2).

Figure GG.2: Detailed example for Tier 0 and Tier 1 assessments (1)

Figure GG.2a: Production

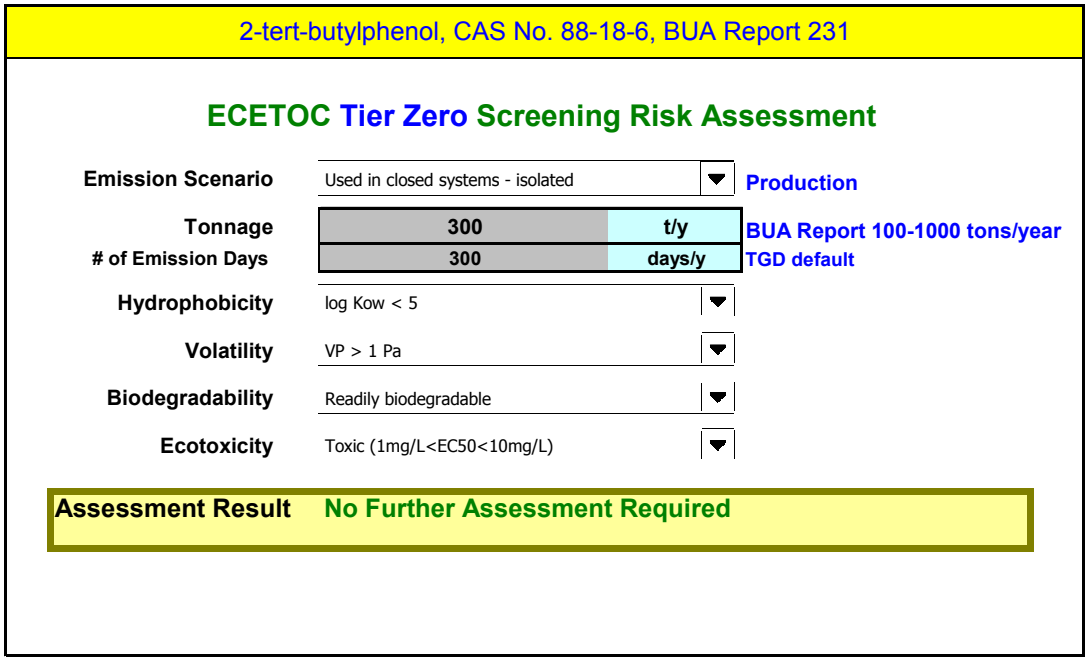
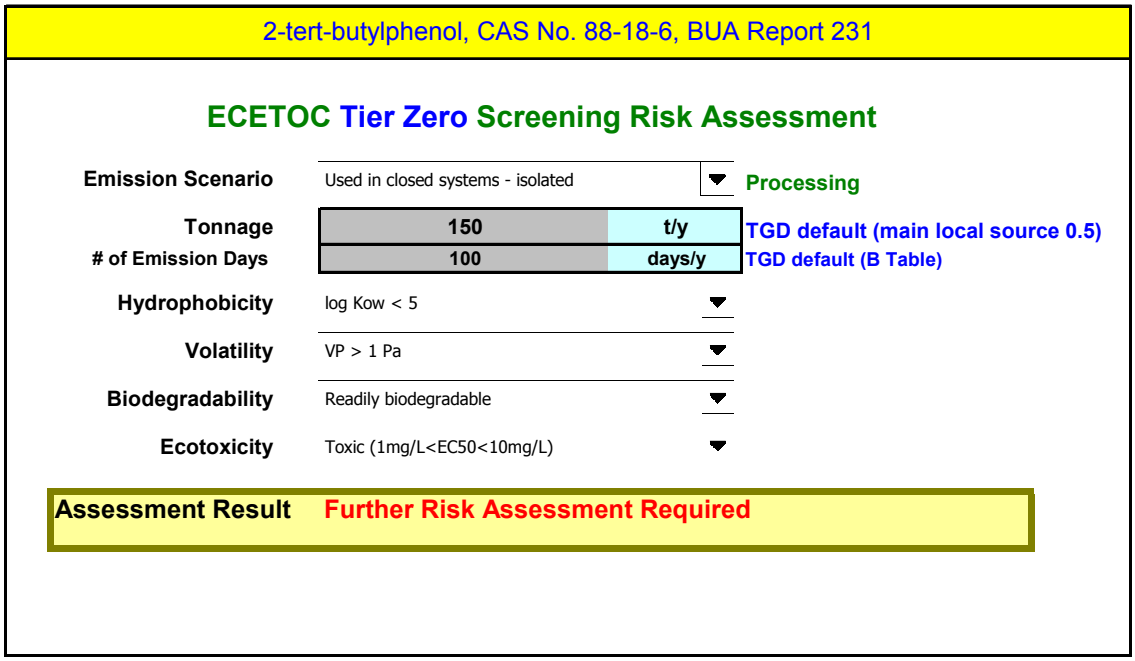


