Risk Assessment of PBT Chemicals

Technical Report No. 98

ISSN-0773-8072-98
Brussels, December 2005

ECETOC TECHNICAL REPORT No. 98

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SUMMARY

Many chemical regulatory schemes exist around the world that contain hazard-based criteria to identify and prioritise persistent, bioaccumulative and toxic (PBT), or very persistent very bioaccumulative (vPvB) chemicals. These are chemicals that have the potential to persist in the environment, accumulate within the tissue of living organisms and, in the case of chemicals categorised as PBTs, show adverse effects following long-term exposure.

Concerns have been expressed within various European Commission documents that risk assessment cannot be applied to chemicals categorised as PBTs or vPvBs due, in part, to the uncertainties involved with current methodologies. These documents argue that decisions on chemical management should be based on the hazard, rather than the risk, of these chemicals. The aim of this report is to investigate whether these concerns over the application of risk assessment to chemicals categorised as PBTs or vPvBs are valid and to identify ways in which the risk assessment process can be improved in order to reduce the uncertainties involved.

The report includes an overview of a number of relevant regulatory schemes and an introduction into the principles of risk assessment and the application to chemicals categorised as PBTs and vPvBs. It also contains sections aimed at identifying the main issues and sources of uncertainty within exposure, bioaccumulation and effects assessments. Recommendations are then made so that a refined, and less uncertain, risk assessment can be produced. This refined risk assessment is considered appropriate for assessing the environmental safety of chemicals identified as being of concern due to their persistent, bioaccumulative and toxic profile.

Risk assessment is a continually developing science and the report concludes with opinions on how this science can be advanced further in order to generate assessments of environmental risk that are even more predictive of the real world.

This Task Force recognises that chemicals policies across the world have been proposed, in part, to more rapidly screen and regulate chemicals to better protect the environment and human health. It has been noted that the existing risk assessment process in Europe is too time consuming and, for chemicals of high concern, too much uncertainty exists in addressing the potential risks posed by these chemicals. The Task Force acknowledges and agrees with these opinions and supports approaches for more rapid, risk-based assessments of chemicals that pose low to medium risks to the environment and human health. These processes, when properly designed and implemented, will result in more rapid and less uncertain assessment of risks posed by chemicals. For those chemicals of higher concern, i.e. chemicals categorised as PBTs and vPvBs, the processes and procedures set forth in this report, will result in more rapid assessments (by the use of exposure modelling and commencing effects assessment at a higher tier). They will also reduce uncertainty through more robust, albeit longer, studies of environmental effects

through the food chain. However, the Task Force believes that the proposals within this report when combined with a well-designed chemicals policy will result in a more expeditious assessment of the risks posed by the majority of organic chemicals.

1. INTRODUCTION

Society is concerned about the potential threat of chemicals to human health and the environment. These concerns have resulted from scientific research over the last 40 years into the presence in the environment and effects of chemicals including DDT, PCBs and dioxins (see, for example, Ritter *et al*, 1995). Following technological advancements in the ability to measure trace levels of such chemicals and their metabolites in various environmental media, as well an increase in knowledge of their behaviour in the environment, many chemicals can now be found in remote environments (e.g. the Arctic, Antarctic and remote Pacific islands) or within the tissues of humans and wildlife. Chemicals such as these can be transported over long distances, are resistant to abiotic and biotic degradation and may accumulate in biota, comprise a small subset of organic chemicals termed persistent organic pollutants (POPs). The issue was first addressed by the United Nations Economic Commission for Europe (UNECE) convention on long-range transboundary air pollution and later by the United Nations Environment Programme (UNEP). Initially twelve substances, nine of which were pesticides that became widely used in the late 1940s, were targeted in the POPs treaty negotiations. Their presence in the environment and the detection of unexpected effects, for example egg shell thinning in birds, particularly raptors as a result of exposure to DDT (e.g. IPCS, 1989), have contributed to a general societal concern over chemicals which have the potential to persist in the environment, accumulate in the fatty tissue of living organisms, and show adverse effects following long-term exposure.

In response to these concerns, governments and other agencies in many parts of the world have developed strategies to identify and prioritise highly hazardous chemicals. This has led to the development of hazard-based criteria to categorise chemicals as persistent and bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB). One example of such a strategy is within the new draft European chemicals legislation, or REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (EC, 2003a). Within REACH, chemicals that meet the criteria of 'very high concern', such as PBT, require 'authorisation' for placing on the European market for specified uses. REACH requires applicants seeking authorisation to conduct an assessment to 'demonstrate that the risks related to the use of the substance concerned are adequately controlled' (EC, 2003a). The risk assessment of chemicals within Europe has traditionally been employed to evaluate the impact of chemicals on both human health and the environment according to the methodologies set out within the European Union (EU) Technical Guidance Document (TGD) on risk assessment (EC, 2003b). However, concerns over the uncertainties involved in the risk assessment process have been voiced by some in society, especially in relation to assessing the risks associated with hazardous chemicals. These concerns are illustrated within the following text taken from the EC interim strategy for the management of PBT and vPvB substances (EC, 2001). 'Any approach to assess and manage the risks caused by (PBT and vPvB) substances must take account of the uncertainties in the estimation of the exposures, the adverse effects and potentially serious consequences of belated action. It has

therefore been suggested that the management of PBT and vPvB substances should be based on minimisation of the exposure of man and the environment by restricting or banning the use in general rather than on detailed quantitative risk assessments where in the end substantial uncertainties will remain. Such an approach would also help to avoid the delays in the adoption of appropriate safety measures caused by the time consuming elaboration and discussion of such risk assessments.' This highlights the dissatisfaction of some over the speed of past risk assessments of existing substances, as well as the ability of current risk assessment methodologies to predict the fate and effect of chemicals within the environment.

Similar concerns over the difficulty in estimating the risks of hazardous chemicals and the ability to protect ecosystems are expressed within the TGD (EC, 2003b). Here, the concerns are focused on the marine environment, where, it is argued, existing risk assessment methodologies may not adequately address:

- The concern that hazardous substances may accumulate in parts of the marine environment and that the effects of such accumulation would be unpredictable and practically difficult to reverse, and
- the concern that remote areas of the marine environment should remain untouched by human activity and that pristine environments should be protected.

Whilst it is recognised that risk assessment, in common with all scientific endeavours, includes a number of uncertainties, calls for hazard- rather than risk-based chemical-management decisions sacrifice evidence-based knowledge for speedy decisions and a supposed increase in environmental protection. Such an approach could deprive society of benefits of chemicals as a result of excessive risk-reduction measures (Calow and Forbes, 2003).

An alternative to hazard-based decision making is to improve the current risk assessment methodologies such that the uncertainties are reduced. It is clear that due to the hazardous nature of chemicals categorised as PBTs or vPvBs, additional information will be required to adequately assess environmental risks. This report is intended to identify and suggest these areas for improvement. These suggested improvements could also aid the assessment of chemicals which have not satisfied all the criteria required to be categorised in this way, as it is recognised that the cut-off values assigned to the P, vP, B, vB and T criteria are somewhat arbitrary.

This identification of possible areas of improvement to risk assessment methodologies could contribute to a more efficient and timely process by the proactive alerting of industry to the extent of data generation required to support chemicals categorised as PBTs. It may also help reduce the often lengthy discussions between industry and regulators on how risk assessments should be done for such hazardous materials. However, it is clear that such chemicals will require additional effort to adequately assess environmental risks. Proposals such as those in the ECETOC report on

targeted risk assessment (ECETOC, 2004a) would allow less effort to be spent on chemicals with little or no concern, thereby allowing effort to be diverted to those categorised as PBTs.

This report includes the environmental risk assessment of organic substances and complex substances[a]. The food chain assessment presented in this report is an element for estimating indirect exposure to humans through the environment. The report does not include the human health risk assessment itself. However, some results of the environmental risk assessment of chemicals categorised as PBTs will justify the need for a further assessment of possible risks to human health. For example, the accumulation of chemicals categorised as PBTs in human dietary sources, as indicated by a food chain accumulation assessment/exposure assessment, will trigger the need for a human health risk assessment.

An ECETOC Task Force (TF) was commissioned to investigate whether the concerns expressed over the inadequacies of current risk assessment methodologies are valid when applied to chemicals categorised as PBTs[b] or vPvBs. The TF had the following Terms of Reference:

- Review how the existing regulatory schemes with criteria for categorising substances as PBT address the risk assessment of those chemicals;
- identify main technical and methodological issues and uncertainties for risk-based decision making of substances that are categorised as PBTs;
- develop and recommend a risk-based strategy to address substances categorised as PBTs within a regulatory setting.

[a] Mixtures comprising a complex mix of individual substances with different water solubility and other physico-chemical properties. In most cases, they can be characterised as a homologous series of substances with a certain range of carbon chain length/number or degree of substitution. These materials are frequently referred to as 'multi-component substances'.

[b] Throughout this report, the abbreviation PBT includes substances categorised as vPvB.

2. DEFINITIONS OF PERSISTENCE, BIOACCUMULATION AND TOXICITY AND REVIEW OF EXISTING REGULATORY SCHEMES

2.1 Definitions

In response to the concerns over hazardous chemicals, governments and other bodies in many parts of the world have proposed threshold values for their potential to persist in the environment, accumulate within the tissues of humans and wildlife and possess toxic characteristics which are likely to cause adverse human health or environmental effects. Chemicals fulfilling these criteria are categorised as PBTs. Similarly, chemicals with a lower potential to degrade and with a higher potential to bioaccumulate may be categorised as vPvBs. These criteria are summarised in Table 1.

Persistence: A substance is considered to be persistent in a given medium if it resists physical, biological and chemical degradation. The degradation of a substance in a given medium is usually expressed by its overall half-life. Half-life is defined as the length of time required to reduce the concentration of a substance by 50%. Strictly speaking, the half-life concept is only valid if the degradation process follows first-order reaction kinetics. It is, however, very often used as a surrogate for DT_{50} which is the disappearance time, i.e. the time needed for reducing the concentration of a substance in a medium by 50% of its initial value, whatever the kinetics of the degradation processes. Half-life or disappearance time as observed under environmental conditions is the net result of many processes and interactions such as partitioning between environmental compartments and all degradation/removal processes, typically hydrolysis, oxidation, photolysis and biodegradation. This complexity and the variability between and within environmental compartments explain why it is difficult to estimate degradation from standardised laboratory tests.

An ECETOC TF has addressed persistence (ECETOC, 2003a) and the role of degradation in environmental exposure assessment is discussed in Chapter 4 of this report.

Bioaccumulation: Bioaccumulation of a substance is its capacity to accumulate in the tissues of organisms, either through direct exposure to water, air or soil, or through consumption of food. It is expressed by the ratio, in a steady-state situation, of its concentration in the organism to the concentration in the medium to which this organism is exposed. This is termed the bioaccumulation factor (BAF).

When the chemical intake in the organism is via the substance dissolved in the medium, generally water, the ratio is called the bioconcentration factor (BCF). When intake is via food the ratio is called the biomagnification factor (BMF).

Table 1: Overview of main PBT and vPvB criteria

	Persistence	**Bioaccumulation**	**Toxicity** [a]
EU PBT from TGD (*differences under REACH are indicated in italics*)	Half-life > 60 days in marine water or > 40 days in freshwater [b] (*or estuarine water*) or > 180 days in marine sediment or > 120 days in freshwater [b] (*or estuarine*) sediment (*or soil*)	BCF > 2,000	Chronic NOEC < 0.01 mg/l or avian chronic NOEC < 30 mg/kg/food or CMR category 1 and 2 or other evidence of chronic toxicity (e.g. endocrine disruption, serious damage due to prolonged exposure)
EU vPvB from TGD (*differences under REACH are indicated in italics*)	Half-life > 60 days in marine, freshwater (*or estuarine water*) or > 180 days in marine, freshwater (*or estuarine*) sediment	BCF > 5,000	Not applicable
OSPAR PBT criteria	Not readily biodegradable or half-life in water > 50 days	Log $K_{ow} \geq 4$ or BCF ≥ 500	Acute aquatic toxicity $L(E)C_{50}$ ≤ 1 mg/l or long-term NOEC ≤ 0.1 mg/l or mammalian toxicity: CMR or chronic toxicity
US-EPA - Control Action [c]	Transformation half-life > 2 months	BCF > 1,000	Toxicity data based on level of risk concern
US-EPA - Ban Pending [d]	Transformation half-life > 6 months	BCF ≥ 5,000	Toxicity data based on level of risk concern
Canada Toxic Substances Management	Half-life in: air > 2 days, water > 6 months, sediment > 1 year, soil > 6 months	BAF or BCF > 5,000 or log K_{ow} > 5 [e]	'Inherently toxic'
UK Chemical Stakeholder Forum - Substances of highest concern	Half-life > 60 days in marine water or > 40 days in freshwater or > 180 days in marine sediment or > 120 days in freshwater sediment	Log K_{ow} > 4.5 or BCF > 2,000 [f]	Acute $L(E)C_{50}$ < 0.1 mg/l or chronic NOEC < 0.01 mg/l or CMR category 1 and 2 or mutagen or reprotoxin category 3 or endocrine disrupting effects
UK Chemical Stakeholder Forum - Substances of concern	Half-life > 2 months in water or > 6 months sediment or soil	Log K_{ow} > 4 or BCF > 500 [g]	Acute $L(E)C_{50}$ < 1 mg/l or chronic NOEC < 0.1 mg/l or CMR category 1 and 2 or mutagen or reprotoxin category 3 or endocrine disrupting effects

[a] $L(E)C_{50}$; NOEC - no observed effect concentration; CMR - carcinogenic, mutagenic or toxic to reproduction

[b] For marine environment risk assessments, half-life data in freshwater and freshwater sediment can be overruled by data obtained under marine conditions

[c] Testing and release control required

[d] Commercialisation denied except if testing justifies removing chemical from 'high risk concern'

[e] BAF preferred over BCF, in the absence of BAF or BCF, log K_{ow} may be used

[f] Experimental BCF < 2,000 overrides log K_{ow} data

[g] Experimental BCF < 500 overrides log K_{ow} data

For some classes of chemicals the tendency of the substance to bioconcentrate has been related to the relative solubility in fat compared to its solubility in water. This property, often used to estimate the bioaccumulation potential of a substance, is the octanol-water partition coefficient (generally named log K_{ow} or log P_{ow}). Log K_{ow} is determined in the laboratory by measuring the partitioning of a chemical in a water and octanol (used as a surrogate for fat) system. For some classes of substances, correlations have been developed which link log K_{ow} and BCF. However, as the use of this coefficient does not consider the ability of the chemical to pass across cell membranes or the ability of the living organism to transform the substance through metabolic pathways, directly measured BAF, BCF or BMF values are more valid.

An ECETOC Task Force addressed bioconcentration (ECETOC, 1995) which, in the context of a bioaccumulation assessment, is discussed in Chapter 5 of this report.

Toxicity: Toxicity is measured in a series of concentration-response experiments on various organisms and endpoints over various exposure periods. Threshold values ascribed via the 'T' criterion establish whether or not a chemical presents a toxic hazard. This toxicity compared against the potential exposure of the chemical in a particular medium determines its environmental risk.

As chemicals categorised as PBTs or vPvBs have the potential to persist longer in the environment, chronic toxicity tests are more relevant than acute studies for assessing the potential effects in the environment. This report addresses the issues of assessing toxicity in Chapter 6.

2.2 Why the focus on PBT and vPvB chemicals?

From a regulatory authority viewpoint, chemicals categorised as meeting the P or vP criteria are of particular concern because of their predicted long environmental half-lives. As a consequence, successive releases over time could result in a build-up in the environment if the rate of release is higher than the rate of disappearance. Additionally, when distribution within the environment occurs, the presence of such chemicals could be observed on a wider geographical scale, therefore spreading the possible concern to remote areas. Moreover, when a toxic substance is not only persistent in the environment, but also able to bioaccumulate, the potential for exposure to living organisms in a higher trophic level to a particular substance is increased. This may lead to possible adverse sublethal effects from chronic exposure that would not have been predicted from standardised laboratory tests.

2.3. Review of existing schemes

The categorisation of PBT chemicals is based on set criteria, i.e. properties with threshold values. In the most part, all the criteria have to be fulfilled simultaneously for a chemical to be considered as being a PBT or vPvB. Various national and international agreements to prioritise hazardous chemicals already exist, some of which are summarised below.

2.3.1 EU TGD and REACH

Currently in the EU, environmental risk assessment of new and existing substances is required by the Existing Substances Regulation EEC 793/93 (EC, 1993) and the Directive on Notification of New Substances 92/32/EEC (EC, 1992), with comprehensive guidance for these provided in the revised version of the TGD (EC, 2003b). The TGD incorporates specific PBT and vPvB criteria aimed at protecting the marine environment (Table 1). Specific criteria for the inherent properties have been proposed to identify potential PBT and vPvB substances. The TGD indicates that for most substances the available data will not allow a definitive categorisation of a chemical as a PBT or vPvB. The TGD therefore proposes the use of screening data to identify whether the substance has a potential to meet PBT criteria. Further testing strategies (e.g. a stepwise approach for the verification of the screening data) are suggested.

According to the TGD, long-term effects with vPvB substances 'can be anticipated anyway', and testing of the T-criterion will not be necessary for those substances.

In principle, substances are categorised as PBTs when they fulfil the criteria for P, B and T. However, certain flexibility exists in the application of the PBT approach, for example, in cases where one criterion is marginally not fulfilled but the others are greatly exceeded.

Normally, the risk assessment of a chemical in the environment is based on a comparison between the levels to which organisms in a particular compartment are exposed, and the maximum levels which the organisms can tolerate without suffering significant adverse effects. The assessment of substances considered to be PBT, as advocated in the TGD, is not a risk assessment *per se* but is based on the intrinsic properties of substances only. Depending on the outcome of the PBT assessment, risk minimisation measures will have to be implemented (e.g. effective measures to reduce the releases to the marine environment).

The PBT assessment in the TGD is different from the risk assessment approaches for the local and regional environment as, it argues, it seeks to protect ecosystems where the risks are more difficult to estimate. The rationale provided in the TGD to support this departure from a risk-based approach includes both the long term unpredictable effects of possible accumulation which

would be difficult to reverse, and the wish for pristine environments, such as remote marine environments, to remain untouched by hazardous substances resulting from human activities.

Recently, the European Commission (EC) proposed a new approach to chemicals management, known as REACH (EC, 2003a). It is proposed that this new legislation will implement an authorisation system for the use of all substances designated to be of 'very high concern'. Those are defined as substances being carcinogenic, mutagenic or toxic to reproduction, those that fulfil the PBT or vPvB criteria, or those deemed to be of 'equivalent concern' (such as endocrine disrupters). In contrast to the TGD, the PBT assessment within REACH applies not only to the marine environment but is intended for use in all environmental compartments.

The criteria for a substance to be considered PBT or vPvB according to REACH are given in annex XII of the proposed legislation (Table 1). Those criteria are essentially the same as in the TGD with the addition of persistence criteria in soil, estuarine water and estuarine sediment. However, according to the proposed legislation, other 'substances considered to be of equivalent concern' can be identified on a case-by-case basis and consequently fall under the authorisation regime.

It is intended that industry will apply for an authorisation to allow specific uses of a chemical. Authorisations may be granted for those uses based on risks to human health, risks to the environment, socio-economic benefits, availability of a reasonable alternative and the health or environmental risks of alternative substances or technologies. For an authorisation to be granted the applicant must demonstrate, through the use of a risk assessment, that exposures arising from specific uses of the chemical can be controlled sufficiently.

In addition to the authorisation of substances considered to be of 'very high concern' the proposed new legislation requires all substances manufactured or imported in quantities of more than 1 tonne per year to be registered with a human health hazard assessment, an environmental hazard assessment and a separate PBT/vPvB assessment.

As currently proposed, the objective of the PBT assessment will be to determine if the substance meets the criteria given in Annex XII and if so, to characterise the potential emissions of the substance. This emission characterisation shall 'contain an estimation of the amounts of the substance released to the different environmental compartments during all activities carried out by the manufacturer or importer and all identified uses, and an indication of the likely routes by which humans and the environment are likely to be exposed' (EC, 2003a).

2.3.2 EU Water Framework Directive

The EU Water Framework Directive (WFD) (EC, 2000b) is a framework for the protection of inland waters, estuaries, coastal waters and ground waters. Its main objectives are to ensure that all waters meet 'good ecological status' by 2015, and to prevent deterioration and to maintain this status. At the same time it is a consolidated approach by repealing older Directives such as the Surface Drinking Water Directive (75/440/EEC), Fish Freshwater Directive (78/659/EEC), Groundwater Directive (80/68/EEC) and elements of Directive on Dangerous Substances Discharges (76/464/EEC). This Directive will contribute to the progressive reduction of emissions of hazardous substances to water and the cessation of release of priority hazardous substances.

To achieve the objectives of the Directive, measures rely in principle on a combination of two approaches: minimum quality thresholds for all substances on the priority list through Environmental Quality Standards (EQSs) and Emission Limit Values (ELVs).

EQSs are designed to protect both human health and the environment. There is a need for clarity on the distinction between Predicted No Effect Concentrations (PNECs) and EQSs, both in how they are derived and used. The CSTEE stated that '...PNECs are often derived as part of a tiered approach, so that those based on a minimum data set and worst-case conclusions will not usually lead to a management decision but trigger the development of a more refined assessment often on the basis of the collection of more exposure and effects data. Caution needs to be exercised in basing EQS on too little and inappropriate data' (CSTEE, 2004). The Task Force agrees with this statement in that an EQS derived from sound scientific principles may provide an appropriate endpoint by which a PNEC could be derived. However, it is not the purpose of this report to determine the appropriate use of EQSs in risk assessment.

In the WFD chemicals are identified as priority hazardous substances that are '.... toxic, persistent and liable to bioaccumulate, and other substances or groups of substances which give rise to an equivalent level of concern'. An initial list of 33 priority substances or groups of substances has been selected.

The 'negligible load' concept, introduced as a possible element in the first draft of the implementation of the WFD (Part III: 'Pollution Control'), was intended to lead to an exposure level of 'no more regulatory concern'. The level of releases corresponding to the 'negligible load' for a priority hazardous substance should ensure that it does not harm human health or ecosystems and that a decreasing trend in environmental concentrations is observed.

2.3.3 The OSPAR convention on the marine environment

The OSPAR Hazardous Substances Strategy seeks to 'prevent pollution by continuously reducing discharges, emissions and losses of hazardous substances, with the ultimate aim of achieving concentrations in the marine environment (of the North East Atlantic) to near background values for naturally occurring substances and close to zero for man-made synthetic substances.' Hazardous substances are identified by OSPAR using their own PBT criteria (Table 1) or on the basis of other properties that give rise to a similar level of concern for the marine environment. These are then prioritised according to the DYNAMEC (Dynamic selection and prioritisation mechanism for hazardous substances) process (OSPAR, 1998).

Risk assessment, combined with other tools and activities, is then used to establish the scale of the threat posed to the marine environment of the prioritised substance. The results of the risk assessment assists the OSPAR Commission to decide on the most appropriate risk management measures, the urgency of these measures and who is best placed to carry them out.

2.3.4 US-EPA - PBT profiler

Syracuse Research Corporation (SRC), on behalf of the US-EPA, has developed the PBT Profiler. This is an internet-based program (www.pbtprofiler.net) designed to assess the hazard characteristics of a chemical against US-EPA criteria (Table 1). The PBT assessment tools were built upon SRC's EPISUITE software that estimates physico-chemical properties, environmental fate and effects of molecules using models that are either fragment or K_{ow} based QSARs, or expert systems, or some combination of the three.

For persistence, the PBT Profiler determines a substance's half-life in air, water, soil, and sediment based on the AOPWIN and BIOWIN 3 models and certain assumptions. The medium (or media) in which a chemical is most likely to be found is identified using a Mackay Level III multi-media mass balance model (fugacity model). This medium is then selected and the model assigns a rank of 'high', 'medium', or 'low' to the chemical by comparing against US-EPA criteria. Bioaccumulation is based on the BCFWIN model and the same rankings are applied depending on the output of the model. Finally, toxicity is determined from the chronic value estimated by the QSARs in ECOSAR and, again, after criteria comparison, the same rankings are applied.

Apart from the fugacity calculation used to determine distribution in the environment, this is a hazard-screening tool that does not consider exposure. It is, therefore, is not a model that assesses the environmental risk of a chemical. Provided the user understands the limitations of the platform models from EPISUITE, the PBT Profiler is useful as a hazard screening tool from

which the user can collect some estimated endpoints and hazard rank a series of chemicals to prioritise them for subsequent testing or risk assessment programmes.

2.3.5 Canadian Domestic Substances List categorisation

Criteria for persistence, bioaccumulation and inherently toxic (PBiT) are being used by Environment Canada to assess approximately 23,000 substances listed on their Domestic Substances List (DSL). Criteria for persistence and bioaccumulation are set out in the Regulations for Persistence and Bioaccumulation (Government of Canada, 2000) and are provided in Table 1. These criteria were developed from the Toxic Substances Management Policy (Government of Canada, 1995), which provides a common science-based management framework for toxic substances in all Canadian federal programmes and initiatives. The definition of inherently toxic to non-human organisms is under consideration by Environment Canada. Those substances found to be persistent or bioaccumulating and inherently toxic will proceed to the second phase, a screening level risk assessment. Depending on the outcome of the screening level risk assessment, one of the following outcomes can occur:

- No further action is taken if the screening level risk assessment indicates that the substance does not pose a risk to the environment or human health;
- the substance is added to the Priority Substances List in order to assess more comprehensively the possible risks associated with the release of the substance;
- it is recommended that the substance be added to the list of Toxic Substances in Schedule I of CEPA (Canadian Environmental Protection Act), if the screening level risk assessment indicates clear concerns. Substances on Schedule 1 can be considered for regulatory controls, including, if the substance is not a naturally occurring substance, virtual elimination.

Under this process, risk assessment principles are applied to priority materials. The screening assessment is a tiered process, with decreasingly conservative assumptions as one proceeds up the tiers. An Estimated Exposure Value (EEV) and a Critical Toxicity Value (CTV) are derived. In Tier I, the EEV will likely be the highest estimated or measured environmental concentration available. The CTV, likewise, will be based on toxicity to the most sensitive organism tested. The CTV is then divided by the necessary assessment factor(s) to derive the Estimated No Effects Value (ENEV). A Tier 1 quotient is calculated by dividing the EEV by the ENEV. If the result is less than 1, the substance is judged not to be ‘toxic’ under CEPA for the assessment endpoint and no further assessment is needed. If it is greater than 1, then the substance is assessed further, using less conservative (more data intensive) assumptions (Tiers II or III). If a substance ‘fails’ in Tier III (EEV/ENEV > 1), then it is considered to be CEPA toxic and put on Schedule 1.

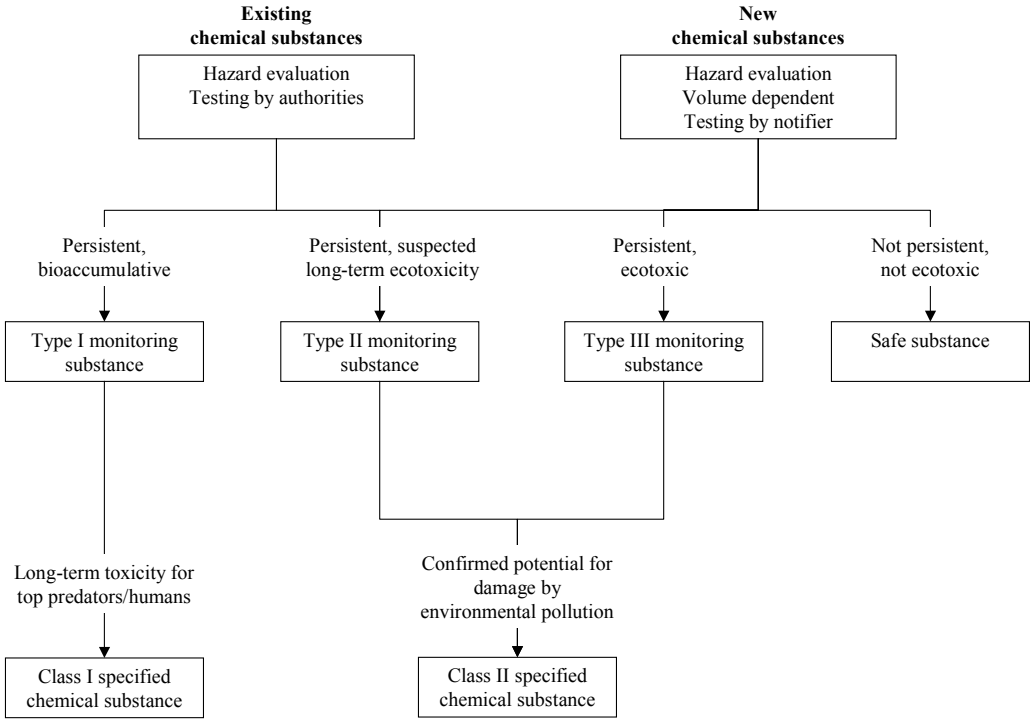
2.3.6 PBT assessment in the Japanese chemical legislation

The 'Chemical Substances Control Law' enacted in 1973 aims at preventing damage to human health caused by environmental pollution from chemical substances. A simplified overview on the framework for the evaluation and regulation of chemical substances in Japan (www.safe.nite.go.jp/english/kasinn/pdf/PROVISIONALTRANSLATION_L1.pdf) according to the latest amendment to the Chemical Substance Control Law of 1st April 2004 is given in Figure 1. New chemical substances undergo a volume-dependent ecotoxicological and toxicological testing scheme by the notifier before approval for manufacture/supply to the Japanese market. In addition, under the Existing Chemical Programme sponsored by the Japanese Government, existing substances which are not covered by the legislation for new chemicals also undergo systematic testing.

Hazard endpoints, such as persistence in combination with ecotoxicity or long-term toxicity or confirmed potential for damage by environmental pollution, can lead to specific classification and regulation of chemical substances as Type II/III Monitoring Substances and Class II Specified Chemical Substances. In addition, substances having been identified as exhibiting persistence and bioaccumulative properties can be placed under legal control by classification as Type I Monitoring Substances or ultimately as Class I Specified Chemical Substances. Currently 13 substances have been designated as Class I specified Chemical Substances. Regulatory measures for Type I Monitoring Substances include mandatory reporting of quantities of manufacture, import and use, risk reduction measures according to a preliminary toxicological evaluation by the authorities and the requirement for further investigation of long-term ecotoxicity/toxicity. In the case of established long-term toxicity for top predators (e.g. birds, mammals) substances can be classified as Class I Specified Chemical Substances to prevent releases into the environment. Class I Specified Chemical Substances are banned for production and import unless they are specifically approved for use by the authorities.

The exact criteria leading to a Classification as Type I Monitoring Substance or as Class I Specified Chemical Substance are not prescribed but seem to depend largely on a hazard, rather than risk-based, evaluation by governmental experts.

Figure 1: Framework for evaluation and regulation of chemical substances in Japan



2.3.7 UK Chemicals Stakeholder Forum

The function of the UK Chemicals Stakeholder Forum (CSF) is to advise the UK government on managing risks to the environment and to human health from chemicals entering the environment through commercial production and use. The CSF consists of a number of stakeholders including non-governmental organisations and other interested bodies. The Forum has no regulatory power, but where it identifies a cause for concern it seeks voluntary agreements on a reduction in emissions or use of a material by industry and/or other stakeholders. Advice on the selection, prioritisation of potentially hazardous chemicals, and the risks posed to the environment and/or human health is provided by the Advisory Committee on Hazardous Substances (ACHS). This is achieved in part by engaging in technical discussions with industry and regulatory bodies such as the Environment Agency of England and Wales.

The CSF has criteria to identify 'Substances of Concern' and 'Substances of Highest Concern'. These have recently been harmonised with the Substances of Highest Concern using the PBT and vPvB criteria of the EU TGD.

The CSF also includes a safety net procedure for chemicals that do not meet the PBT or vPvB criteria but where there are reasons to believe that the chemicals raise equivalent concerns, including:

- Substances which are very persistent (vP) and have a wide dispersive use, whether or not there is any evidence of harmful effects;
- substances that are very bioaccumulative (vB) by whatever mechanism (not necessarily just lipophilic compounds, but also those that accumulate in bone, bind to proteins, etc.);
- substances that are both bioaccumulative and toxic (i.e. B and T), especially if the rate of input is greater than the degradation rate;
- organic substances that may persist in the environment for many years (half-life > 10 years, vP), or for shorter periods where evidence suggests that adverse effects to the environment and human health may occur;
- substances that may cause adverse effects measured, or detected, as novel toxicity endpoints. Such substances may cause sublethal effects that might result in population level effects for exposed species, and could, for example, include endocrine-disrupting chemicals;
- substances identified on other priority lists such as OSPAR, which apply to the UK as a consequence of European and/or international commitments.

Substances identified under the safety net criteria would require case-by-case consideration by the ACHS prior to the CSF's consideration for risk management.

2.3.8 Conclusions

Concerns over the risks to human health and the environment have led to the development of strategies from governments and other bodies in many parts of the world that are aimed at identifying and prioritising hazardous substances. Most of these strategies define persistence, bioaccumulation and toxicity in terms of half-life, BCF and chronic aquatic toxicity. Each of these endpoints has specific difficulties over their measurement, interpretation and use within risk assessment and these are discussed further in Chapters 4, 5 and 6 of this report.

Each of the relevant regulatory schemes identified which categorise PBT or vPvB chemicals in some way have been briefly described. In each of the schemes the role of risk assessment and the consequences of categorisation vary. Within the draft EU REACH regulations, for example, categorisation as PBT or vPvB results in an authorisation process. This process is aimed at protecting human health and the environment by limiting the use of hazardous chemicals. Authorisations may be granted based on the risks to human health and the environment as well as on an assessment of socio-economic benefits and the availability and risks of alternatives. Under authorisation, risk assessment is expected to inform risk management decisions by identifying

those uses of a hazardous chemical which can be considered acceptable or unacceptable to human health, the environment and society as a whole. In this case, identification of appropriate risk management measures, if required, can result from a suitable scientific risk-based assessment. Such a strategy is discussed further in Chapter 7.

3. PRINCIPLES OF RISK ASSESSMENT FOR PBT AND vPvB CHEMICALS

3.1 Principles

Risk analysis, which includes the processes of risk assessment, risk management and risk communication, is a fundamental component of public decision making (Hart, 2004). These elements can be briefly defined as:

- Risk assessment - a science-based process consisting of hazard identification, hazard characterisation, exposure assessment and risk characterisation (CODEX, 1999);
- risk management - the process used to decide between policy alternatives taking account of the results of risk assessment and other factors (e.g. social and economic considerations) (Hart, 2004);
- risk communication - the interactive exchange of information and opinions concerning risk and risk management among risk assessors, risk managers, consumers and other interested parties (CODEX, 1999).

The four components of risk assessment can then be briefly defined (CODEX, 1999) as:

- Hazard identification - identification of the biological, chemical or physical agents that may have adverse effects;
- dose-response assessment (or hazard characterisation) - determining in either quantitative and/or qualitative terms the nature and severity of the adverse effects;
- exposure assessment - evaluating the probability of exposure to the agent under study;
- risk characterisation - qualitative and/or quantitative estimation of the probability, frequency and severity of the known or potential adverse effects occurring. This takes into account the three preceding steps and depends largely on the uncertainties and assumptions made at each stage. When insufficient or inconclusive data are available, a protective, or conservative, approach is taken to arrive at a worst-case hypothesis. When such hypotheses are combined, the result will be an overestimation of the real risk, but which will provide a level of assurance or protection. Based on the results of the risk characterisation step, a risk assessment may be refined in a tiered manner and more knowledge gained to arrive at a more predictive, or realistic, risk characterisation (Forbes and Calow, 2002; ECETOC, 2004a).

On the basis of these definitions, there are clear differences between the roles of risk assessors and risk managers. The role of assessors is to characterise risk based on the science available while the role of managers is to make decisions that take account of the assessed risk and socio-economic factors (Hart, 2004). Assessors must generate a scientifically balanced analysis presenting information on hazard, dose response, exposure and risk while defining uncertainties

and assumptions (both conservative and non-conservative) (US National Research Council, 1983). They do not make decisions on the acceptability of any risk. Risk managers, on the other hand, are the users of the assessment and must integrate these assessments into a wider decision making process. Matters such as the acceptability of particular risk levels and the role that the precautionary principle plays within the process, are firmly within the responsibilities of the risk manager, not the risk assessor.

3.2 Role of the precautionary principle within risk analysis

Prominence was given to the precautionary principle in the 1992 Rio Declaration (UNCED, 1992). This refers to taking regulatory action when there are threats of serious irreversible damage, but a lack of scientific evidence. Since this time, the use of the precautionary principle has been the source of much debate and often conflicting views.

Decisions based on the precautionary principle are sometimes argued as an alternative to scientific evaluation of the risks involved. However, application of the precautionary principle should be preceded by some level of scientific evaluation of the risks and the uncertainties involved (EC, 2000a; Douben, 1998). Risk assessors must attempt to assess risks before risk managers decide on the use, or not, of the precautionary principle. This decision must balance the freedom and rights of individuals, industry and organisations with the need to reduce the risk of adverse effects to the environment, or to human, animal or plant health (EC, 2000a).

It is important to distinguish the precautionary principle, which is used by decision makers in the management of risk, from the element of caution or conservatism that risk assessors apply in their assessment of scientific data.

3.3 Principles of environmental risk assessment

Environmental risk assessment forms an essential element in many national and international chemical regulations. For example, since the 1990s legislation has been developed within the EU requiring the assessment of environmental risks of industrial chemicals. This led to the publication of the TGD on risk assessment, which has recently been revised (EC, 2003b). The principle of environmental risk assessment as detailed in the TGD is to evaluate the likelihood of harm being caused to the environment by examining environmental exposures of individual substances resulting from release and the effects of such emissions on the structure and function of the ecosystem. In practice this involves determining the concentration that is unlikely to cause harm in exposed systems, the Predicted No Effect Concentration (PNEC), with an estimate of the concentration likely to occur in the environment, the Predicted Environmental Concentration

(PEC). If the PEC exceeds the PNEC then an unacceptable risk is assumed, based on the information available. In such cases there may be options to refine the risk assessment by targeted generation of further information to more closely reflect the real world.

There are a number of sources of uncertainty within the risk assessment methodologies detailed in the TGD and elsewhere. These uncertainties can be based on a lack of understanding (which, in principle, could be reduced through the generation of further, appropriate information) and true variability (which is an inherent property of the environment and cannot be reduced, only investigated for further understanding) (Forbes and Calow, 2002).

Due to an acknowledgement of the uncertainties involved in understanding the exposure and effects of chemicals in the environment, as well as the need to keep risk assessment cost effective, a tiered structure has evolved. This tiered structure is based on the principle that initial tiers are worst case or conservative relying on less data, but are protective of the environment. If these assessments indicate negligible risk, then no further information is required. Should, however, these assessments indicate a concern, further study is required to more closely predict exposure and effects in the environment. This rationale leads to a prioritisation of chemicals for further study, which may involve substantial resources (time, manpower and money). A suggested improvement to this approach is detailed within the ECETOC report on Targeted Risk Assessment (ECETOC, 2004a), which addresses the process of prioritisation and the rapid removal of chemicals of low concern from the assessment process.

3.4 Risk assessment for chemicals categorised as PBTs or vPvBs

Within the draft EU REACH regulations, authorisation of a chemical categorised as PBT or vPvB can be granted if it can be demonstrated that the risks to human health and/or the environment are adequately controlled or if the socio-economic benefits outweigh the human health or environmental risks (EC, 2003a).

However, due to concerns over the uncertainties of current risk assessment approaches, it has been argued that risk assessment should not be applied to chemicals with a potential to persist in the environment, bioaccumulate in living tissues and show long-term ecotoxicity (EC, 2001). These concerns have led some to argue that risk management is the next sequential step following hazard identification through the restriction or banning of chemicals categorised as PBTs and vPvBs. This argument is based on the uncertainties involved in exposure and effects assessments as well as the potentially serious consequences of belated action.

The TGD specifically states that the concerns over the environmental fate and effects of chemicals with PBT characteristics are of particular relevance for the marine environment since

this compartment is considered more diverse and sensitive (EC, 2003b). The TGD argues that a 'safe' concentration in the marine environment cannot be established with sufficient reliability for chemicals categorised as PBTs. Specific concerns exist surrounding the potentially irreversible long-term impact of PBT-classified substances and that cessation of emissions will not necessarily result in a reduction in chemical concentration and that any effect will be difficult to reverse. When commenting on this version of the TGD the CSTEE argued, however, that it sees no reason why, in principle, estimates of effects and exposure cannot be made for any environmental compartment, recognising that for PBT substances long-term food chain exposure should be considered using studies that address chronic oral toxicity (CSTEE, 2002).

The argument within the TGD assumes that 'zero' emission of a chemical is the only way of protecting the environment. However, 'zero' emission is, in many cases, almost impossible to achieve and goes against a fundamental principle of risk assessment that there is always some level of emission, however small, which would be environmentally negligible.

While focusing on the uncertainties involved in risk assessment it should be noted that considerable uncertainties exist even within a hazard-based approach. These uncertainties can lie within the measurement and interpretation of the data used to categorise a chemical as P, B or T. For example, assessing the environmental persistence of a chemical is far from straightforward. Persistence is not an intrinsic property of a chemical but highly dependent on environmental conditions (e.g. microbial diversity, oxygen content, temperature, bioavailability, co-metabolism). Persistence cannot be measured directly., It must be inferred from the presence of the chemical in the environment or from the results of degradation tests in the laboratory. Both means of extrapolation carry uncertainties that will affect the categorisation of chemicals as P (or vP). This issue has been covered in depth by ECETOC (2003a).

The aim of this report is to evaluate whether PBT chemicals can be assessed for risk. The categorisation of a chemical based on arbitrary cut-off values does not mean that the risks of those chemicals cannot be evaluated. It is clear, however, that a chemical with a more hazardous profile than others may require additional effort and resources in order to assess the risks. In addition, the uncertainties involved within the risk assessment become more important. But uncertainties are a feature of all assessments, both hazard and risk, and should become less significant the more knowledge that can be gained. Uncertainty and decision support tools are discussed in Appendix A.

This report identifies ways in which the risk assessment process can be improved in order to make more transparent, or reduce, the uncertainties involved in evaluating the likelihood of harm being caused to the environment of chemicals categorised as PBTs or vPvBs. This recommended risk-based approach can then be used to make chemical management decisions. The general risk assessment process itself should not differ for chemicals that exceed categorisation criteria for

PBT or vPvB, but the methods with which the uncertainties are reduced, or made more transparent, within the exposure and effects assessment may be different from those used for non-PBT chemicals.

Due to the impending requirements of REACH, the improvements to the risk assessment process suggested in this report are intended to work with the tools or methods currently available, while research will be recommended to further advance environmental risk assessment methodologies to move towards an even more predictive assessment.

4. ENVIRONMENTAL EXPOSURE ASSESSMENT

4.1 Introduction

Environmental exposure assessment is the process of deriving concentrations of chemicals in the environment to which organisms are exposed. These exposure concentrations can be obtained by measurements or by model predictions. Once chemicals are released into the environment they undergo a range of advection and inter-compartment transfer processes and as a result, environmental exposure may occur in various compartments. Hence, multiple exposure concentrations need to be established in environmental risk assessment. In this chapter, exposure assessment is restricted to concentrations in the environmental compartments excluding biota. Assessment of indirect exposure resulting from bioaccumulation will be dealt with in Chapter 5.