Figure GG.2b: Processing



For the Tier 1 rule-based environmental risk assessment

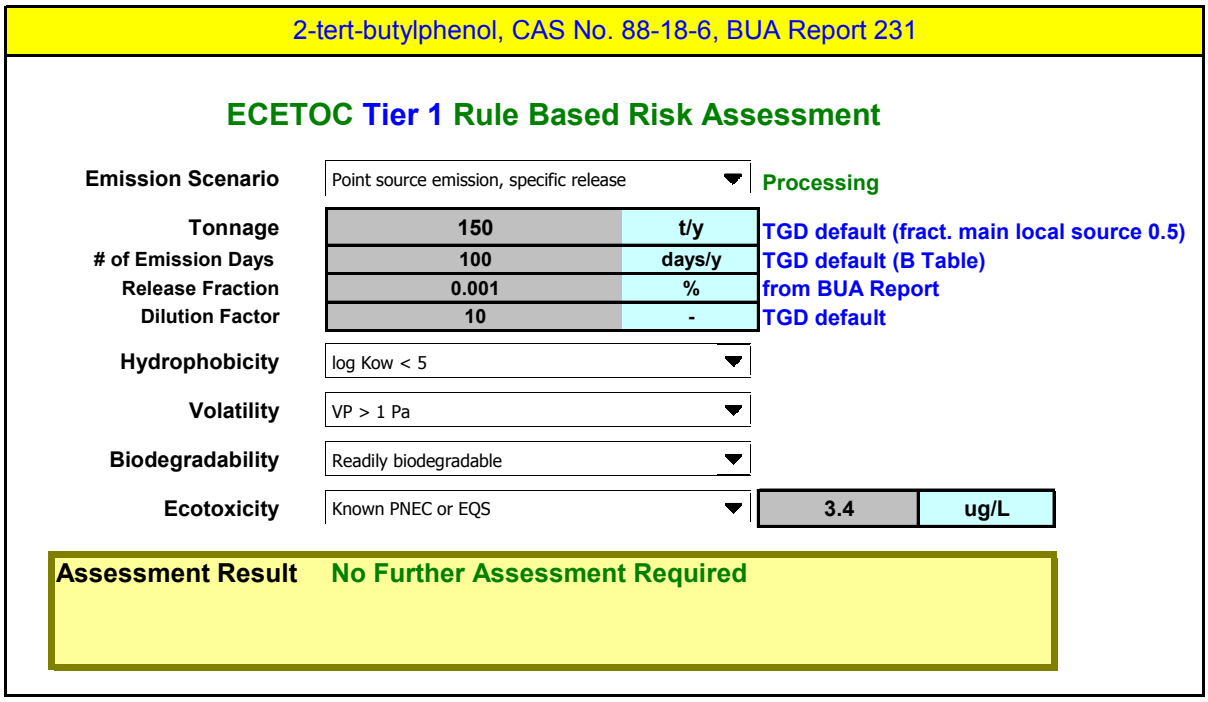
Refinement step 1 uses specific exposure data (i.e. release fraction and/or specific emission days) and specific effect data (to derive the $PNEC_{water}$) from the BUA reports instead of using ranges from Classification and Labelling, but the dilution factor is not changed (TGD default value, D=10) (see Figure GG.3).

Result of the refinement step 1: in 5 out of 8 cases the result of the ERA changed to 'no further assessment required'. The use of specific effect data ($PNEC_{water}$) did not change the outcome.

Refinement step 2 uses, in addition to the specific data of step 1, specific dilution factors derived from Hydrological Source Books.

Result of the refinement step 2: In 2 out of 8 cases, refining release data and the dilution factor changed the result of the ERA to 'no further assessment required'. In one case a refinement in dilution factor could not be achieved; in this case also Tier 1 rule-based ERA led to the conclusion 'further risk assessment required'.