The TGD approach and tools for performing 'higher tier' exposure assessment are discussed below with regard to the uncertainties in the exposure prediction. The uncertainties in the input variables for exposure assessment are discussed in a quantitative manner for chemicals categorised as PBTs and compared with those for chemicals not categorised as PBTs. Their repercussions on the uncertainty of the estimation of PECs are discussed and strategies are developed to facilitate exposure assessment of chemicals categorised as PBTs.

4.1.1 Establishing PECs using monitoring data

Measuring environmental concentrations is the obvious option to learn about environmental exposure. However, a thorough environmental exposure assessment of chemicals categorised as PBTs requires a well-conceived set of measurements. The fundamental considerations underlying each environmental measuring campaign have been described previously (ECETOC, 1999) and are outlined later.

4.1.2 Establishing PECs using model predictions

Environmental concentrations can also be estimated using mathematical models. These models can be viewed as calculators that perform a set of algorithms combined with a set of assumptions relating to the properties of the environment. The algorithms represent our knowledge on the processes that determine the environmental fate of chemicals. Using the models, the assessor can derive PECs of the chemical in different environmental compartments from a given amount of chemical released into the environment. To handle the complexity of calculating environmental concentrations, the mathematical models have been computerised. The most frequently used modelling tool for assessing the environmental risks of chemicals in Europe is the European Union System for the Evaluation of Substances (EUSES 2.0, 2005) (see also

http://ecb.jrc.it/home.php?contenu=/documents/existing-chemicals/EUSES/EUSES_2.0/) which reflects the methodology set out in the TGD (EC, 2003b). This is the default methodology for the environmental risk assessment of chemicals in Europe.

4.2 Uncertainties in exposure assessment

4.2.1 Experimental uncertainties

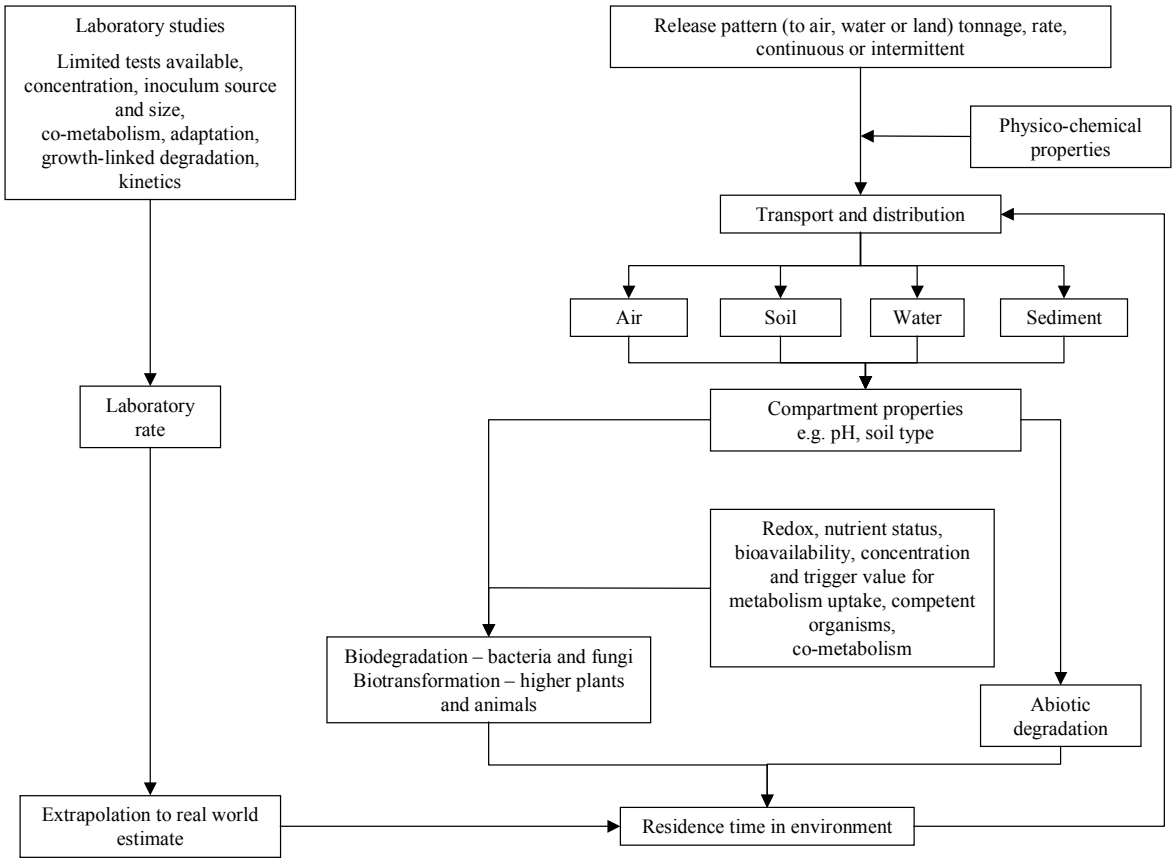
4.2.1.1 Uncertainties in the assessment of degradation

Any substance released into the environment will have a tendency to partition preferentially to a particular compartment and its subsequent fate will be dictated by the characteristics of that compartment and the chemical. While it is possible to measure distinct rates of degradation in laboratory-based test systems, the validity of these rates for predicting degradation in the real world will always be questionable. Such rates tend to reflect a specific type of reaction kinetics resulting from a prescribed test protocol. It is however, neither practical nor indeed possible to measure degradation rates under all environmental conditions and for all environmental compartments. It is, therefore, necessary to attempt to relate/extrapolate laboratory test results from one or two degradation studies, representative of one or more environmental compartments, to degradation rates in multiple environmental compartments. Extrapolation is therefore a major component (and source of uncertainty) of any strategy to assess the degradation of a chemical in the environment.

Degradation in the environment occurs mainly as a result of biodegradation, hydrolysis or photolysis or any combination thereof. These processes can take place at different rates and with different kinetics. There is, therefore, considerable uncertainty associated with the extrapolation of single degradation rates or type of reaction kinetics to describe the behaviour of a substance in the environment. The factors that influence the rate and extent of degradation processes in the laboratory and field have been thoroughly reviewed (ECETOC 2003a; Beek *et al*, 2001; Aronson and Howard, 1999) and are summarised in Figure 2. The factors are interdependent and combine to determine not only whether degradation will occur but also the rate at which it occurs. Any one of these factors in isolation has the potential to limit the overall rate of, or even prevent, degradation occurring. The environment is dynamic and the inherent conditions of any given compartment are constantly in a state of flux. This state of flux makes it impossible to identify a distinct rate of degradation, biotically or abiotically, it can only be described by a range of rates that reflect changes in environmental conditions (see Section 4.2.1.1.4). The uncertainty associated with each factor is further increased when the results from the laboratory are extrapolated to the field and reflects:

- Nature and inherent limitations of laboratory-based biodegradation tests;
- dynamic, heterogeneous and adaptive nature of the environment.

Figure 2: Factors that influence degradation in the laboratory and field



4.2.1.1.1 Biotic metabolism

Biodegradation is considered to be the major mechanism of degradation for most chemicals released into the environment. Although the currently available standardised tests for biodegradability are suitable for very water-soluble substances there are practical problems and issues associated with their use to assess the biodegradation of poorly soluble and/or volatile substances (ECETOC, 2003b). The uncertainties associated with extrapolation from laboratory results to field half-lives are shown in Table 2 and are discussed by ECETOC (2003a). These uncertainties apply to all chemicals. Provided the tests are carried out in an appropriate fashion and based on a thorough understanding of the physico-chemical properties of the chemical, there

is no scientific reason why the extrapolation of degradation rate constants of chemicals categorised as PBTs should be different from non-PBT chemicals.

Table 2 Uncertainties associated with extrapolating biodegradation rates from laboratory studies to a field half-life

Issue	Underlying reason	Suggested improvement
Concept of half-life	Mixed kinetics	Use a DT_{50} distribution
Suitability of standard aquatic tests	Not designed to measure rates	Use results in probabilistic approach
Extrapolation from one environment to another	Different organisms and kinetics in different environment	Use a DT_{50} distribution
Test concentration	Different kinetics at low concentrations	Use a DT_{50} distribution
Effect of adaptation	Rates will depend on presence of competent organisms	Allow adaptation before testing. Measure length of adaptation period and then apply an extrapolation factor.
Degradation endpoint	Rate of primary and ultimate degradation may be very different	Build results into DT_{50} distribution

The limitations associated with the currently available standardised biodegradation tests, the areas where there are no suitable tests and some suggested improvements, are summarised in Table 3. An assessment of these limitations suggests that they all lead to possible underestimates of the degradation rate and consequently extrapolation to the environment based on such tests would lead to a conservative half-life (ECETOC, 2003a).

Other biotic factors contributing to degradation

Metabolism by animals

This is not a major process for degradation for many chemicals, nor a major source of uncertainty. However uptake and metabolism in animals e.g. worms in sediments (ECETOC 2003a) may lead to a reduction in the local concentration and may need to be considered in certain cases.

Table 3: Experimental difficulties and problems in interpretation of results from biodegradation studies

Issue	Underlying reason	Improvement
Measurement of biodegradation endpoint	Low substrate concentration results in CO_2 production or O_2 uptake below the limits of detection.	Use specific substance analytical methods or use radio-labelled material.
Use of pass/fail criteria	Percentage removal is based on total concentration not concentration in solution.	Re-analyse results for evidence of degradation (e.g. is CO_2 production > 20% evidence of degradation?).
	At low substrate concentrations the amount of carbon going to CO_2 will often be below the pass level.	Re-evaluate pass levels (extent and rate) for low concentrations.
Absence of competent organisms in inoculum	Substance is not present in environment at high enough concentrations to sustain sufficient numbers of appropriate micro-organisms.	Allow adaptation.
Water/sediment simulation tests not representative of real world	Seawater tests done in low volumes with low bacterial density and hence probability of presence of competent organisms is low.	Pre-concentrate inoculum and/or use larger test volumes.
Test duration	There may be a long lag phase. Degradation may be slower than allowed for by the duration of test.	Extend test duration.
Single carbon source	Precludes co-metabolic pathways.	Allow use of additional carbon sources.
Anaerobic tests [a]	Limited to methanogenesis and high test compound concentrations.	Develop tests with alternative electron acceptors and improve sensitivity of endpoints.
Limited to bacterial degradation	Current tests are focused on bacteria as agents for degradation.	Include fungi [b]
Bioavailability reduction	Hydrophobicity driven association to particulate and/or dissolved organic carbon reduces the fraction of test substance that is available for uptake.	

[a] Whilst two anaerobic methods exist for soils (draft OECD 307 and OPPTS 835.5154), these again rely on addition of the test chemical as the sole carbon source. More significantly, in these tests the anaerobic conditions are induced by flooding previously aerobic soils and, as a result, only facultative anaerobic bacteria are likely to be present; obligate anaerobes will not be found. Furthermore, the redox potential is frequently poorly characterised.

[b] Many high molecular weight polymeric natural substances, such as lignin, are not readily biodegradable by bacteria. However certain fungi (particularly white rot fungi) secrete hydrogen peroxide and a peroxidase, which initiate degradation (Paszczynski *et al*, 1985; Tuisel *et al*, 1990).

Degradation in and on plants

Wania and McLachlan (2001) conclude that vegetation is an important factor affecting the atmospheric transport and degradation of organic chemicals. Two foliage-related processes can reduce transport of volatile and semi-volatile substances:

- Partitioning from the atmosphere gas phase into leaves and subsequent litter fall;
- enhanced degradation in and on plants/leaves.

Bennett *et al* (1998) suggest that photodegradation of substances on foliage may be important for some lipophilic chemicals. Metabolism in plant tissue is thought to be less relevant to nonionic airborne substances.

For the majority of chemicals, which do not fall into the above categories, the uncertainty linked to degradation in vegetation will probably be of little importance.

4.2.1.1.2 Abiotic degradation

The significance of abiotic degradation processes has been considered by ECETOC (2003a). They concluded that the degradation of many chemicals by abiotic processes appears to follow first-order or pseudo-first-order rate kinetics. For the more reactive types of substances (Q)SAR predictions may be appropriate (as far as hydrolysis and photolysis are concerned) when assessing degradation. However, the current tests (and hence (Q)SARs) may not be appropriate for assessing the degradation of the less reactive type chemicals, where a combination of abiotic, followed by biotic degradation may be possible, e.g. polydimethylsiloxane (Stevens, 1998).

It has been shown that there are several mechanisms by which chemicals may undergo abiotic degradation in soil (Xu *et al*, 1998; Klupinski and Chin, 2003). Although standard soil studies may not explicitly measure these mechanisms, appropriate test design should allow for them to be addressed.

4.2.1.1.3 Use of monitoring and modelling in assessment of degradation half-lives

Monitoring and laboratory data have integral roles alongside fate and exposure models in predicting environmental concentrations of chemicals categorised as PBTs. However it is often difficult to estimate the environmental lifetime of a chemical from the results obtained in the laboratory, particularly if only one environmental compartment is considered. Consequently, empirical approaches have been developed to correlate, in one way or another, the results of

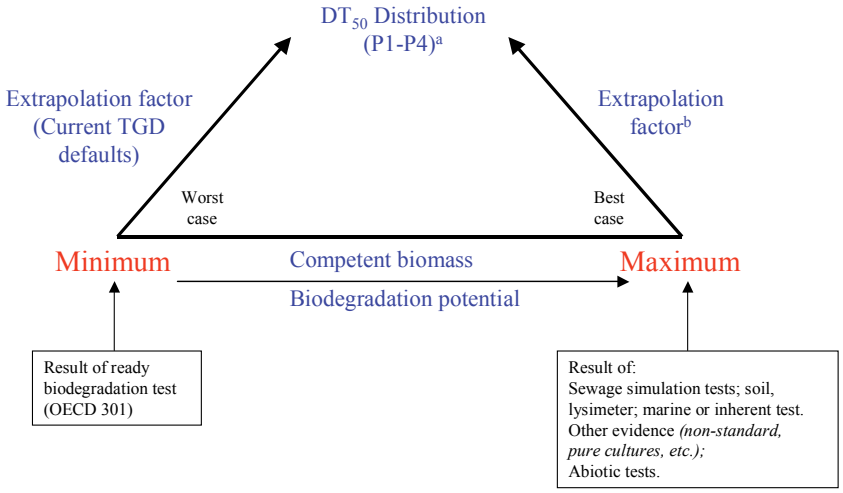
laboratory studies and half-life in the environment (EC, 2003b). The use of measured concentrations in the different environmental compartments (air, water, sediment, soil and biota) to estimate both the degradation of chemicals under field conditions and bioaccumulation in the food chain can therefore play an important role in estimating true environmental degradation.

Multi-media models are used increasingly by the authorities to assess the behaviour of chemicals in the environment. Environment Canada, for example, uses these models to screen and prioritise chemicals. However, the models are not often used in a dynamic mode, for example, to predict as a function of time, the accumulation of chemicals in the environment. Instead, they are used for ranking purposes to define a steady state without considering the possible evolution with time of emissions and environmental concentrations. By integrating measured environmental concentrations over a given period of time, it should be possible to derive temporal trends which can then be compared to the observed monitoring data, at least on a relative basis. The monitoring trends observed in the different compartments (air, water, sediment, soil and biota) for a given substance could be combined to estimate field degradation rates by using partitioning coefficients and transfer kinetics. These parameters are difficult to measure with a high degree of precision and frequently vary with the field conditions. The model parameters reflecting the environmental properties can be adjusted by calibrating the model using compounds for which the degradation profiles are known.

4.2.1.1.4 Strategy for estimating degradation

ECETOC (2003a) have proposed a pragmatic science-based strategy which advocates making effective use of all available degradation and partitioning data, standard or non-standard, to assess the degradation of a chemical. It is based on the premise that it is more valid to extrapolate from laboratory data to field half-lives from best case studies (i.e. increased/adapted biomass) than from worst-case studies (e.g. negative results from stringent ready biodegradation tests) (Figure 3).

Figure 3: Estimation of biodegradation half-life by extrapolation from laboratory data

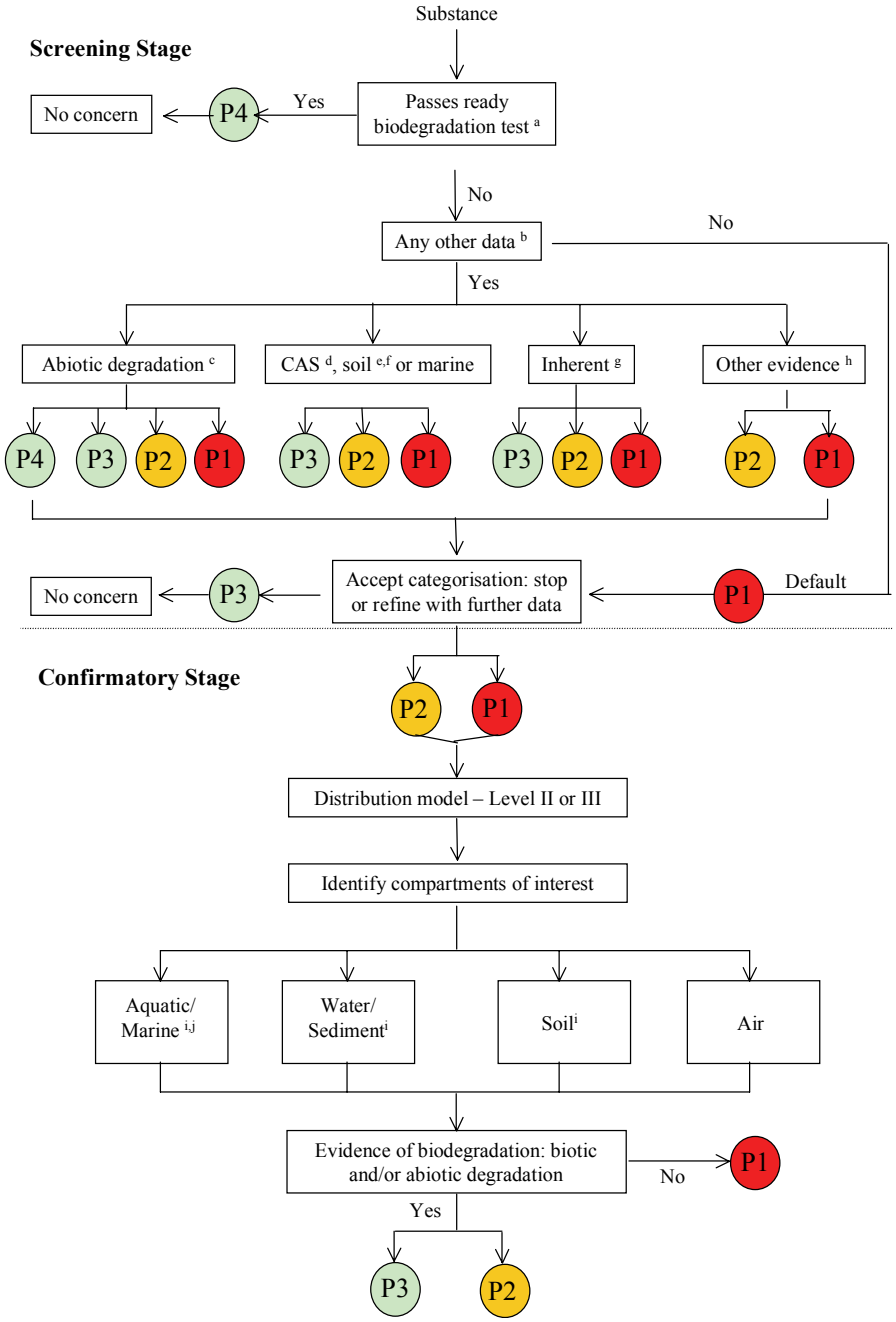


[a] See Table 4
[b] Factor to be agreed based on existing biodegradation data sets

The ECETOC approach (see Figure 4) promotes the active development of new, focused degradation test protocols that can decrease the uncertainty in degradation assessments. In addition, wherever possible, tests should be designed and conducted to reflect the release pattern and distribution of a chemical in the environment. The more environmentally realistic tests (i.e. field studies) should be given higher priority than the most stringent laboratory tests (i.e. ready biodegradation tests).

ECETOC (2003a) also propose an alternative to the use of single rate parameters. They suggest considering a range of values that reflect spatial and temporal differences in environmental conditions and in the different types of kinetics that may be operating. The ranges are designed to reflect the overall removal from the environment (i.e. they include half-life (T½) distribution curves for waters, sediments and soils). Figure 5 is a simple illustration of this concept. The shape of the overall T½ distribution and the T½ distribution for individual compartments will depend on the physico-chemical properties of the substance. The compartment and the factors are described in Section 4.2.1.1. The degradation assessment is therefore not reliant on a single half-life value, as is currently proposed in most regulatory criteria and does not give weight to one single environmental medium over another e.g. marine degradation data over freshwater data as in the revised TGD (EC, 2003b).

Figure 4: ECETOC strategy for assessment of degradation



[a] Classified as P2 due to the presence of metabolites or bound residues.

[b] QSAR or 70% degradation achieved outside the guidance detailed in Section 2.3.6.4 of the TGD.

[c] Abiotic degradation testing can be applied at all stages. The usefulness will depend on the specific substance and the distribution between the environmental compartments. Abiotic degradation may be combined with degradation to assess persistency.

[d] Sewage simulation tests

[e] Includes phytodegradation. Although current database is limited, phytotransformations in soil and water environments should be considered.

[f] T½ for soil is measured directly in laboratory soil die away tests or in field studies.

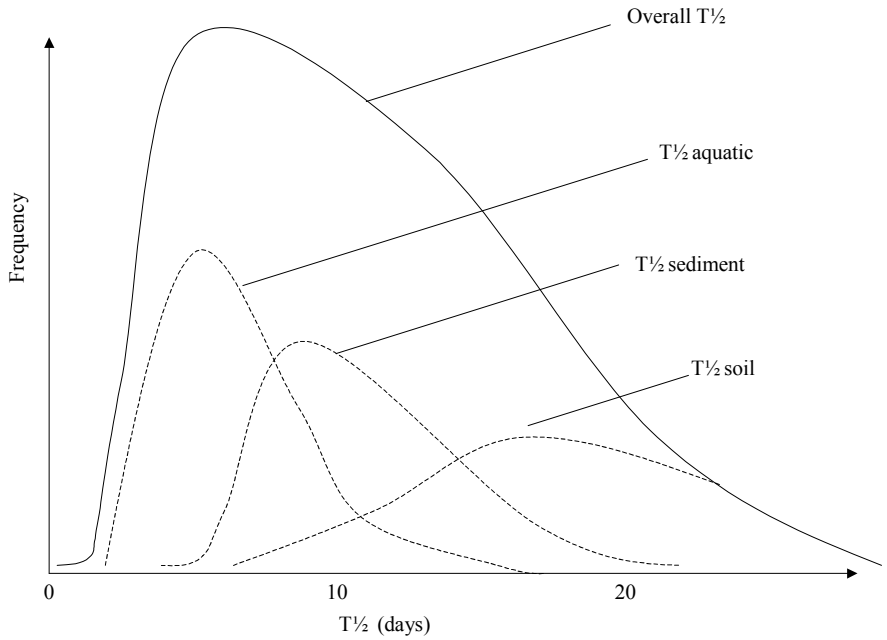
[g] Passing an inherent or simulation test has been defined in the specific OECD guidelines.

[h] Monitoring data.

[i] Option to expose for 0, 7, 14, 21 and 28 d for continuously released substances.

[j] Enhanced biomass studies for batch marine and river water studies.

Figure 5: Illustration of T½ distribution and range concept



Within the ECETOC strategy for assessment of degradation, a chemical is assigned to one of four persistency classes (P1, P2, P3 and P4, with P1 being the most persistent and P4 the most rapidly degradable) (see Table 4) based on all the data. The T½ ranges proposed are based on currently available laboratory and field data (ECETOC, 2003a). An ECETOC TF is preparing a database of measured biodegradation rates published in the peer-reviewed literature. As this and new data become available, especially for the marine environment, the T½ ranges will need to be reviewed and revised as necessary.

Each of these persistency classes has a distinct range of associated T½ values (Table 4). Substances that are assigned P4 and P3 are considered not to be persistent and pose no long-term threat to the environment whereas, substances assigned P1 and P2 will need to be assessed in greater detail.

Table 4: Summary of categories P1 to P4 (ECETOC 2003a)

Category	Test results	Overall T½ distribution	Probability of degradation in the environment	Classification
P4	Pass result from standard ready tests (OECD, 1992) or ready test with minor modifications	< 25 days	Very high	Non-persistent
P3	Fails the standard or modified ready test but passes either a sewage simulation test (Husmann or porous pot (OECD, 2001)), an inherent biodegradation test, a ready test using an adapted inoculum, standard laboratory soil study, or standard marine biodegradability study.	5 - 50 days	High	Non-persistent
P2	Fails standard inherent tests. Only partial degradation in sewage simulation, soil studies or marine studies.	10 - 150 days	Uncertain	Will need further studies to establish DT_{50} distribution/ metabolites
P1	Fails all of the above tests, substances with no evidence of degradation	> 150 days	Low	Persistent

In addition to the ECETOC approach, Blok (2000) proposed a novel classification scheme with eight different classes of biodegradation, which differentiates six types of inherently degradable substances. Beek *et al* (2001) and the Dutch Strategy on Management of Substances (SOMS, 2002) also advocate the use of persistency classes based on the relative power of the test, the test result, the endpoint measured, the extent of degradation and the potential for bound residues or metabolites to exist.

4.2.1.2 Physico-chemical properties

4.2.1.2.1 Aqueous solubility

Provided the limit of solubility is not reached, the aqueous solubility of a chemical will have limited direct impact on the estimation of the distribution of a chemical in the environment. However, uncertainties in the solubility may impact the calculation of Henry's law constant (H). This fact and its repercussion for the exposure assessment are discussed later (see Section 4.2.1.2.4).

4.2.1.2.2 Octanol-water partition coefficient (K_{ow})

The octanol-water partition coefficient, K_{ow}, more commonly expressed as the $\log_{10}$ of the partition coefficient or log K_{ow}, is an extremely important property in predicting the fate of a chemical. Log K_{ow} is used in many relationships that describe how a chemical partitions in the environment. In particular, the extent to which a chemical partitions to solids, into fish, plants and earthworms will all be dependent upon the value of log K_{ow} used in the assessment. Some of these will interact, for example where a chemical passes through a WWTP it will be modelled as adsorbing to solids and thus enter the terrestrial compartment through sludge disposal to land. The higher the log K_{ow}, the higher the mass in the terrestrial compartment. In contrast, the mass within the aquatic compartment will be reduced, initially due to partitioning in the WWTP and then due to partitioning to suspended matter or sediment in the aquatic compartment.

4.2.1.2.3 Vapour pressure

Vapour pressure is important because it is used in combination with aqueous solubility to calculate Henry's law constant (H).

4.2.1.2.4 Henry's Law Constant

H is an important parameter as it enables the potential of a chemical to enter the atmosphere from water to be evaluated. Even though a chemical may have very low vapour pressure, if it also has a very low aquatic solubility it can preferentially partition to the atmosphere. As the measurement of H is difficult, this parameter is usually calculated as the ratio of the vapour pressure (Pa) and the aqueous solubility (mol/m^3). It is thus not unsurprising that H is very sensitive to temperature and errors in vapour pressure and/or aqueous solubility. It is also important to realise that K_{aw}, the partitioning coefficient between air and water, is defined as H/RT (R = gas constant, T = temperature (°K)). H in combination with K_{ow} is useful in determining partition to vegetation.

4.2.1.2.5 Uncertainty reduction in physico-chemical property data

The individual physico-chemical properties of a chemical are interrelated by fundamental thermodynamic relationships. These relationships can be used to calculate a set of internally consistent physico-chemical property data, e.g. from literature data. Li *et al* (2003) have outlined an approach along these lines. It consists of data collection, data quality rating, and synthesis of a consistent set of physico-chemical property data, which have less uncertainty than the individual data.

4.2.2 Uncertainties in modelling

4.2.2.1 Input values

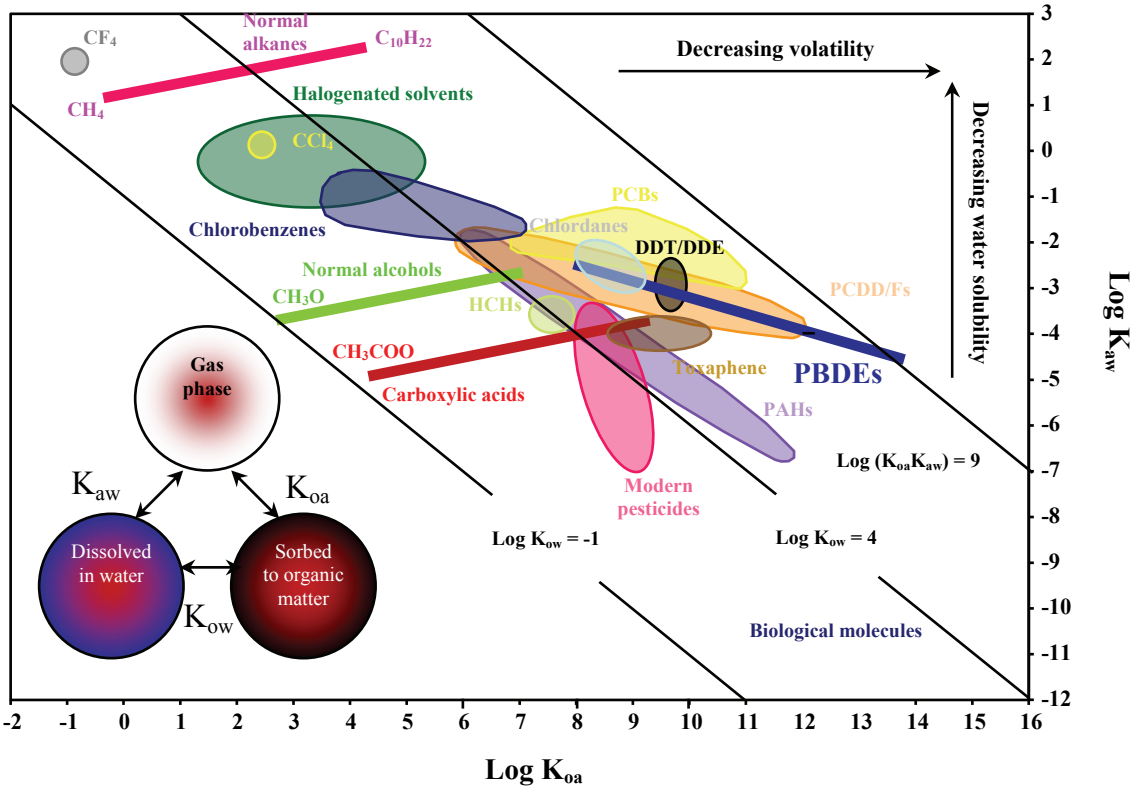
Models for PEC prediction require input on a given chemical, such as information on properties (e.g. stability of the chemical towards degradation reactions and partitioning properties), on amounts released to the environment and information on the environmental compartment into which the chemicals are released. The uncertainty of the input data is an important determinant of the uncertainty of the PEC results. This holds true for the assessment of all chemicals.

Values for the input variables are obtained from experimental measurements or as estimates on the basis of structure-property relationships. Both, estimates and measured values are associated with errors that propagate in the model, making the outcome less reliable. In this regard it needs to be stated that most chemicals categorised as PBTs belong to the group of 'difficult to test substances.' They commonly display a combination of properties such as high log K_{ow}, low solubility, strong sorption to soil, glass, etc. The resulting experimental difficulties increase as the properties move to the extremes. Consequently, careful experimentation is required to obtain meaningful results (ECETOC, 1996; ECETOC, 2003b).

4.2.2.2 Uncertainties in exposure estimates

Predictions of PEC are arrived at using models of different degrees of complexity. As a general rule more complex models allow for a more accurate description of the processes at hand and thus less uncertainty in the prediction. The trade-off for increased realism is a requirement for improved quantity and quality of data. The sensitivity of the model predictions of environmental concentrations to the various chemical and environmental parameters varies as a function of partition coefficients. For example Figure 6 shows where environmentally relevant chemicals are located in a partitioning coefficient plane defined by the coefficients for air-water (log K_{aw}) and octanol-air (log K_{oa}). Note that in this diagram the diagonals from upper left to lower right represent lines of equal log K_{ow}. Looking at PCBs, DDT/DDE, PCDD/PCDFs and other compounds fulfilling the criteria of the PBT definition it can be inferred that PBT and vPvB chemicals are found in the sector spanned by the log K_{aw} range from -7 to -1 and log K_{oa} range from 6 to 14. The analysis by Meyer *et al* (2005) indicates that the most important environmental characteristics for environmental transport of such chemicals are those related to the flow of the air, scavenging mechanisms from air (water and particles), the organic carbon content of particles in the various media and movement and loss of these particles, for example, through burial in sediment.

Figure 6. Localisation of environmentally relevant chemicals in the partitioning coefficient plane defined by the coefficients for air-water (log K_{aw}) and octanol-air (log K_{oa}) (Meyer et al, 2005)



When degradation does not influence the PEC predictions, i.e. when degradation half-lives exceed one year in soil or several days in air, the PEC prediction is strongly influenced by the environmental and physico-chemical characteristics. The uncertainty associated with PEC in relation to the physico-chemical characteristics can be approximated. Cowan *et al* (1995) gave guidance on the expected level of uncertainty in the environmental exposure concentrations for a series of chemicals. This ranged from 2× to 150× depending on the media of interest, the media of release and how well the partitioning properties of the chemical are known. For slowly degrading chemicals the maximum uncertainty of the PECs is a factor of about 20×. It should be noted, however, that the degradation half-lives remain the critical parameter in the EUSES model.

4.2.3 Uncertainties in emissions

Uncertainties within a risk assessment due to emissions arise for three reasons. First, the assumed emission is initially based on a default, which by its nature will be an average or a worst-case assumption and therefore an approximation. This will be an issue for all chemicals regardless of their properties/categorisation. However, it is useful to ensure that this is improved early in the

risk assessment of chemicals categorised as PBTs, thus reducing the level of uncertainty and perhaps highlighting key environmental compartments.

Secondly, the EUSES emission assessment based on defaults assumes that a fixed percentage of the amount of a chemical produced and used will be emitted to the environment. This approach ignores that chemicals categorised as PBTs are typically only sparingly soluble in water and have a high tendency to adsorb to solids and to partition to organic phases in the wastewater stream. As a result, such chemicals adsorbed to particulate materials can be removed by sedimentation of particles. This process is used in wastewater treatment and settling tanks. As a consequence, sewage sludge and precipitates obtained during wastewater treatment lead to a reduction of high log K_{ow} chemicals from the wastewater stream. Sludge generated during municipal wastewater treatment may be applied to land for soil improvement. Then there will be a need to follow the fate and effects of the chemical into the terrestrial environment. This environmental pathway is described by EUSES. However, a large fraction of municipal sewage sludge and the majority of the sludge produced in industrial wastewater treatment processes are incinerated or disposed to landfill. Hence, the actual emissions of chemicals categorised as PBTs to the environment may be smaller than estimated on the basis of the default assumptions.

Finally, industrial wastewaters may have an organic film at the air/water interface. As a result of their partitioning properties, chemicals categorised as PBTs will partition to the organic film rather than to the water. Removal of the film by skimming is part of the industrial wastewater treatment and will transfer high log K_{ow} chemicals to the 'scum', which is incinerated or disposed of in hazardous waste landfills. Again, the actual emissions of chemicals categorised as PBTs to the environment are smaller than estimated.

Hence, uncertainty in emissions estimates can be reduced by careful investigation of the amounts used, the emission reduction measures that are in place at a given site and the waste disposal practices. Note that the above issues are similar for all chemicals whether or not they are categorised as PBTs. However, the issues might have to be addressed in more detail for chemicals categorised as PBTs.

4.2.4 Uncertainty in bioavailability affecting the risk assessment

In the TGD, it is assumed that the bioavailable fraction of a substance can be represented by the concentration in the water included in the interstitial spaces and pores of the soil or sediment particles. This is the equilibrium partitioning approach (EqP). The issues relating to this have been discussed previously (ECETOC, 2000; 2004b). In the context of this report, the main conclusion is that, while there may be an underestimate (by a factor up to ×5) of the actual uptake

for chemicals with a log K_{ow} > 5, there is also an overestimate due to other factors, such as sediment and soil ageing or biological effects linked to the species habitat.

Chemicals with a log K_{ow} > 5 display a strong tendency to partition away from water. Even within the aqueous phase, such chemicals tend to partition to organic carbon in the water, be it present as fine particulates or as dissolved organic carbon. A determination of the concentration of such a chemical in soil, sediment or water by using an exhaustive extraction procedure does not distinguish between the biologically available and the unavailable fraction of a chemical. Novel soft extraction techniques, such as measuring the soil or sediment desorption kinetics or determination of the freely dissolved concentration allow for such distinctions. Those methods have been employed to demonstrate that reduced biological availability due to slow sediment desorption kinetics or due to humic acid binding can limit the rate of biodegradation and the extent of bioaccumulation (Kraaij *et al*, 2003). The Dutch authorities evaluated the two soft extraction techniques noted above with regard to their potential use in risk assessment. Both techniques were considered promising, since they appear to be able to reflect the effect of ageing and strong sorption on the biological availability (Sijm *et al,* 2002). However, the database supporting the validity of the two methods is too narrow at present. Therefore, prior to implementation further experimental work is required. It also needs to be stated that the EqP approach is conservative. This is discussed further in Section 6.2.4.1.1.

4.2.5 Uncertainty related to the region of concern

Chemical risk assessment according to the TGD addresses the following default scenarios: *Local* - with respect to manufacturing, formulation and use; *Regional* - a specified default representing approximately 10% of the EU; *Continental* - a default continental region; and *Marine* - similarly a default marine region.

The different scenarios are characterised by an increasing distance from the source and increasing geographical size. This implies that the chemicals are transported over a longer distance to reach the target region. This leads to further uncertainty, since a longer transport pathway can be predicted less accurately than a short one. Furthermore, the time required for transport may also increase with the distance. The uncertainty associated with degradation rates is magnified by the time required for a chemical to be transported to the more remote regions. As a result, the assessment in the model environments of the continental and the marine scenarios are the most uncertain.

4.3 Screening level fate assessment

In the usual stepwise approach to the environmental exposure assessment of chemicals, evaluative, unit world models, as developed by Mackay *et al* (1992), are used in the initial tiers. The default model for environmental risk assessment of chemicals in Europe, EUSES 2.0, is a model of this type and can be regarded as the computerised version of the risk assessment rules as they are laid down in the EU TGD (EC, 2003b). EUSES models transformation processes by assuming the pertinent reactions follow (pseudo)-first-order kinetics. For transport processes, phase transfer processes and advective transport have to be considered. Phase transfer processes are simulated on the basis of a) partition coefficients of the chemical between different environmental compartments and b) assumptions about the mass transfer process between the compartments. A detailed description of the representation of the environmental fate processes can be found in van den Berg *et al* (1995). EUSES predicts steady-state environmental concentrations on different scales and in different compartments on the basis of defined but adjustable parameters which describe the environment.

The algorithms of EUSES represent general environmental processes, which all organic chemicals undergo. The modelling assumptions about the environment relate in the same manner to all chemicals, whether or not they are categorised as PBTs. Therefore, EUSES can, in principle, be applied to all organic chemicals. It should be noted, however, that the errors associated with the input values (e.g. physico-chemical properties, degradation rates) may be propagated through the model and will likely increase the uncertainty of the output.

The key data necessary for the screening level are values for aqueous solubility, K_{ow}, vapour pressure, and biodegradation based on the OECD 301 series (OECD, 1992). The primary goals of this screening level assessment of chemicals are to (a) obtain an initial estimate of environmental concentrations of concern and (b) determine the processes controlling the fate of the chemical. The results at this level will target the refinement steps necessary for further work by identifying key processes and compartments.

4.3.1 Influence of biodegradation on screening level assessment results - sensitivity analysis

Biodegradation is a key parameter in assessing the environmental fate of a chemical. In the TGD at the screening level, this importance is further highlighted as the category assigned to a chemical based on the result of standard biodegradation tests, i.e. readily biodegradable, inherently biodegradable and non-biodegradable, leads to an aquatic half-life which are then extrapolated to the terrestrial and sediment compartments (EC, 2003b). An alternative approach for obtaining environmental half-lives from monitoring data or from results of biodegradation tests is discussed in Sections 4.2.1.1.3 and 4.2.1.1.4 above.

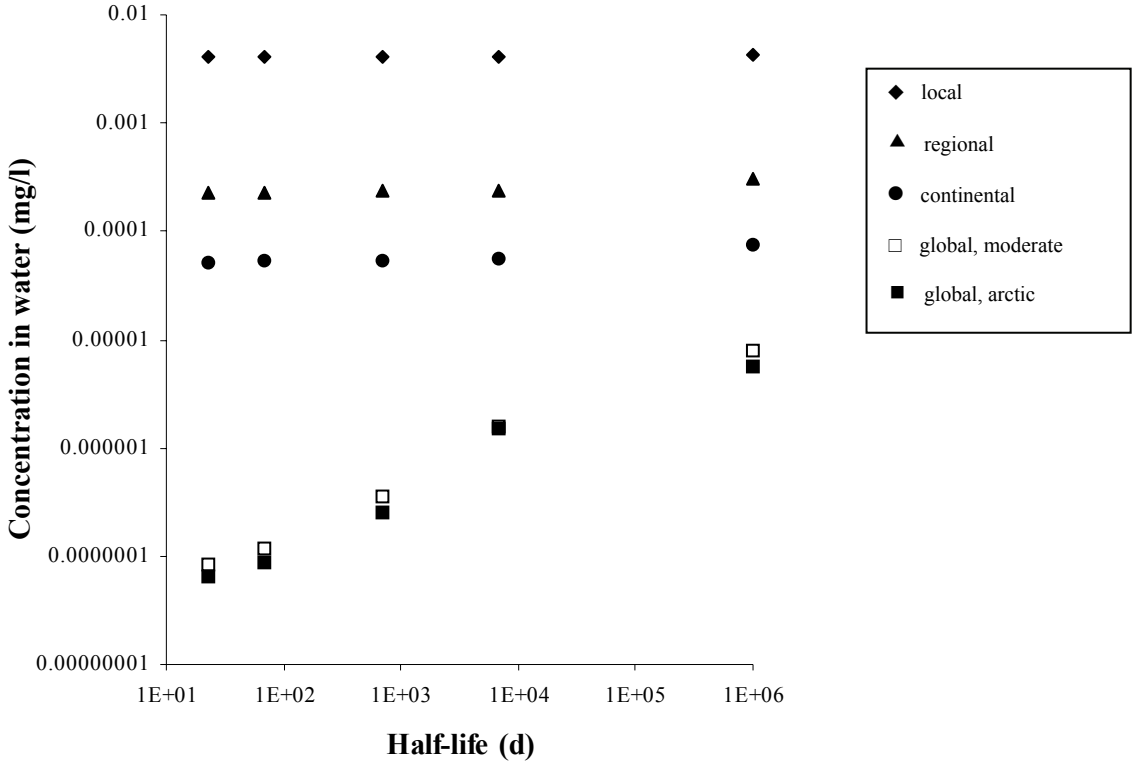
Figures 7 and 8 show the EUSES predictions of PEC in water and soil, respectively, as a function of the degradation half-live in soil (Tolls, 2005). The soil degradation half-life was chosen since the soil compartment can be expected to be an important sink for PBT chemicals. The model calculations performed to derive PEC_{water} and PEC_{soil} incorporate all relevant environmental processes such as degradation (characterised by half-lives in the different media), partitioning-related transport (phase transfer processes, characterised by the respective coefficients) and advective processes (characterised by model defaults relating to exchange of water and air between the EUSES-model compartments). The partitioning and advective processes are responsible for the transport of chemicals from the regional level to the continental and global level.