Figure GG.3: Detailed example for Tier 0 and Tier 1 assessments (2)



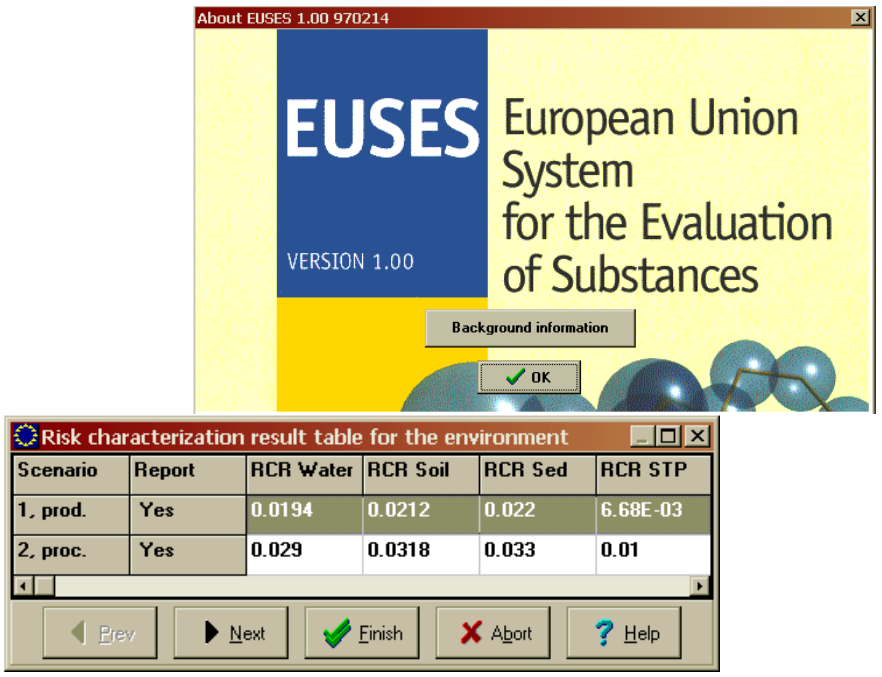
For the Tier 1 EUSES environmental risk assessment

The refined data from the refinement steps 1 or 2 of Tier 1 rule-based ERA were applied (see Figure GG.4) together with:

- Precise values of physico-chemical parameters and available aquatic ecotoxicity data.

Figure GG.4: Detailed example for Tier 0 and Tier 1 assessments (3)

2-tert-butylphenol, CAS No. 88-18-6, BUA Report 231



The results from EUSES ERA confirmed in all cases the results from Tier 1 rule-based ERA.

Summary of LPV case studies

The results for the LPV case studies based on the data and refinements outlined above (see Figure GG.5) can be summarised as follows:

Tier 0 screening environmental risk assessment

In 7 out of 8 cases the Tier 0 result was 'further risk assessment required' and for the other case, which was identified as 'no further assessment required', it was limited to production only.

Tier 1 Rule-based environmental risk assessment

- In 7 out of 8 cases the Tier 1 result was 'no further assessment required';
- in 5 out of 8 cases this was achieved by improvement of the release data;
- in 2 out of 8 cases this was achieved by improvement of the release and dilution data;
- in 1 out of 8 cases the refinement of release data alone was insufficient and, as the dilution data could not be improved, the result was 'further risk assessment required'.

Tier 1 environmental risk assessment with EUSES 1.0

In all 8 cases the Tier 1 EUSES assessment confirmed the result from Tier 1 rule-based environmental risk assessment as given above.

Figure GG.5: Summary on ERA Tier 0 and Tier 1[a]

CAS No.	Name	Life cycle steps assessed		Tonnage	Biodeg	Ecotox	Tier 0	Tier 1	Tier 1
		Production	Use	Tonnes/y			Screening	Rule based	EUSES
60-09-3	4-aminoazobenzene			200					
78-94-4	Methyl vinyl ketone			500					
78-95-5	Monochloroacetone			200					
79-07-2	2-Chloroacetamide			999					
88-18-6	2-tert-butylphenol			300					
				150					
107-19-7	Propargyl alcohol			750					
130-15-4	1,4-naphthochinone			630				Data missing	Data missing
636-30-6	2,4,5-trichloroaniline			750					
				450					