A model chemical with log K_{ow} of 5.9, a vapour pressure of 0.07 Pa and an aqueous solubility of 1.5 mg/l i.e. those of a model hydrophobic chemical displaying a certain tendency to volatilise and to dissolve in water, was used in the calculations. Rate constants for environmental degradation processes were set to the default values assigned by EUSES, i.e. 6.9×10^{-7} d^{-1} corresponding to a half-live of 10^6 d, except for the overall sediment half-live (fixed at 6.9×10^6 d^{-1}) and the half-life in soil which was varied to study the influence soil biodegradation can have on PEC prediction.

The chemical enters the environment via 'wide dispersive use' such that the chemical is subject to wastewater treatment. With these assumptions the chemical is modelled to partition strongly to sewage sludge. Consequently, the chemical is modelled to end up in agricultural soil via sludge amendment. The major mass fractions predicted within soil amount to > 99% in the regional model and > 96% in the continental model. Hence, the sensitivity analysis was performed by varying the rate constant for soil degradation and recording the PEC_{soil} and PEC_{water} in different modelled environments.

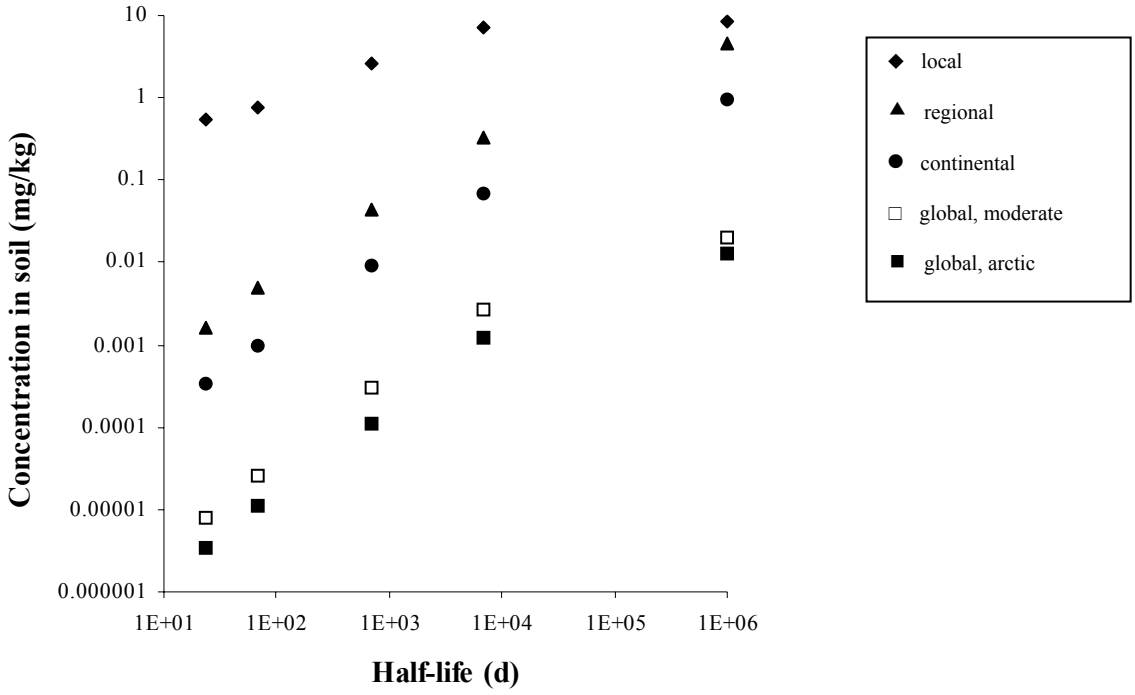
Figures 7 and 8 demonstrate that the concentration in the water compartment is highest close to the source, i.e. the local water concentration. Even at the longest half-lives, the concentration in the local environment is more than two orders of magnitude higher than in the global environment. The predicted concentrations in the global environment are a result of transport from continental to the global environment. Hence, the concentration difference is due to dilution of the chemical and the influence of even very slow reactions, occurring over a long time span. The water concentrations (Figure 7) are largely unaffected by the degradation in soil. Only the global water concentration decreases appreciably as the chemical's half-life in soil decreases, since soil is the primary sink on the local scale but becomes the primary source in the global scale.

Figure 7: Relationship between the EUSES PEC_{water} for a hypothetical hydrophobic chemical and its half-life in soil at different geographical scales



In contrast, as expected, the concentrations in soil (Figure 8) decrease as the half-life decreases. In the local concentrations this dependency is weaker since the local concentrations are largely influenced by the continuous input of the chemical. The decrease in half-life from 700,000 d to 7,000 d has no effect on the PEC_{local}, which again is mostly determined by the continuous input of the chemical. In contrast, the PEC predictions for the regional, continental and global (moderate and arctic) scale decrease significantly with reduced half-lives. This highlights the need for obtaining half-life estimates.

Figure 8: Relationship between the EUSES PEC_{soil} for a hypothetical hydrophobic chemical and its half-life in soil at different geographical scales



4.4 Investigative phase

At the investigative phase, there may be a need for models that are more spatially specific and allow for temporal and/or seasonal variation in the key environmental parameters that influence the fate and exposure of the chemical. The models that are used in this phase will usually contain more environmental compartments, have more complex partitioning equations, and contain a greater number of parameters. In many cases, the models will cover a geographical range of environments that will also add to the complexity. Accuracy generally increases together with the complexity of the model. However, model developers have found that one cannot continuously gain accuracy by increasing the complexity of the models. Beyond a certain level, the amount of data required increases the overall uncertainty of the inputs and therefore the uncertainty of the model outcome. For example, it is suggested that there is an optimum spatial resolution for a multi-media model (Wania, 1999). In environmental sciences, it is difficult to know where this optimum lies and its position will depend on the question being addressed (OECD, 2004a). Nevertheless, this trade-off should be kept in mind when choosing a more complex, spatially and temporally resolved model for further evaluation of fate and exposure.

Examples of more complex models that could be employed in the investigative phase of the assessment include:

- The Baltic Sea model which has been shown to predict the concentrations, in this region, of chemicals categorised as PBTs (Wania *et al,* 2004);
- the GREAT-ER model for European catchments (www.great-er.org);
- various spatially and temporally resolved models developed under the EMAP project in UNECE. (Jacobs and van Pul, 1996; Pekar *et al,* 1999);
- list of multi-media fate transport models for predicting persistence and long range transport potential (ECETOC, 2003a);
- OECD website of models (http://webdomino1.oecd.org/comnet/env/models.nsf);
- regional population-based model (Cousins and Mackay, 2003);
- the GEMCO model for estuarine environments (Baart *et al*, 2005; Le Gall *et al*, 2003).

Regardless of how complex the models are, uncertainty will still remain, and there should be, as with the simpler models, an awareness of the probable sources and the magnitude of the major uncertainties.

Alternatively, a refined assessment can be obtained by improving the quality and quantity of the input data. The results of the first tier of the risk assessment will be informative as to which processes are critical to the assessment and hence, the refinement of which particular input data is most efficient for improving the exposure assessment.

4.5 Confirmatory phase

4.5.1 Introduction

The confirmatory level of a risk assessment is normally required as concerns remain over the estimated risk arising from the manufacture, use and disposal of the chemical. It is at this stage of an assessment that monitoring data can be used. For well-studied chemicals suitable monitoring data may be available. If not, it may be necessary to define a monitoring programme. This monitoring programme may be designed to test the model predictions.

4.5.2 Use of existing monitoring data

Environmental monitoring has recently been reviewed by ECETOC (1999). There are also numerous procedures and guidelines on the design and execution of environmental monitoring programmes (for example, US-EPA, 1982; UN/ECE, 1996; Berg, 1982; HMSO, 1986; WRc, 1989; Groot and Villars, 1995; ECETOC, 1999; Holt *et al,* 2000) that should be referred to for

detailed advice. Improving the use of monitoring data in the exposure assessment of industrial chemicals was addressed at an OECD workshop (OECD, 2000a). The use of living organisms for environmental monitoring of chemical concentrations with a potential for uptake and accumulation in tissue has also been reviewed by ECETOC (1999).

For risk assessment purposes, measured data should be suitable for:

- Describing the spatial distribution of a range of physical, chemical, biological and other parameters (including demography, inputs, specific activities);
- determining temporal trends, either as a means of assessing the effectiveness of policy measures, or to assess, by the use of suitable indicators, changes and variability in the quality of the environment; and
- establishing relations between anthropogenic activities and observed spatial and temporal trends in the environment.

Unlike some environmental contaminants (e.g. sulphate, heavy metals), chemicals categorised as PBTs can be difficult to analyse reliably and quantitatively.

Section 2.2 of the TGD (EC, 2003b) gives guidance on how to evaluate measured data, in terms of quality (including sample storage and analysis), how representative the data are (e.g. sampling regime) and whether they represent the local or regional compartment. In particular, the TGD gives clear guidance on the quality of the data and how they should be evaluated. This guidance on the selection of data and how environmentally representative they are apply equally to PBT and non-PBT chemicals.

Appropriate use of statistics is necessary to represent the data when accounting for spacial and temporal variability of the concentration. At a local scale, the TGD suggests that the 90^{th} percentile of concentration data could be considered as a reasonable worst-case approximation to PEC_{local}. At the regional scale, full justification should be given for any measured data suggested to be representative of a $PEC_{regional}$. This approach has been used to assess the risk to the marine environment of several chlorinated organic substances (De Rooij *et al*, 1998a; 1998b; 1998c; Boutonnet *et al*, 1998). Establishing temporal trends requires collection of samples over a sufficient period of time. Some research indicates that one year before an event and one year after an event does not allow the establishment of a temporal trend (Bignert, 1994; Bignert *et al*, 1995). Recently, a methodology has been proposed to statistically combine measured data from different locations and thus derive a distribution of concentrations representative of a region (Govaerts *et al,* 2004).

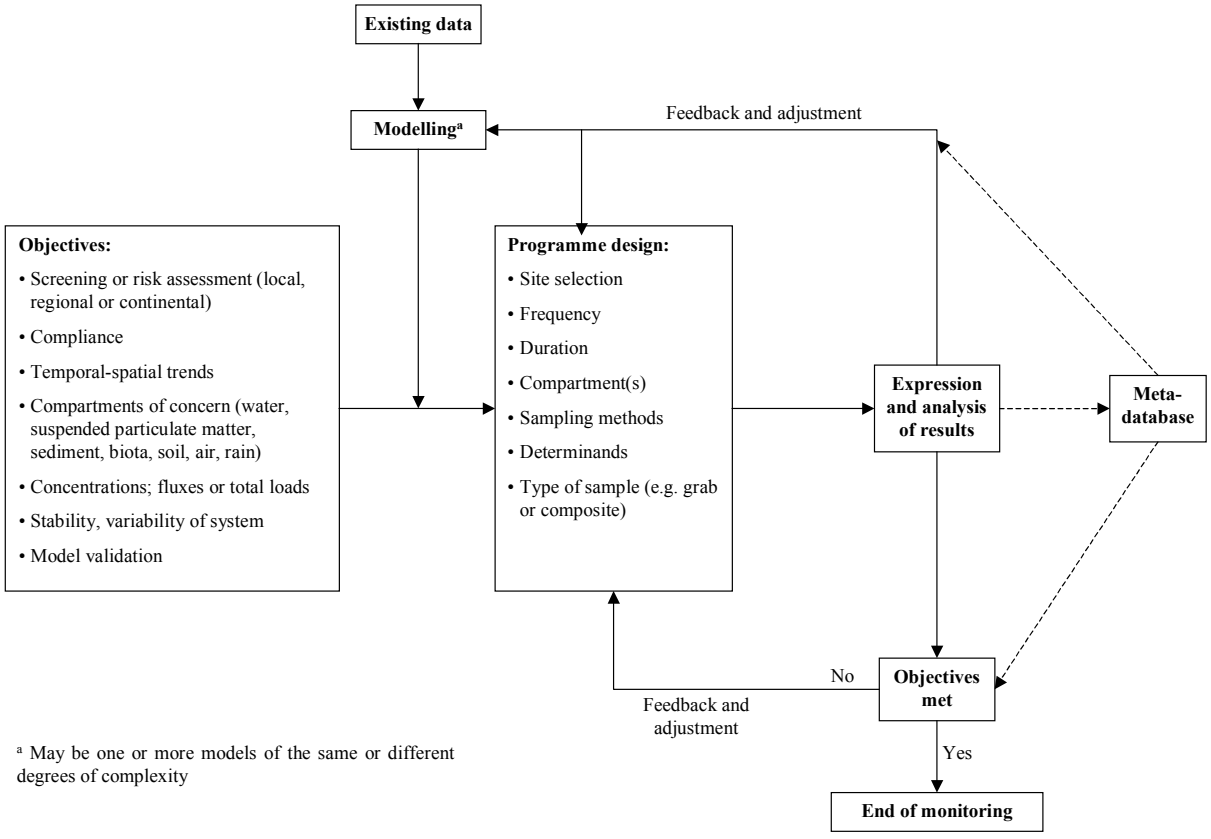
A recent development has been the release of MonitoringBase, a compilation and evaluation of measured environmental concentrations of organic chemicals and of existing and planned

monitoring programmes across Europe. This may be a useful resource for obtaining monitoring data, www.rivo.dlo.nl/?ShortCut=(2,175,1,1.

4.5.3 Designing monitoring studies for confirmatory risk assessment

If existing monitoring data are insufficient and the risk assessment still requires refinement, it is necessary to design a monitoring study to provide representative data. This monitoring programme may also be used to investigate the robustness of the model predictions. Guidance on the design of monitoring programmes to support risk assessment and/or model validation are included within the TGD (EC, 2003b) and were discussed by ECETOC (2003c). This is illustrated in Figure 9.

Figure 9: Design and execution of monitoring programmes



An example of the combined use of modelling and existing monitoring data has been provided by Cousins and Mackay (2003) who found that median PEC predicted by a regional population-based model varied by a factor of four from the observed environmental concentrations. A

sensitivity analysis identified the rates of emission and degradation as the primary sources of uncertainty. Hence, the combined modelling and monitoring exercise also identifies the input parameters that are most effective when it comes to further refinement of the assessment.

4.5.4 Probabilistic exposure assessment

Probabilistic exposure modelling is a tool to account for the uncertainty of the input values in the prediction of the environmental concentration resulting from experimental error and environmental variability. It provides exposure estimates as probability distributions of the predicted environmental concentrations thereby providing a means to quantify uncertainty. Important characteristics of a PEC distribution are its mean and width. The difference between the 10^{th} and 90^{th} percentiles (defined as the width) has been used as a reasonable estimate of uncertainty of the PEC within risk assessment (Matthies *et al*, 2004). The 90^{th} percentile could also be taken as a realistic worst-case estimate of the PEC for risk characterisation. Alternatively, the overlap between the PEC distribution and the distribution of environmental monitoring data can be evaluated in order to learn about the quality of the exposure prediction. This information together with a sensitivity analysis can help to identify which of the parameters need to be addressed in order to achieve the maximum refinement of the exposure assessment (i.e. reduction in uncertainty and/or improved agreement between measured and predicted data).

4.6 Conclusions

- A number of uncertainties exist within the exposure assessment of all chemicals, regardless of PBT categorisation;
- models with different degrees of complexity are available for estimating PECs. EUSES is a suitable tool for initial assessments;
- degradation half-lives are a key parameter when assessing exposure for all chemicals, whether or not they have been categorised as PBTs;
- measured environmental concentrations obtained from well-executed monitoring programmes constitute the most valid approximation of PEC and can be used in combined monitoring/modelling exercises to derive field degradation rates;
- distributions of environmental degradation half-lives can be derived from laboratory tests and from monitoring data. These distributions provide an approach to describe the natural variability of degradation kinetics resulting from the heterogeneous and dynamic nature of the environment;
- half-life distributions can be employed in probabilistic exposure assessments to yield estimates of how likely it is that certain concentrations are reached.

5. ASSESSMENT OF BIOACCUMULATION

5.1 Introduction

The assessment of bioaccumulation is the process of establishing whether chemicals are accumulated from the environment along a food chain or in a food web. Hence, this chapter focuses on transport of chemicals from both the abiotic environment and from prey into predator organisms.

Bioaccumulation can be studied experimentally in the field (Kucklick and Baker, 1998; Kelly and Gobas, 2001), however such studies are complex and location-specific due to specific food-web structures, etc. (Bentzen *et al*, 1996; Kidd *et al*, 1998). Bioaccumulation modelling provides a tool to obtain generic information about the transport of chemicals from the abiotic environment into and through a food chain (Gobas and Morrison, 2000).

The assessment of bioaccumulation is particularly relevant for organisms of higher trophic levels that are predominantly exposed to chemicals via the food rather than directly from their environment. In that regard, the concentration of a given chemical in a prey constitutes the oral concentration to which the predator is exposed.

In the risk assessment methodology currently applied in the EU (EC, 2003b) the assessment of bioaccumulation is termed 'secondary poisoning' assessment. This terminology clearly expresses that bioaccumulation is not an endpoint in itself but is a tool to define the exposure of higher-trophic-level organisms via their food.

The goal of this chapter is to identify the uncertainties associated with the assessment of bioaccumulation. To that end, the reliability of the input variables for the bioaccumulation assessment as well as the general uncertainties related to modelling bioaccumulation is evaluated.

5.2 Uncertainties in bioaccumulation assessment

When assessing the uncertainties in the assessment of food chain bioaccumulation of chemicals categorised as PBTs, it has to be recognised that the resulting overall uncertainty of the assessment is caused by the following:

- Uncertainties related to the difficulties of obtaining experimental bioaccumulation data (e.g. BCF and dietary BMF), and
- uncertainties related to food chain modelling.

5.2.1 Uncertainties originating from experimental input data

5.2.1.1 Uncertainties arising from bioconcentration testing

The OECD 305 (OECD, 1996) bioconcentration assay is the standard experiment used to provide input data for the assessment of aquatic food chain bioaccumulation. In this assay fish are exposed to a chemical via water exclusively. When discussing the applicability of this assay to chemicals categorised as PBTs, it has to be considered that a chemical fulfilling the B-criterion will most likely have a high log K_{ow}, which is usually accompanied by poor water solubility (Miller *et al*, 1985). As discussed by ECETOC (2003b), a number of experimental issues render the determination of the BCF more difficult as the hydrophobicity of a chemical increases. These issues are compiled in Table 5 and lead to increased uncertainty.

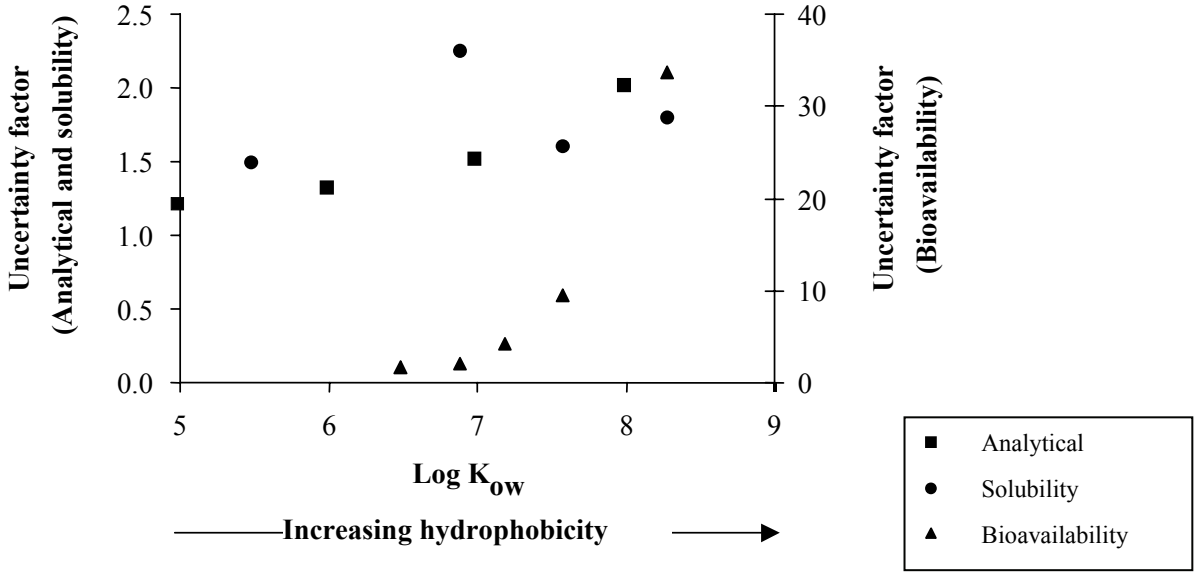
Table 5: Processes and issues causing uncertainty in experimental determination of the bioconcentration factor together with possibilities to obtain less uncertain input data

Item	Issue	Underlying process	Estimated magnitude of uncertainty	Improvement
1	Experimental failures increase with increasing length of the experiment.	Duration of a valid bioconcentration experiment > weeks/ months.	See text	Shorten experiments (dietary exposure). Tight control of experimental parameters.
2	Generation of truly dissolved exposure solutions	Dissolving sparingly soluble chemicals in water is not trivial.	Up to a factor of 2.5× (see circles, Figure 10)	Employ systems for buffering exposure concentration (Mayer *et al,* 1999; Brown, *et al,* 2001).
3	Analytical verification of concentration in exposure solution	Poorly water-soluble substance may not be detectable at its solubility limit.	Up to a factor of 2× (see squares, Figure 10).	Dietary exposure experiment - no measurements in water.
4	Bioavailability reduction	Hydrophobicity driven association to POM/DOM reduces fraction of test compound available for uptake.	Up to a factor of 30× (see triangles, Figure 10).	Modelling to correct for POM/DOM interactions (Burkhard, 2000), measure concentration bioavailable (Kraaij *et al*, 2003).

Figure 10 illustrates how increasing hydrophobicity (expressed as log K_{ow}) results in increased uncertainty. Shiu and Ma (2000) equated the experimental error observed in aqueous solubility to an uncertainty factor of 2.5. The bioavailability reduction, quantified as the fraction of the concentration of chemicals in water which is available for uptake by fish (Gobas *et al*, 1989),

represents the uncertainty due to partitioning of chemicals categorised as PBT from water to particulate or dissolved organic matter. The uncertainty associated with the analytical determination of sparingly soluble chemicals is expressed as the relative standard deviation of measuring chemicals at concentrations close to the limit of quantification. According to experience, the experimental error in determining the aqueous concentration increases exponentially as the concentration to be measured approaches the limit of quantification of a given analytical method. The error and thus the uncertainty amounts to a factor of 2 for the most hydrophobic chemical.

Figure 10: Uncertainties relating to experimental errors involved in determination of the bioconcentration factor according to OECD TG 305, expressed as factors



As shown in Table 5, Item 1 has not been assigned a quantitative measure of uncertainty. Either the factors involved in the uncertainty can be controlled (temperature, water quality etc.) or accounted for (growth during the experiment etc.) or they lead to failure of the experiment such that the data generated become invalid. The combined uncertainties associated with generating and measuring low concentrations of difficult to test substances (Items 2 and 3), account for a factor of five. The uncertainty related to bioavailability can be accounted for by either experimentally assessing the bioavailable fraction or by employing model calculations. These calculations correct for the effect of organic material in the exposure solution. A factor of two can be considered a reasonable worst-case estimate to account for this phenomenon. Taken together, the uncertainty associated with the experimental determination of the BCF amounts to a factor of approximately 10.

5.2.1.2 Dietary biomagnification testing as an alternative to bioconcentration testing

The protocol for fish dietary biomagnification developed by (Parkerton *et al*, 2001) offers an approach to resolve all four issues for highly hydrophobic chemicals. In this experiment, fish are exposed to the chemical via the food. The EU PBT Working Group has accepted the protocol as a technical guideline for assessing the bioconcentration behaviour of certain types of chemicals. The outcomes of this experiment are the uptake efficiency, the biomagnification factor, and the rate constant of depuration of the chemical from the fish ($k_{depuration}$). The depuration rate constant is related to the depuration half-life ($t_{1/2}$) according to:

$$t_{1/2} = 0.693/k_{depuration}$$

The biomagnification factor is employed as input in modelling food chain bioaccumulation according to the EU TGD (EC, 2003b). In addition, another key parameter in aquatic food chain modelling, the BCF, can be calculated as $BCF = k_u \times t_{1/2}/0.693$ using the experimentally determined value of the depuration half-life ($t_{1/2}$) and the uptake rate constant (k_u). k_u can be estimated according to an allometric relationship (Parkerton *et al*, 2001).

The dietary biomagnification experiment has a number of advantages over the bioconcentration assay according to OECD TG 305 (OECD, 1996). As a result of exposing the fish via the food, the low solubility of the chemical does not limit the uptake. Second, the problem of generating a constant concentration of a sparingly water-soluble compound is avoided. Third, the experimental error due to measuring the concentration of sparingly soluble chemicals in water is avoided. Finally, bioavailability reduction as a phenomenon occurring as a consequence of association of the tested chemical to constituents of the aqueous exposure solution is irrelevant in the dietary exposure experiment. Hence, the information generated in the dietary biomagnification experiment is expected to be less uncertain than that obtained in the standard bioconcentration assay according to OECD TG 305.

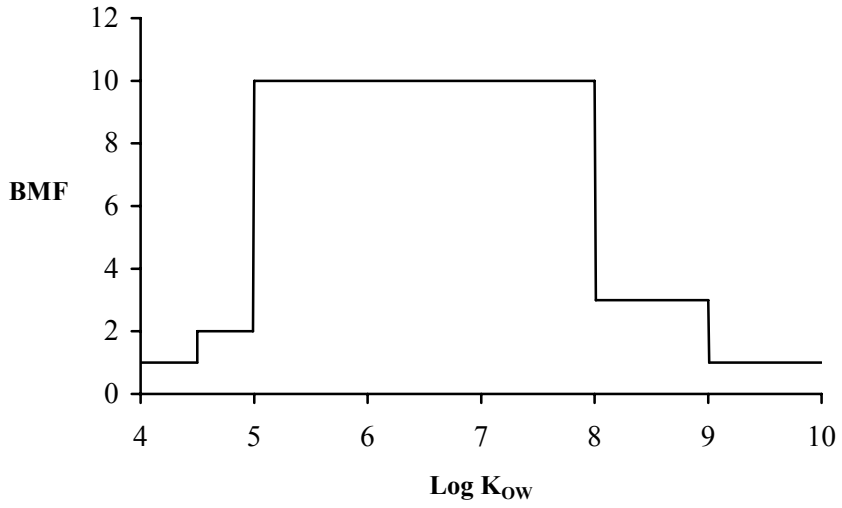
5.2.2 Uncertainty caused by modelling issues.

5.2.2.1 Modelling BMF and BCF

Experimentally derived BMF data are not often available. Hence, default BMF estimates according to Figure 11 are employed in EUSES. ECETOC proposed a less conservative algorithm to estimate BMF in dependence of log K_{ow} for chemicals with log K_{ow} between 4 and 8 ($BMF = \log K_{ow} - 4$) (ECETOC, 2001). Recent studies have shown that estimation of the BMF on the basis of log K_{ow} is associated with considerable uncertainty. This is because the correlation between these parameters is rather poor as biomagnification is mainly related to slow metabolism in (prey) organisms (González-Doncel *et al*, 2003). Estimating BMF from log K_{ow} will thus

overestimate the risk of bioaccumulation/biomagnification in those cases where more efficient elimination pathways exist in mammals as compared to fish. In addition, recent publications on dietary bioaccumulation of polychlorinated biphenyls suggest that the BMF value of 10 for a trophic accumulation step is conservative, even for metabolically stable compounds (Buckman *et al*, 2004). Given that a certain degree of conservatism is desirable in a low tier bioaccumulation assessment, the use of the TGD approach to estimate BMF appears acceptable. At higher levels of assessment, processes relevant to bioaccumulation that are not reflected by log K_{ow} need to be considered explicitly (e.g. by comparing toxicokinetic data, using *in vitro* studies, etc.). One more source of uncertainty arises from the lack of experimental data for the bioconcentration factor in the 'aquatic organism' (aquatic food chain) and in the earthworm (terrestrial food chain). These data need to be estimated, either on the basis of log K_{ow} or based on extrapolation from fish data. These steps are also associated with uncertainty.

Figure 11: Default BMF values according to the TGD (EC, 2003b) based on log K_{ow}



5.2.2.2 Food chain modelling

A second source of uncertainty within food chain modelling is due to the assumptions made about the structure of the food chain, the food consumption patterns and the environmental concentrations employed in calculating the concentrations in the food chain organisms. EUSES, for instance, assumes that 50% of the top predator's diet originates from an area close to the point of discharge (annual average PEC_{local}) and 50% comes from a regional area (annual average $PEC_{regional}$), which usually displays a lower concentration. In higher tier bioaccumulation

assessments refinement is possible by employing environmental concentrations estimated by more refined approaches or by measured concentrations.

The generic food chain in EUSES for bioaccumulation modelling comprises one (terrestrial), two (freshwater) or three (marine) trophic transfer steps. The food consumption pattern in EUSES is quite simplistic by excluding risks due to the consumption of other organisms outside these simplified food chains. The predator-prey-relationships can be refined in higher tiers of bioaccumulation assessment in order to reduce modelling-related uncertainty (Wania *et al*, 2004).

The EUSES algorithm used in the assessment of bioaccumulation in the marine food chain is therefore equivalent to that proposed by ECETOC (ECETOC, 2001), provided the values of BMF and BCF are the same for both trophic levels. In this regard it has to be noted that, following the logic of fixed biomagnification factors, omission of trophic transfer steps leads to underestimation of the food chain bioaccumulation by the magnitude of the biomagnification. González-Doncel *et al*, (2003) conclude that the food chain properties are an important determinant of the overall food chain bioaccumulation. The GEMCO model results (Le Gall *et al*, 2003) however, show that the extent of bioaccumulation in the pelagic and the (epi-)benthic food chain is similar regardless of different lengths of the two food chains. This suggests that detailing the assessment of food chain bioaccumulation beyond a certain degree does not necessarily decrease the uncertainty of the assessment.

5.2.3 Additional considerations

ECETOC (2001) highlight some aspects for the bioaccumulation assessment in the marine environment which require special attention. First, assessment of bioaccumulation in remote sites should be based on appropriate background concentrations as recommended by ECETOC (2001). EUSES now allows for the calculation of relevant background concentrations.

ECETOC (2001) also recommend that the effects of seawater on bioaccumulation, which are particularly pronounced for chemicals that undergo speciation changes as a result of changes in water chemistry (e.g. pH, ionic strength, etc.) should be considered.

5.3 Assessment of bioaccumulation at the screening level - EUSES

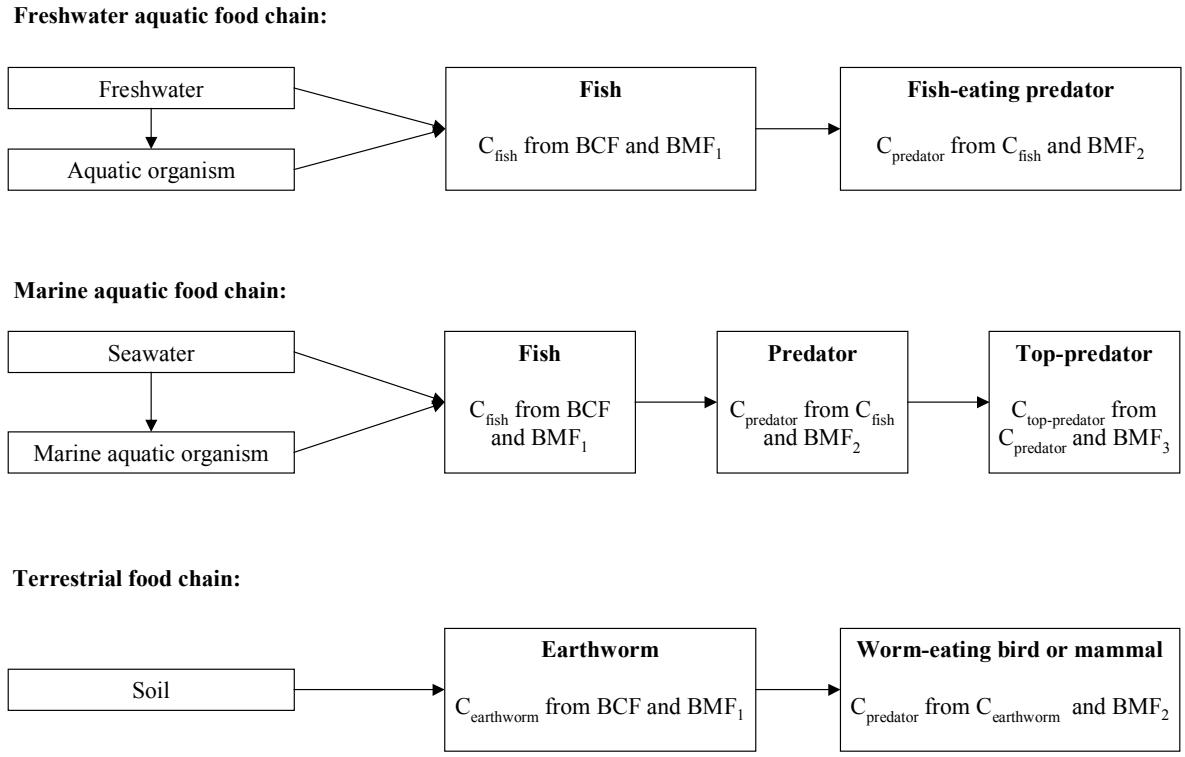
The secondary poisoning assessment as implemented in the TGD (EC, 2003b) can be considered as a first tier assessment of bioaccumulation. This approach is to model two simple food chain scenarios estimating potential effects on birds and mammals in the environment via uptake through the aquatic food chain.

The assessment of risks for secondary poisoning is based on simple food chain scenarios.

- Aqueous: water → aquatic organism → fish → fish-eating bird/mammal
- Terrestrial: soil → earthworm → worm-eating birds/mammals.

The food chains are depicted in Figure 12.

Figure 12: Secondary poisoning via food chain according to the TGD (EC, 2003b)



5.3.1 Calculation of PECs for secondary poisoning

The TGD risk assessment is based on steady-state calculations (EC, 2003b). As a result, the assessment of bioaccumulation involves BCFs to describe uptake of chemical directly from the environment and BMFs to model uptake via the food chain. The TGD secondary poisoning assessment (EC, 2003b) predicts concentrations in prey organisms which can be used to define a value of $PEC_{oral,\ predator}$. $PEC_{oral,\ predator}$ is the predicted concentration to which a predator is exposed when ingesting its food. The risk to predators is then calculated as the ratio between the concentration in the food and the no-effect concentration for oral intake.

5.4 Assessment of bioaccumulation at the investigative level

Assessment of bioaccumulation at the investigative level leads to a refinement in comparison with the secondary poisoning assessment as outlined in the TGD. A refined assessment can be achieved by a) employing additional information, b) refined modelling approaches, and c) by monitoring. Table 6 identifies which information may be relevant, how modelling approaches need to be defined and how monitoring data can serve to improve the assessment of bioaccumulation.

Table 6: Overview of issues related to refining the food chain

Information	Issue	Proposal
Monitoring data	Accuracy of model predictions	Check model: Are input data (also PECs) sufficiently accurate? Are all crucial processes included?
Food chain structure	Model is not sufficiently realistic	Select model which fulfils as many validity criteria as possible (appropriate representation of relevant food chains, validation, appropriate representation of processes)
Seasonal variation		Refine PEC assessment Select model which addresses temporal variability

At this stage of the assessment, additional information is taken into account. Most of it may not have been generated in standardised experiments. A SETAC workshop (Sijm *et al*, 1997) has addressed which information relating to biotransformation might be relevant for assessing the extent to which a chemical might accumulate in an organism. The workshop document also identified the need for formalised processes for introducing this information into the quantitative assessment of food chain bioaccumulation. Hence, investigative level assessment tools might be required to facilitate the use of higher tier information as input for the investigative bioaccumulation assessment. Table 7 provides an overview of higher tier information, which can be employed in investigative assessment of bioaccumulation. In addition to specifying the different types of information (left column) the table also indicates which process can be described with a certain piece of information (central column) and provides a proposal on how the information can be employed (right column). Three of the types of information relate to the role of biotransformation in the assessment of bioaccumulation.

Table 7: Overview of a) information which can be relevant for the assessment of food chain bioaccumulation, b) issues related to employing this information and c) proposals to facilitate the use of this information

Information	Issue	Proposal
Empirical evidence for metabolism	Translation from information to input values for food chain models	Use read-across to derive: - BMF estimate (input for steady-state models, e.g. EUSES) - Appropriate rate constant (dynamic models) Use ADME models to translate metabolic rate data into BMF
QSAR evidence for biotransformation/metabolism	Translation from information to input values for food chain models	Use read-across to derive: - BMF estimate (input for steady-state models, e.g. EUSES)
Uptake limited by lipid solubility, steric parameters	Translation from information to input values for food chain models	Use read-across to derive: - BMF estimate (input for steady-state models, e.g. EUSES) - Appropriate rate constant (dynamic models) Perform appropriate bioaccumulation experiment to obtain relevant input
Biota concentration data	Translation from information to input values for food chain models	Use read-across to derive: - BMF estimate (input for steady-state models, e.g. EUSES) - Appropriate rate constant (dynamic models)
Biota concentration data	Agreement with model predictions	Use results to refine model input by reverse modelling and check for consistency with independent data
Mammalian metabolism data	Translation from information to input values for food chain models	Use ADME models to translate metabolic rate data into BMF

Once there is solid evidence for the chemical being metabolised, then a rationale needs to be constructed for using a number different from the default BMF value. This can be achieved, for example, by comparison of the information on the compound with that for other chemicals for which more is known about the biomagnification behaviour. Similarly, if the bioaccumulation processes are represented as first-order rate constants, then an argument has to be constructed which supports the derivation of a rate constant that accounts for metabolism. Alternatively, information on metabolism needs to be translated into enzyme kinetic parameters if a physiology-based toxicokinetic (PBTK) model is to be used.

Advanced bioaccumulation models offer the opportunity to describe and model the processes involved in food chain bioaccumulation in a more realistic manner than the standard tool. As highlighted by Borgå *et al* (2004) they should provide a realistic representation of the food chain

and of biotransformation, since trophic transfer and metabolism are the principal biological factors influencing bioaccumulation.

The applicability of such models has been demonstrated in proof-of-principle exercises. The food chain model described by Czub and McLachlan (2004) is an example of a model that describes bioaccumulation in terms of rate constants. Consequently, this model requires a rate constant for the process of reduction of the chemical concentration in the organisms' interior via metabolism. PBTK models (Barron *et al*, 1990; Nichols *et al,* 1991) are another option. These models are explicit mathematical representations of the physiological processes that are relevant for toxicokinetics. In addition to data on the rate of metabolism, they require data for describing the partitioning behaviour in the body as well as parameterisation of the model towards a specific organism.

An empirical approach to explicitly account for biotransformation in bioaccumulation modelling has been developed in the GEMCO model (Le Gall *et al*, 2003). Such approaches are of particular relevance since even a very slow rate of metabolism may markedly reduce bioaccumulation. This has been recognised by González-Doncel *et al* (2003) who suggest that biomagnification in food chains need to be represented/modelled as a sequence of bioaccumulation steps each of which depends on toxicokinetic parameters. The models used in GEMCO (Le Gall *et al*, 2003) and ACC-HUMAN (Wania *et al*, 2004) follow this recommendation. Modelling of bioaccumulation of PCBs (representatives of persistent chemicals) in the food chain in estuarine environments (GEMCO) and in the Baltic Sea and in the Arctic (ACC-HUMAN) yielded predictions comparable with measured data. The applicability domain of these models has yet to be defined.

5.5 Assessment of food chain bioaccumulation at the confirmatory level

An assessment of food chain bioaccumulation at the confirmatory level will be carried out if concerns remain from lower tier assessments over the estimated risk or associated level of uncertainty for a given chemical. Under these circumstances it will become necessary to define a biota monitoring programme. However, as all organisms cannot be monitored, modelling will remain an intrinsic part of the assessment. The results of the biota monitoring programme can be used to provide information that will help improve the model.

The assessment of food chain bioaccumulation at the confirmatory level is subject to the same considerations as the assessment of environmental exposure concentrations (see Section 4.5). Therefore, this section focuses on those aspects that are specific for the assessment of food chain bioaccumulation.

5.5.1 Use of existing monitoring data

In addition to the comments in Section 4.5.2, it should be noted that the assessment of food chain bioaccumulation is ideally based on concentrations in biota and the abiotic environment that are spatially and temporally related, since concentrations in the sampled biota are related to the concentrations in the abiotic environment via the food chain. Therefore, information on the different biological causes for variations in biota concentrations such as migratory behaviour, feeding ranges, mobility, starvation/feeding, and loss through lactation, need to be carefully considered in the selection of the biota data such that meaningful conclusions are possible.

5.5.2 Designing monitoring studies for confirmatory risk assessment

If the existing monitoring data are insufficient it becomes necessary to design a monitoring study following the considerations outlined in Sections 4.5.3 and 5.5.1. This is a prerequisite for the generation of data that allow for meaningful conclusions on the food chain bioaccumulation behaviour of a given substance.

5.5.3. Examples of the use of monitoring data in food chain bioaccumulation assessment

The use of food chain monitoring for assessing bioaccumulation in a food chain is illustrated by the work of MacIntosh *et al* (2004). They benchmarked phthalic acid diesters against known bioaccumulative substances, PCBs, to confirm that phthalic acid diesters do not bioaccumulate in a marine food web. A similar approach has been used to discriminate PCB congeners that undergo biomagnification in marine mammals from those that do not (Kannan *et al*, 1995). In addition, food chain monitoring data can be employed to establish biomagnification factors that might be used in modelling other food chains of concern.

5.6 Conclusions

- A number of uncertainties exist within the bioaccumulation assessment of all chemicals, regardless of PBT categorisation;
- the secondary poisoning module of EUSES provides the tool for the screening level assessment of bioaccumulation;
- the uncertainty in BCF, and BMF values, as input data for a bioaccumulation assessment, can be reduced by performing dietary biomagnification experiments;
- the assumption of a fixed BMF leads to an overestimation and hence introduces an element of conservatism into the assessment;

- divergent non-standard information can be used as input into a higher tier bioaccumulation assessment. A case-by-case evaluation of this type of information is required. As a result, a flexible assessment process is required;
- assessing bioaccumulation at the highest tier requires measurements of concentrations in organisms and their environment.

6. ENVIRONMENTAL EFFECTS ASSESSMENT

6.1 Introduction

It needs to be recognised, when addressing possible environmental effects of chemicals categorised as PBTs or vPvBs, that there are limitations to the existing test methodologies in design and applicability to highly hydrophobic chemicals. The current assessment methodologies were developed for water-soluble substances. However, many chemicals categorised as PBTs will have high K_{ow} values and, therefore, be poorly soluble. These physico-chemical properties can pose problems when performing standard ecotoxicity tests. For example, sufficient material may not go into solution to induce an effect in an organism and materials may be highly sorptive due to their high K_{ow}. Guidance on testing and assessment procedures for these materials exists (OECD, 2000b; ECETOC, 2003b).

While these limitations of test methodology also exist for chemicals not categorised as PBTs, it is because of the hazardous profile of PBT chemicals that greater attention must be paid to these limitations. It is for this reason that an environmental effects assessment should specifically focus on longer-term tests in the various environmental compartments of concern and provide a more refined food chain/secondary organism effects assessment than would be the case for chemicals not categorised as PBTs.

6.2 Factors affecting uncertainty in effects assessment

While suitable protocols exist for the determination of the ecotoxicological effects of many chemicals, their application to chemicals categorised as PBTs is not without some concern. Uncertainties arise from test design, the physico-chemical properties of the chemicals themselves (e.g. poor water solubility), test duration, route of exposure and bioavailability.