[a] See Figure GG.1 for colour codes

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[b] Resigned end of 2003

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No. 3	Risk Assessment of Occupational Chemical Carcinogens
No. 4	Hepatocarcinogenesis in Laboratory Rodents: Relevance for Man
No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology)
No. 6	Acute Toxicity Tests, LD_{50} (LC_{50}) Determinations and Alternatives
No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies
No. 8	Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment (Summary)
No. 9	Assessment of Mutagenicity of Industrial and Plant Protection Chemicals
No. 10	Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man
No. 11	Eye Irritation Testing
No. 12	Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity/teratogenicity)
No. 13	DNA and Protein Adducts: Evaluation of their Use in Exposure Monitoring and Risk Assessment
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No. 16	Early Indicators of Non-Genotoxic Carcinogenesis
No. 17	Hepatic Peroxisome Proliferation
No. 18	Evaluation of the Neurotoxic Potential of Chemicals
No. 19	Respiratory Allergy
No. 20	Percutaneous Absorption
No. 21	Immunotoxicity: Hazard Identification and Risk Characterisation
No. 22	Evaluation of Chemicals for Oculotoxicity
No. 23	Receptor Mediated Mechanisms in Chemical Carcinogenesis
No. 24	Risk Assessment for Carcinogens
No. 25	Practical Concepts for Dose Selection in Chronic Toxicity and Carcinogenicity Studies in Rodents
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No. 27	Aneuploidy
No. 28	Threshold-Mediated Mutagens - Mutation Research Special Issue
No. 29	Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment
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No. 31	Guidance on Evaluation of Reproductive Toxicity Data
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No. 2	The Mutagenic and Carcinogenic Potential of Formaldehyde
No. 3	Assessment of Test Methods for Photodegradation of Chemicals in the Environment
No. 4	The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man (updated by TR No. 17)
No. 5	Toxicity of Ethylene Oxide and its Relevance to Man
No. 6	Formaldehyde Toxicology: An Up-Dating of ECETOC Technical Reports 1 and 2
No. 7	Experimental Assessment of the Phototransformation of Chemicals in the Atmosphere
No. 8	Biodegradation Testing: An Assessment of the Present Status
No. 9	Assessment of Reverse-Phase Chromatographic Methods for Determining Partition Coefficients
No. 10	Considerations Regarding the Extrapolation of Biological Data in Deriving Occupational Exposure Limits
No. 11	Ethylene Oxide Toxicology and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 5
No. 12	The Phototransformation of Chemicals in Water: Results of a Ring-Test
No. 13	The EEC 6th Amendment: A Guide to Risk Evaluation for Effects on the Environment
No. 14	The EEC 6th Amendment: A Guide to Risk Evaluation for Effects on Human Health
No. 15	The Use of Physical-Chemical Properties in the 6th Amendment and their Required Precision, Accuracy and Limiting Values
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No. 17	The Toxicology of Glycol Ethers and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 4 (updated by TR No. 64)
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No. 19	An Assessment of Occurrence and Effects of Dialkyl-o-Phthalates in the Environment
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No. 28	Evaluation of Anaerobic Biodegradation
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No. 32	Methylene Chloride (Dichloromethane): Human Risk Assessment Using Experimental Animal Data
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No. 68 Assessment Factors in Human Health Risk Assessment
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No. 70 Chronic Neurotoxicity of Solvents
No. 71 Inventory of Critical Reviews on Chemicals (Only available to ECETOC members)
No. 72 Methyl *tert*-Butyl Ether (MTBE) Health Risk Characterisation
No. 73 The Value of Aquatic Model Ecosystem Studies in Ecotoxicology
No. 74 QSARs in the Assessment of the Environmental Fate and Effects of Chemicals
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No. 90 Persistence of Chemicals in the Environment
No. 91 Aquatic Hazard Assessment II