6.2.1 Poorly water-soluble substances

Substances meeting PBT criteria are often of very low solubility in water and of high lipophilicity. These properties can cause specific problems in ecotoxicity testing and interpretation of study results.

For example, false positive results may be observed as a consequence of problems such as the production of heterogeneous stock/test solutions or physical impairment of the test species by hydrophobic liquids coalescing at concentrations above their water solubility to form a film or droplets leading to, for example, entrapment of small test organisms such as *Daphnia magna*.

Adsorptive effects may also be observed on the surfaces of materials or biota used in standard test systems.

In addition to physical effects, there may be other explanations to account for effects that occur above the water solubility limit including the presence of water-soluble impurities or degradation products. Furthermore, these poorly soluble chemicals may also present problems in analysis at the low concentrations that are expected to be required in testing PBT chemicals.

Another concern is that lack of effects at the solubility limit may represent a false negative result. This latter may be attributed to insufficient exposure time to permit steady state to be achieved between the concentration of the test substance in the organism and the test medium (de Bruijn and Hermens, 1995). These issues of testing have been addressed in various reports and proposals have been made to overcome them (OECD, 2000b; ECETOC, 1996, 2003b).

6.2.2 Test duration

Due to the hydrophobic nature of chemicals categorised as PBTs, equilibration of the test organisms with the surrounding medium is not likely to occur within the duration of the standard acute toxicity test. Hence, the question arises whether the organisms in a 96 h or a 28 d aqueous exposure experiment for a hydrophobic chemical attain a steady-state concentration and therefore whether the internal concentration was at its maximum. The organism body size determines the kinetics of contaminant uptake/elimination and this has been addressed in a comprehensive modelling exercise (Hendriks *et al,* 2001). This study states that the fundamental biological processes involved in transport of organic contaminants into and out of organisms are coupled to the flux of water and food as well as of subsequent allocation of energy to respiration, growth and reproduction. Hendriks *et al* (2001) provide relationships that allow simultaneously accounting for the influence of body size and hydrophobicity of the chemical on the value of the rate constant for elimination via ventilation, egestion and growth dilution. This modelling exercise shows that the t_{95} (time required to attain 95% of the equilibrium concentration) increases as the log K_{ow} increases. This relationship demonstrates that, in the case of highly hydrophobic chemicals, the test duration in certain test systems (e.g. 21 d chronic *Daphnia* study) should be extended to ensure the t_{95} has been reached. This approach has limitations, as tests cannot be extended indefinitely, however a NOEC obtained at the t_{95} would provide a more certain estimate of effects.

6.2.3 Route of exposure

The bioavailability of PBT chemicals is expected to be low, especially under laboratory conditions. The categorisation of PBT chemicals is based on test results obtained under unrealistic environmental conditions using constant waterborne concentrations. For instance, when determining the uptake from water, the BCF is measured under flow-through conditions. Gut contents and cuticular/muscular adsorption are sometimes mistakenly included in the BCF calculation.

Certain classes of compounds, notably ionising compounds, may bind to substrates via ionic interactions. For non-ionising substances, the compound is expected to be bound mainly to the organic fractions in the compartment of concern. However, in some cases, e.g. ionising organic molecules such as cationic substances, a greater proportion of the substance may be bound to the inorganic rather than the organic fraction of sediment due to the high anionic charge of the clay fraction. Certain types of organic matter (e.g. humic acids) also have strong ionic binding capability. Indeed the whole concept of sediment-substance interactions using log K_{ow} as a predictor of sediment concentration needs to be expanded by accounting for additional interactions as suggested by Qiu and Davis (2004). Many studies have made use of river water for testing of fish and invertebrates in order to provide a more realistic assessment of toxicity than that proposed by the TGD (i.e. 1% of waterborne concentration adsorbed to the sediment) (ECETOC, 2003b).

The appropriate route of exposure should be considered for experiments on chemicals categorised as PBTs. Dietary exposure may be more appropriate than exposure via the water alone for determination of long-term effects in sediment dwelling as well as water column dwelling organisms.

6.2.4 Compartment-specific considerations

6.2.4.1 Sediment and soil

6.2.4.1.1 Equilibrium partitioning method

In the absence of effects data on soil and sediment organisms the TGD recommends the EqP method to calculate $PNEC_{sediment\ or\ soil}$ (EC, 2003b). EqP is the theory that toxic effects and body residues in soil and sediment-dwelling organisms can be predicted from the partitioning of a chemical between the soil, water and organism phases at thermodynamic equilibrium (Di Toro *et al*, 1991). The underlying assumptions are that (i) organisms within the sediment and water columns have equal sensitivity, (ii) concentrations of the substance in sediment, interstitial water and benthic organisms are in equilibrium and can be predicted using the relevant partitioning

coefficients (K_p), (iii) sediment or soil/water partitioning coefficients can be measured or derived on the basis of a generic partitioning method from separately measurable characteristics of the sediment or soil and chemical in question, and (iv) uptake of the chemical into the organism is via the pore water only, it does not take into account uptake of a chemical from the sediment or soil via ingestion (ECETOC, 2004b). The uptake of chemicals via ingestion of sediment/soil is analogous to ingestion of food. In terms of Gobas's biomagnification model (Gobas and Morrison, 2000) the concentration of the contaminant in the organism will increase if the soil/sediment/food is digested to such an extent that the capacity of this soil/sediment/food to absorb chemicals is significantly reduced. For instance, digestion of food leads to a significant deprivation of lipids from the gut content. As a result, the capacity of the gut contents to act as a partitioning medium for hydrophobic chemicals is significantly reduced. Consequently, hydrophobic organic chemicals will partition away from the gut contents into lipid rich tissues of the animal. This does not happen to the same extent with soils/sediments. Depending on the conditions in the gut and the chemical/particle interaction, soils/sediments will largely retain their partitioning capacity even though the binding strength may change. Hence, the assumption of bioaccumulation of soil/sediment can be described as equilibration between pore water and organism. Consequently, according to the EqP theory, the plateau concentration should be equivalent to aqueous exposure. To account for an argued underestimation of uptake for chemicals with high log K_{ow} the TGD applies an additional factor of 10 to the $PEC_{sediment\ or\ soil}/PNEC_{sediment\ or\ soil}$. However, this approach is not consistent with the theory proposed by Di Toro *et al* (1991), who state that:

> '*.... assuming that the equilibrium partitioning of the chemical between sediment organic carbon and pore water is at equilibrium ... the organisms receive an equivalent exposure from a water only exposure or from any equilibrated phase; either from pore water via respiration; from sediment carbon via ingestion; or from a mixture of routes. Thus, the pathway of exposure is not significant*. '

Crucial in maintaining the conservative nature of the EqP method for hydrophobic chemicals is the use of an appropriate K_p value. K_p values estimated on the basis of log K_{ow} and the organic carbon content result in higher predicted pore water concentrations and are thus conservative (Kraaij *et al*, 2003) and protective within a lower tier risk assessment.

When the sediment or soil compartments are of concern for a specific PBT or vPvB, EqP should only be used at the lower tier or evaluative level of the risk assessment due to its overly conservative nature. Sediment and soil toxicity testing are required for a more refined assessment of effects within these compartments.

6.2.4.1.2 Testing consideration

Spiking methodology for ecotoxicological tests is still in its infancy. Low toxicity tertiary solvents are often used in an attempt to achieve testing concentrations that are termed aqueous solutions. These may be used as stock solutions for aqueous tests or for spiking sediment, soil and food. Aqueous solutions produced using solvent 'carriers' are often little more than emulsions and are rarely completely dissolved. Contaminant sediment/soil interactions are still poorly understood and methods to achieve environmentally realistic spiking methods are not proposed in guideline studies.

Highly hydrophobic chemicals (i.e. log K_{ow} > 5) will adsorb strongly to suspended solids, sediment or soil. Alexander (2000) provided evidence that the bioavailability of certain substances in soil and sediment declines dramatically with ageing due to continuous diffusion and retention into inaccessible regions of the soil/sediment matrix. This has been visualised as a two step process with a weaker bound short step and a more strongly bound long step differing in rate, for example, by about two orders of magnitude for chlorobenzenes, PCBs and PAHs (Qiu and Davis, 2004; Cornelissen *et al*, 2000; Kan *et al*, 2000; Ten Hulscher, 2005). The distinction is referred to as the linear and non-linear domain (Burgess *et al*, 2003). Thus even adsorption/desorption kinetics are difficult to quantify. Desorption, and the resulting uptake in the gut, may be influenced by digestive juices (which may contain pH modifiers and natural surfactants) (Lyytikäinen *et al,* 2003). There is also evidence to the contrary, i.e. aging not leading to a marked reduction in bioavailability (Kraaij *et al*, 2002). This is further evidence of the necessity to obtain good measurements of the exposure.

Choice of species is also an important testing consideration. It may be better to choose a target species that is likely to be more exposed to the chemical in question rather than one which has been demonstrated to be sensitive to the chemical in acute effects tests but which will not be significantly exposed. For example, if a limnic species is the most sensitive species but the substance is highly sorptive, the results from a test involving a benthic organism may be more suitable.

Even within the sediment dwellers there may be radically different exposure scenarios either due to habitat or physiological differences. Brooks (2005) reported that uptake of adsorptive chemicals via the gut from ingested sediment was positively correlated with gut retention time of the animals tested. In this case, uptake was greater for a *Chironomus* species than for *Asellus aquaticus*, a caddis species and for *Gammarus pulex* despite the fact that natural gut surfactants were greater for all these species than for the chironomid. Thomas *et al* (2005) found that EC_{10} for *Caenorhabditis elegans* can be predicted based on cationic exchange capacity (CEC) for similar surfactants to those used by Brooks (2005).

Spiking methods, substrate and species need to be considered prior to testing so that the most appropriate species are used together with the most environmentally realistic test conditions.

6.2.4.2 Marine

The marine environment, from a purely precautionary perspective, often ends up being the ultimate protection goal. The current methodology in the TGD adds an additional factor of 10 to the already conservative assessment factors developed for freshwater systems:

- To add additional protection for extrapolation of freshwater endpoints to marine organisms, and
- to account for potentially more sensitive species in the marine environment that do not exist in the freshwater environment.

As noted in the ECETOC report on aquatic hazard assessment (ECETOC, 2003d), when making a comparison of the sensitivity between freshwater and marine organisms, it has been shown that:

> '*There does not appear to be any marked difference in sensitivity between freshwater and saltwater biota that systematically applies across all three trophic levels considered. ... Where differences in the apparent sensitivity of freshwater and marine biota were observed for individual compounds, such differences were consistently within a factor of 10 (< 1 log unit) and usually somewhat less.*
>
> *... In addition, the relative sensitivities of aquatic organisms occupying the three different trophic levels in both freshwater and saltwater environments were also established. In most cases, the differences in sensitivity observed between the trophic levels in fresh water and salt water were as great or greater than that observed between the paired species from a common trophic level across the two media (LeBlanc, 1984). This would appear to suggest a physiological similarity between species belonging to similar taxonomic groups, regardless of their freshwater or marine origins.*
>
> *... there is no conclusive evidence to suggest that freshwater species are either more or less sensitive than saltwater species. There is still limited information on saltwater organisms and more data need to be generated to improve our understanding of the effects of chemicals on the marine aquatic environment.*'

The strategy in this report recognised that, despite the limited availability of test methods and marine data, the approach recommended by the TGD is adequately protective of the marine

environment. Furthermore, extrapolation from the body burden approach from freshwater studies to marine organisms, discussed below in Section 6.3.3, should provide sufficient protection to the levels described within the TGD.

6.2.4.3 Biota - secondary poisoning extrapolation

In the assessment of secondary poisoning, the environmental risks of chemicals to higher trophic-level organisms are assessed. The organisms include fish-eating birds, mammals (marine) and predatory fish. The TGD requires a minimum set of experimental data (both for mammals and birds) for chemicals with a potential to bioaccumulate. This information is used to derive a $PNEC_{oral}$ value that specifies the concentration in prey that must not be exceeded. This minimum data set is:

- Mammalian repeat-dose toxicity study (subacute, subchronic or chronic) or reprotoxicological study via dietary or oral route. NOEC values based on mortality, reproductive parameters or growth are considered of main relevance as bases for interspecies extrapolation. The use of further information on genotoxicity or carcinogenicity is of limited value in the environmental setting, as stated in the TGD (EC, 2003b);
- avian dietary study of at least 5 days duration or alternatively a repeat-dose toxicity or reprotoxicological study (OECD test 205 or 206 (OECD, 1984a,b)). Extrapolation from mammalian data to avian toxicity is not considered scientifically sound, as large differences in sensitivity have been documented (Hill, 1994).

Based on the minimum data set described above, the following uncertainties in extrapolation from laboratory data to wildlife are recognised:

Extrapolation to lifetime exposure

For mammalian toxicity studies, widely accepted exposure duration factors have been established to account for differences in test duration and to allow for extrapolation from subacute/subchronic toxicity studies to lifetime exposure (Groeneveld *et al*, 2004).

Variation of body burden in different species

Body burdens are the result of bioaccumulation processes. They are strongly influenced by toxicokinetics. This has been discussed in Chapter 5. For the assessment of secondary poisoning

of chemicals categorised as PBTs, the estimation of wildlife body burden encounters a series of specific uncertainties such as:

- Experimental biomagnification factors in the food chain are scarcely available. The use of generic estimation values is typically the only alternative. This leads to additional uncertainty (Hendriks *et al*, 2001);
- enzymatic activities and metabolic rate vary significantly in various species (Watkins and Klaassen, 1986);
- differences in caloric content in different food types influence the amount of overall food intake and therefore lead to differences in body burden of herbivores, omnivores, carnivores, or fish-eating organisms, respectively (Traas *et al*, 1996; McDonald and Wilcockson, 2003);
- elimination half-lives of stable fat soluble compounds have been shown to be largely dependent on the total body fat content of the organism. This can lead to higher body burdens in organisms with high fat content (Geyer *et al*, 2002);
- normal versus extreme environmental conditions; differences in metabolic rate during reproduction or depletion of fat reserves, e.g. during hibernation or migration, lead to a release of accumulated burdens in fat and fluctuations in tissue concentrations (Kelly and Gobas, 2003);
- relative sensitivity of animals to certain chemicals; differences in biotransformation of certain compounds between taxonomic groups of birds or mammals. The US-EPA uses a species sensitivity factor (SSF) that ranges from 1 to 0.01 (EC, 2003b).

Allometric scaling is a commonly used interspecies extrapolation approach expected to produce the same internal dose (e.g. area under the curve for chemical in blood in both species). It is based on the observation that many biological properties vary directly with body weight or a power of body weight, such that:

$$A = a\,(BW)^b,$$

where A = biological attribute, a = empirical coefficient, BW = body weight, b = allometric scaling factor. Allometric scaling factors that have been applied in toxicology include: $BW^{0.66}$ (equivalent to body surface area) (Pinkel, 1958), $BW^{0.75}$ (equivalent to metabolic rate) (Travis and White, 1990), and BW^{1} (simple body weight scaling). Scaling based on metabolic rate has been further refined for both mammals and birds depending on thermoneutral zones or field activities (e.g. existence versus free living metabolic rate). Especially for mammals, the slope of the field-metabolic rate has been shown to be significantly higher than that of the basal metabolic rate (US-EPA, 1993, 1999).

Various experimental data have shown that extrapolation from daily dose is not a suitable metric to extrapolate from laboratory animals to wildlife species as key parameters in physiological

differences are not addressed adequately. Although a matter of debate for years, caloric demand scaling compared to body weight scaling seems to be a viable alternative as an interspecies extrapolation method in the absence of specific measured data for various species (Schneider *et al,* 2004).

Intra-species differences based on a wide range in phenotype and genotype variability are well known in humans, i.e. intra-individual susceptibility. Specific safety factors are typically used in extrapolation of animal data to humans to account for these differences (Schneider *et al*, 2004). In ecotoxicological risk assessment, however, intra-species differences are not well documented but the use of specific factors to account for intra-species variability in sensitivity is unnecessary, as the protection goal is the survival of a population and not of the individual (Canadian Tissue Residue Guidelines, 1998).

6.2.5 Assessment factors

A concern has been expressed that chemicals categorised as PBTs cannot be subject to risk assessment because assessment factors have not been developed to predict long-term effects not addressed by the specific test or effects occurring in the food chain. Uncertainty is a fundamental part of life and, although in environmental effects assessment the aim is to reduce uncertainty as much as possible, it must be accepted that it cannot be removed completely. However, given the longer exposure period studies recommended in the strategy presented in this report, and the fact that food chain studies must be performed, existing assessment factors within the TGD are considered to be sufficient.

In environmental effects assessment, assessment factors are applied in order to address uncertainties such as:

- Extrapolation of data from the laboratory to field;
- interspecies variability in measurements of toxicological response;
- differences between acute and chronic effects within species, chronic to multi-generation, and non-traditional endpoints (beyond mortality, reprotoxicity, growth);
- sensitivity of different life stages (e.g. juvenile versus larval);
- presence of other chemicals in the environment (toxicity of mixtures).

Microcosm and mesocosm studies, if well interpreted, could overcome the limitations of single species standard long-term studies.

Assessment factors currently used to address these uncertainties in deterministic risk assessments (i.e. providing protection of the most sensitive species) as recommended by the TGD have been

shown to be conservative in their protection of the environment compared to more probabilistic approaches (i.e. providing ecosystem-level protection) (Lemaire *et al*, 1999). They compared statistical methods and assessment factors and found that the current recommendations for assessment in the TGD were considerably more conservative than statistical models based on many more data points.

These uncertainties hold true for the risk assessment of any chemical, including PBT and vPvB chemicals. However, some further issues may arise with these types of chemicals, which should be addressed in order to maintain an acceptable level of conservatism in risk assessments. These include:

- The mode of action (MOA) of a chemical, which may change with the duration of exposure;
- the critical body burden in different organs and for different choices of endpoints may not be known precisely, (critical body burdens are discussed further in section 6.3.3);
- the potential for long range transport may trigger the question of the appropriateness of the species tested against a target species of concern or the appropriateness of the compartment tested; or
- bioaccumulation factors as determined in standard tests may not necessarily translate into biomagnification up the food chain.

Therefore, when necessary, in order to perform a more refined risk assessment, experimental data should be generated under conditions as realistic as possible. For example, food chain studies could address some of the concerns noted above. Consequently, uncertainty is addressed and reduced by employing refined input data for the assessment rather than by assessment factors themselves.

6.3 Additional considerations

There are several areas that may need to be addressed to provide a more complete assessment of the effects of PBT and vPvB chemicals in the environment or are promising alternatives to address concerns for protecting organisms from longer-term effects. These are discussed below.

6.3.1 Population endpoints

The protection goals of the PBT risk assessment are aimed at determining risk quotients for all compartments and target organisms, notably top predators. Naturally, no risk assessor can perform studies on these potential target organisms and a surrogate must be used in conjunction with extrapolation tools.

Chronic studies involving reproductive endpoints are considered appropriate in the absence of higher-level studies such as mesocosms. Studies that are sufficiently long and robust for this use are the multi-generation fish study and certain invertebrate reproduction studies, all of which would be generated if the first tiers of the PBT risk assessment indicated any level of concern. However, it should be noted that population effects may be difficult to take into account if the initial density is not carefully controlled.

Models are under development to predict spatial or temporal trends in population density based on laboratory-generated toxicity data (Topping *et al*, 2003) that can be applied to the results of the laboratory tests on populations. Using these techniques in conjunction with each other, it should be possible to derive a conservative model to predict PNECs for populations of top predators.

6.3.2 Endocrine disruption

The phenomenon of endocrine disruption is not new, but there is no comprehensive guidance as to how such effects should be characterised in current risk assessment. Conducting risk assessment on endocrine disrupting chemicals (EDC), including chemicals categorised as PBTs with endocrine disrupting activity, can be difficult for several reasons. For example:

- Very low concentrations of these chemicals may induce endocrine effects, as EDCs may affect physiological mechanisms that are already active;
- sensitive windows for endocrine disruption appear to be during periods of rapid cell division, such as sexual differentiation and sexual development and so there may be a significant delay between the exposure and irreversible effects becoming evident; or
- uncertainty about long-term effects causing minor perturbations to hormone concentrations and hormone sensitive tissues.

The lack of comprehensive guidance could, in part, be due to the lack of validated tests available and the TGD acknowledges this. Several protocols are available but many have not been validated. The Endocrine Disruptor Methods Validation Subcommittee (EDMVS), who work closely with the OECD, currently has a programme in place to validate a series of *in vitro* and *in vivo* methods over the coming years, with completion for many expected in 2005.

The strategy presented within this report does not recommend systematic endocrine screening of all PBT chemicals. For those that are identified as potentially reprotoxic or are suspected endocrine disruptors, based on available tools (e.g. validated QSARs or empirical screening assays), this strategy recommends a chronic multi-generation fish study be performed. In addition, it might be noted that the higher tier population-based test will yield information on

reproductive effects which can be used to establish or confirm evidence of endocrine disruption (Hutchinson *et al*, 2000; Brown *et al*, 2003). Moreover, while biomarkers such as vitellogenin or aromatase activity may give important mechanistic information to help decide on the design of chronic tests, current evidence does not support the use of biomarkers for PNEC calculations (Hutchinson *et al*, 2005).

6.3.3 Critical body burden

The major compartments of concern for PBT chemicals are likely to be soil and freshwater sediments and (perhaps more importantly) marine sediments. Chronic test methodologies on species dwelling in these compartments, especially within marine sediments, are the least available and most poorly validated of all guideline recommendations. The TGD recommends a number of studies for these environmental compartments. Unfortunately, the studies proposed are mainly open literature publications and an in depth examination of the tables in which these studies are listed leads the reader to understand that effects assessment of any of the compartments other than water column cannot be convincingly achieved based on current methodology.

For PBT substances the no effect level at equilibrium must be determined in order to set a realistic PNEC. The normal strategy for this used in risk assessment is to move progressively to longer-term studies simultaneously reducing the assessment factor. But for highly hydrophobic chemicals the equilibrium time may be very long and never reached over the test period. However, it is expected that this would be the exception rather than the rule, especially when testing with smaller organisms.