Joint Assessment of Commodity Chemicals (JACC) Reports

No. Title

No. 1 Melamine
No. 2 1,4-Dioxane
No. 3 Methyl Ethyl Ketone
No. 4 Methylene Chloride
No. 5 Vinylidene Chloride
No. 6 Xylenes
No. 7 Ethylbenzene
No. 8 Methyl Isobutyl Ketone
No. 9 Chlorodifluoromethane
No. 10 Isophorone
No. 11 1,2-Dichloro-1,1-difluoroethane (HFA-132b)
No. 12 1-Chloro-1,2,2,2-tetrafluoroethane (HFA-124) (updated by JACC No. 25)
No. 13 1,1-Dichloro-2,2,2-trifluoroethane (HFA-123) (updated by JACC No. 33)
No. 14 1-Chloro-2,2,2-trifluoromethane (HFA-133a)
No. 15 1-Fluoro 1,1-dichloroethane (HFA-141B) (updated by JACC No. 29)
No. 16 Dichlorofluoromethane (HCFC-21)
No. 17 1-Chloro-1,1-difluoroethane (HFA-142b)
No. 18 Vinyl Acetate
No. 19 Dicyclopentadiene (CAS: 77-73-6)
No. 20 Tris-/Bis-/Mono-(2 ethylhexyl) phosphate
No. 21 Tris-(2-butoxyethyl)-phosphate (CAS:78-51-3)
No. 22 Hydrogen Peroxide (CAS: 7722-84-1)
No. 23 Polycarboxylate Polymers as Used in Detergents
No. 24 Pentafluoroethane (HFC-125) (CAS: 354-33-6)

No. 25 1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (CAS No. 2837-89-0) (updated by JACC No. 46)
No. 26 Linear Polydimethylsiloxanes (CAS No. 63148-62-9)
No. 27 *n*-Butyl Acrylate (CAS No. 141-32-2)
No. 28 Ethyl Acrylate (CAS No. 140-88-5)
No. 29 1,1-Dichloro-1-fluoroethane (HCFC-141b) (CAS No. 1717-00-6)
No. 30 Methyl Methacrylate (CAS No. 80-62-6)
No. 31 1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)
No. 32 Difluoromethane (HFC-32) (CAS No. 75-10-5)
No. 33 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) (CAS No. 306-83-2)
No. 34 Acrylic Acid (CAS No. 79-10-7)
No. 35 Methacrylic Acid (CAS No. 79-41-4)
No. 36 *n*-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9)
No. 37 Methyl Acrylate (CAS No. 96-33-3)
No. 38 Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3)
No. 39 Tetrachloroethylene (CAS No. 127-18-4)
No. 40 Peracetic Acid (CAS No. 79-21-0) and its Equilibrium Solutions
No. 41 *n*-Butanol (CAS No. 71-36-3)
No. 42 Tetrafluoroethylene (CAS No. 116-14-3)
No. 43 *sec*-Butanol (CAS No. 78-92-2)
No. 44 1, 1, 1, 3, 3-Pentafluoropropane (HFC-245fa)
No. 45 1, 1-Difluoroethane (HFC-152a) (CAS No. 75-37-6)
No. 46 1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) CAS No. 2837-89-0 (Second Edition)

Special Reports

No. Title

No. 8 HAZCHEM; A Mathematical Model for Use in Risk Assessment of Substances
No. 9 Styrene Criteria Document
No. 10 Hydrogen Peroxide OEL Criteria Document (CAS No. 7722-84-1)
No. 11 Ecotoxicology of some Inorganic Borates
No. 12 1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0)
No. 13 Occupational Exposure Limits for Hydrocarbon Solvents
No. 14 *n*-Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document
No. 15 Examination of a Proposed Skin Notation Strategy
No. 16 GREAT-ER User Manual
No. 17 Risk Assessment Report for Existing Substances Methyl *tertiary*-Butyl Ether

Documents

No.	Title
No. 32	Environmental Oestrogens: Male Reproduction and Reproductive Development
No. 33	Environmental Oestrogens: A Compendium of Test Methods
No. 34	The Challenge Posed by Endocrine-disrupting Chemicals
No. 35	Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances
No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction
No. 43	Contact Sensitisation: Classification According to Potency, A Commentary

Workshop Reports

No.	Title
No. 1	Workshop on Availability, Interpretation and Use of Environmental Monitoring Data 20-21 March 2003, Brussels
No. 2	Strategy Report on Challenges, Opportunities and Research needs arising from the Definition, Assessment and Management of Ecological Quality Status as required by the EU Water Framework Directive based on the workshop EQS and WFD versus PNEC and REACH - are they doing the job ? 27-28 November 2003, Budapest
No. 3	Workshop on the Use of Human Data in Risk Assessment 23-24 February 2004, Cardiff
No. 4	Influence of Maternal Toxicity in Studies on Developmental Toxicity 2 March 2004, Berlin