Tissue residues have been proposed as a more appropriate indicator of adverse effects in aquatic biota than external water concentrations as they should represent a more toxicologically relevant dose (McCarty and Mackay, 1993). This concept of critical body burdens (CBBs[a]) is reasonably well established, particularly for acute effects of chemicals that act via a narcosis mode of action (McCarty and Mackay, 1993; McCarty, 1986). A number of reviews have been made on this concept, Barron *et al* (1997, 2002), Sijm and Hermens (2000) and Thompson and Stewart (2003). McCarty (1991) recommended merging acute, chronic and bioaccumulation tests into one to greatly increase the information that could be obtained from a single test. This approach, although having a number of practical difficulties, could provide a more robust method for determining lethal concentration, BCF and chronic effects while adhering to the principle of validated guideline studies rather than performing three standard tests under subtly different conditions and trying to combine the results of the studies.

[a] Within this report we refer to LBBs as being the internal body concentrations causing lethality and CBBs as being the internal body concentrations causing a specific sublethal effect of interest, e.g. effect on reproduction.

Di Toro *et al* (2000) recommend a method to develop water quality criteria for MOA I substances based on acute studies using lethal body burden (LBB). According to these authors, many groups of chemicals fall under the non-polar narcotic category. They found that aliphatics, ethers, alcohols and aromatics were all standard MOA I substances with predictable LBBs. Further, the toxicity of halogenated chemicals, ketones and PAHs can be predicted using a correction factor to the standard regression line. The authors went on to demonstrate how they used species sensitivity distributions of CBBs to reach a protective value for the final acute value, which would protect 95% of the species (determined as 35.3 μmol/g). In their proposal, Di Toro *et al* determined an acute to chronic ratio of 5.09 and observed that use of this factor on acute studies would be suitable to replace chronic studies. Lastly, they derive a final chronic value from the preceding data, which they considered predictive of protective water quality criteria. Mayer *et al* (1986) found that the lower tail ($LC_{0.01}$) of the distribution of the acute lethal toxicity probit line is equivalent to the MATC or LOEC for growth and survival (but not reproductive toxicity) that could be used to predict acute to chronic ratios.

Di Toro and McGrath (2000) went on to propose a method to take into account sediment using the equilibrium partitioning method.

An approach such as this is highly reliant on the accuracy of the predictions based on a limited data set. However, it is detailed here to suggest that when using the body burden approach, a limited data set can be employed instead of an exhaustive and perhaps contradictory data set for risk assessment purposes. In any case, a number of acute studies would need to be performed in which the body burden of the organisms was analysed along with the water concentrations, a practice that is currently not followed. To reduce risk of error, certain validated chronic studies could be employed to verify the approach.

The body burden approach is, however, not without problems. Landrum *et al* (2005) reported that the lethal body residue (LR_{50}) decreases with increasing test time. These authors used a 'damage assessment model' to predict the body burden equilibrium time. Use of this model may help to make predictions of acute to chronic ratios as a complement or alternative to the coefficient determined by Di Toro *et al* or the $LC_{0.01}$ approach from Mayer *et al* (1999).

Other points such as the number of trophic levels to be tested or the relative importance of the species in terms of biomass or as 'keystone' species also need to be considered.

6.4 Conclusions

- A number of uncertainties exist within the toxicity assessment of all chemicals, regardless of PBT categorisation;

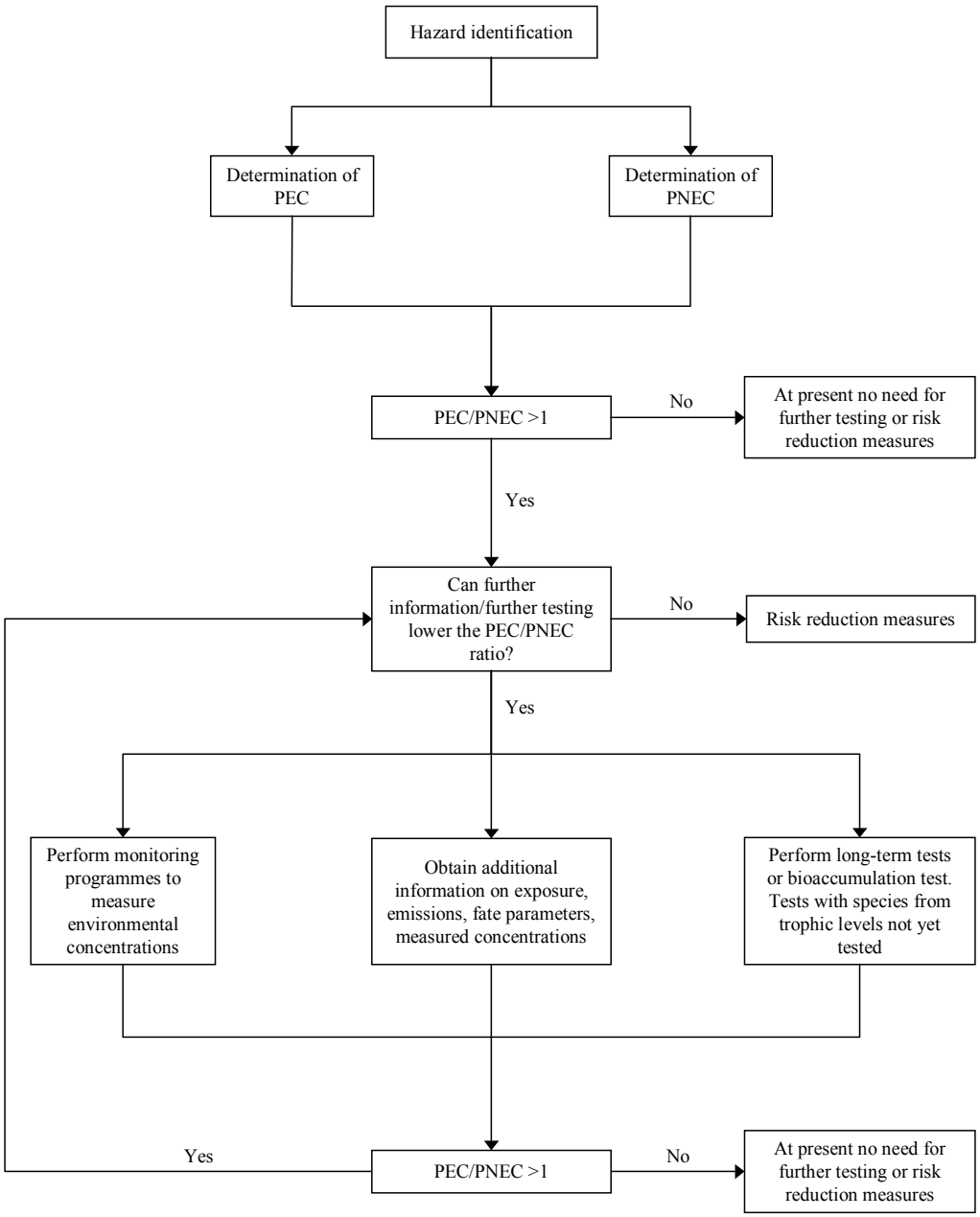
- to avoid problems due to poor water solubility, the recommendations found in OECD (2000b), ECETOC (1996), and ECETOC (2003b) should be adopted;
- chemicals categorised as PBTs are likely to be highly hydrophobic and uptake from an aqueous medium is expected to be slow. Tests to measure effects in the environment should take these kinetics into account as much as possible to ensure steady-state concentrations within the organism are achieved. This can be aided by exposure to the chemical through the diet;
- EqP is an appropriate and conservative lower tier or evaluative methodology to estimate sediment and soil PNECs for hydrophobic chemicals;
- for certain PBT and vPvB substances, life-cycle studies in sensitive species may be an appropriate method for addressing long-term effects (e.g. reproduction and endocrine disruption);
- for higher tier risk assessment of chemicals categorised as PBTs, conventional methods of determining PNEC could be refined and replaced with estimates and measurements of LBBs and CBBs.

7. RECOMMENDED RISK ASSESSMENT STRATEGY FOR PBT CHEMICALS

7.1 Introduction

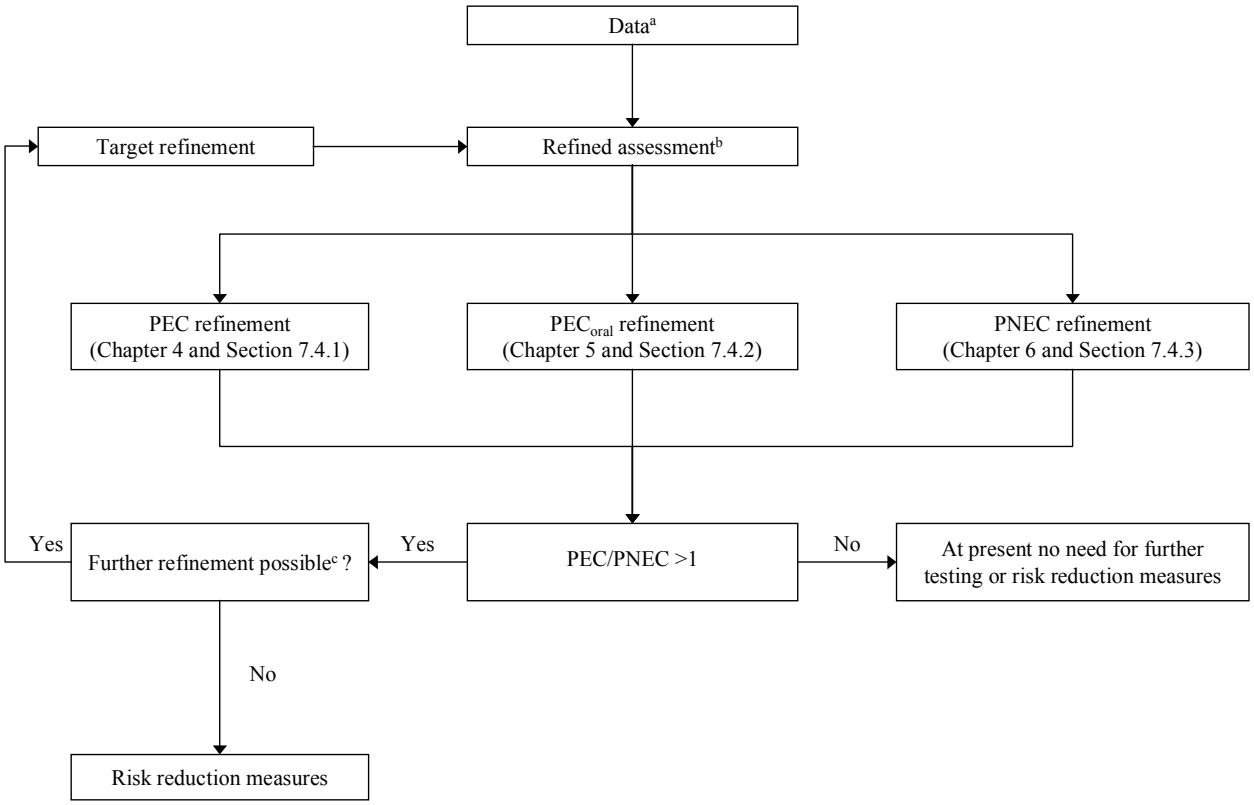
As discussed in previous chapters, environmental risk assessment is an appropriate tool with which to address the environmental harm a chemical may pose. Figure 13 displays a general schematic of the risk assessment process within the EU TGD.

Figure 13: Risk assessment strategy for chemicals not specifically categorised as PBTs



Whilst concerns have been expressed over the applicability of risk assessment on chemicals categorised as PBTs, this Task Force believes that risk assessment is an appropriate tool for all chemicals. The previous chapters of this report have detailed the reasons why the current tools available within environmental risk assessment are applicable following certain modifications and additions. A strategy has been developed which follows the general guidance described in the TGD designed to reduce the uncertainties involved and is shown in Figure 14.

Figure 14: Schematic of the risk assessment approach for PBT chemicals



[a] Refers to evaluative phase in Figures 15, 16 and 17.
[b] Refers to investigative phase in Figures 15, 16 and 17.
[c] Refers to confirmatory phase in Figures 15, 16 and 17.

As can be inferred by comparison of the two schematics, the assessment strategy for chemicals categorised as PBTs differs from those of non-PBT chemicals in the following ways:

1. The PBT environmental risk assessment starts with a refined assessment at a higher tier. This takes advantage of the additional data that will be available compared to most general chemicals due to the testing conducted to inform the PBT categorisation. In addition, the

higher tier assessment would use any available monitoring data in the environment and in organisms.
2. The assessment strategy includes evaluation of expected environmental exposure concentrations in geographical regions that may be remote from the site of the chemical's use and emission to the environment (see Chapter 4).
3. The refined assessment explicitly includes an evaluation of secondary poisoning due to bioaccumulation in food chains (see Chapter 5).
4. The effects assessment will be based on chronic tests (simple and advanced) and uses such parameters as mode of action and body burdens to better assess endpoints of concern (see Chapter 6).

By performing a multi-compartment/multi-region analysis, including bioaccumulation in the food chain and assessment of effects on higher-level predators, the risk assessment of a PBT chemical can be comprehensive. Hence, it addresses the concerns about chemicals exerting effects spatially and temporally distant from the source of emission.

7.2 General refinement strategy

Targeted refinement of the risk assessment according to Figure 14 is key to advancing the assessment. In a stepwise process, the assessor can be informed about which elements of the risk assessment need refinement, i.e. which additional data may be necessary to assess adequately and comprehensively the risks associated with these chemicals. We propose that this stepwise refinement of the assessment of the PEC, PEC_{oral} and PNEC can occur in a combination of three tiers – evaluative, investigative and confirmatory (see sections below). The evaluative phase yields information on how to target the refinement, while the actual refinement takes place in the investigative and confirmatory phases. It can be achieved by using higher tier models as predictive tools. For example, a reduction of uncertainty of the exposure assessment and food chain bioaccumulation might be achieved by replacing the generic EUSES model with higher tier models. Complementary to this, additional higher tier data can be generated through testing and monitoring. The decision on which type of information might be most efficient for improving the assessment can be obtained from an analysis of prior assessments. Finally, probabilistic approaches can be employed to better quantify the uncertainty of the risk assessment.

7.3 General guidance on employing data in risk assessment of PBT chemicals

Selection and quality. As outlined above, PBT chemicals are assessed for risk at an advanced tier. This implies that the quality of the information employed at this stage of the assessment has been thoroughly characterised. To that end, care needs to be taken in the data selection and

documentation of the quality of the data employed. If information from non-standard tests is to be used for deriving input data for the assessment, there is a need to document why and how this information is used. For read-across of information on related substances, guidance can be found in the OECD Manual for investigation of HPV chemicals (OECD, 2004b).

Availability. At this stage of the assessment, a rather complete set of data is likely to be available. It includes the physico-chemical properties of the chemical, data relating to the fate of the chemical such as the environmental half-lives in the different compartments and emission estimates. Information on effects of the chemical would include data on chronic endpoints. All information available on mammalian species might prove valuable since it could be employed for interspecies extrapolation, e.g. from rat or mouse data to mammalian wildlife, such that a valid hazard assessment for top predator species can be obtained. The same holds true for the evaluation of food chain bioaccumulation.

Uncertainty and decision support tools. Identification and quantification of uncertainties must be a key element of a strategy to assess the environmental risks of chemicals categorised as PBTs. Tools to do this are discussed in Appendix A.

7.4 Refining the assessment of PEC, PEC_{oral}, and PNEC

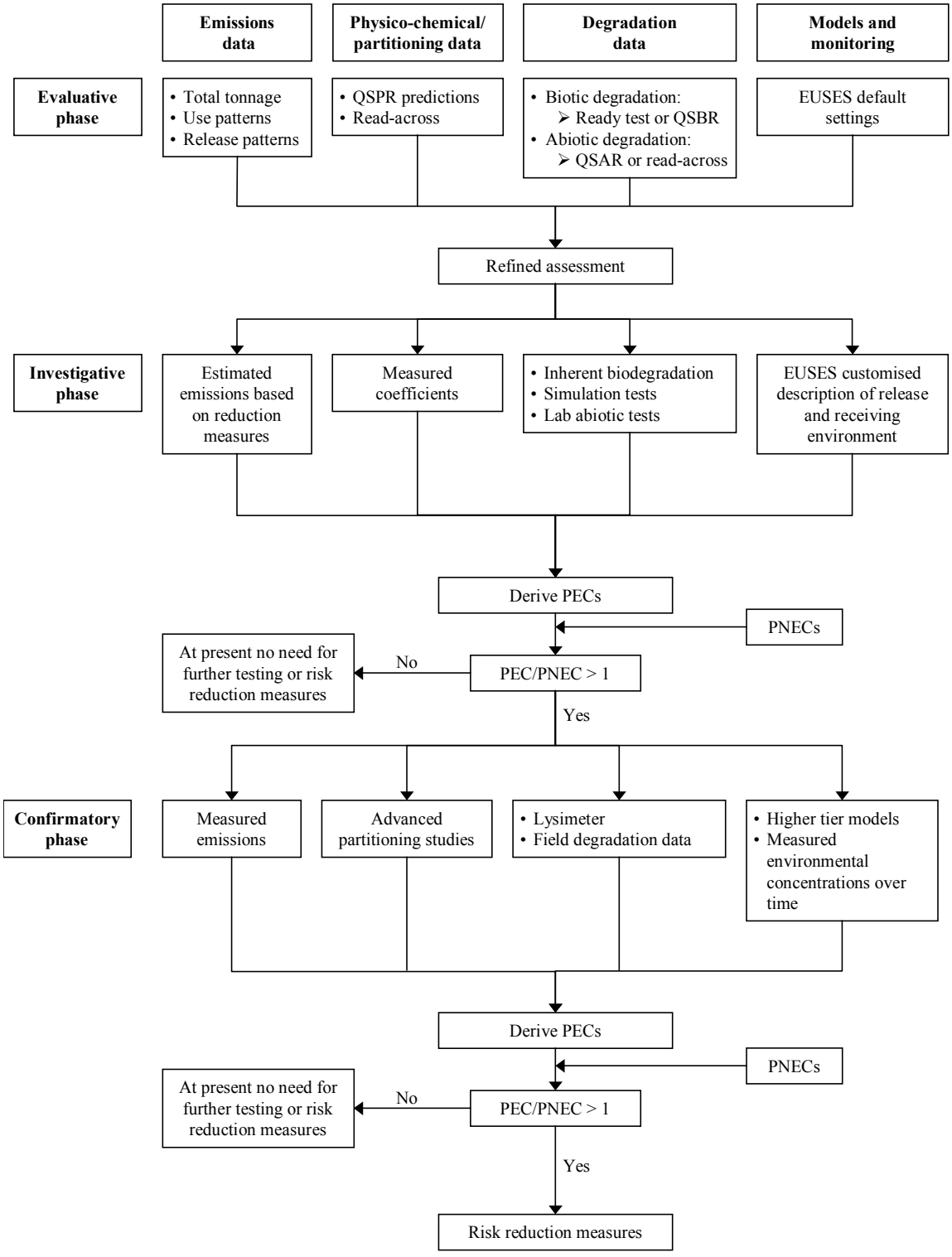
Overviews of the options for refining the assessment of PEC, PEC_{oral} and PNEC are outlined below. The proposed flow charts are meant to give an indication of options for refining the assessment rather than being prescriptive. A flexible approach can then be taken where elements from each phase within each refined assessment can be pieced together to form a more predictive, less uncertain risk assessment for PBT chemicals. The evaluation of the efficiency of a refinement must balance the cost with the expected magnitude of improvement.

7.4.1 Refining PEC

Figure 15 shows the four elements that can be refined to arrive at an improved assessment of PEC. These are emissions, partitioning data, degradation data and models/monitoring.

Emissions. The emissions assessment defines how much of a chemical is released into the environment and via which pathway. It starts with an estimate of the total tonnage and default data relating to the use and the release patterns. In the investigative phase, the emissions estimates might explicitly account for installed emissions control measures. The confirmatory assessment might go as far as employing measured emissions data.

Figure 15: Schematic of the strategy for refining the PEC assessment



Partitioning data. In the evaluative phase, the partition coefficients (e.g. K_{ow}, K_{oa} and K_d) might be estimated on the basis of physico-chemical data using quantitative structure-property relationships (QSPRs). Chapter 4 presents approaches that allow for quantifying and reducing the uncertainty in physico-chemical property data. The estimates can be replaced in the investigative phase by measured partition coefficients. At the highest level of refinement, advanced partitioning studies might be performed which address issues such as reduced bioavailability due to kinetically controlled desorption, etc. Considering that many chemicals categorised as PBTs display extreme partitioning behaviour, it should be noted that refinement of the partitioning data does not significantly affect the PEC estimates, since the models are not sensitive to very high log K_{ow} (> 6) and log K_{oa} (> 12) values (OECD, 2004a).

Degradation data. In the evaluative phase, the results of tests on ready biodegradability or estimates derived on the basis of quantitative structure-biodegradation relationships (QSBRs) might be employed in the PEC assessment. In the investigative phase, results of tests on inherent biodegradability, of simulation tests and of abiotic degradation tests are likely to be available. ECETOC (2003a) observed that, in general, the default half-lives assigned according to results of standard tests tend to overestimate the measured half-life. The proposal is that the degradation be categorised into a range that would represent the uncertainty in the degradation. The categorised ranges could be those used by Mackay *et al* (2000), or those suggested in ECETOC (2003a) and given in Table 4. The ranges to be used should be decided after the uncertainty analysis is completed. In the confirmatory phase, degradation data obtained, e.g. in lysimeters, in aquatic mesocosms, or inferred from monitoring studies (see Chapter 4), might be employed in estimating PEC.

Models and monitoring. EUSES modelling with its default settings will be the tool to perform PEC assessment in the evaluative phase. In the investigative phase, EUSES might still be the assessment tool, but the settings might be customised such that the modelling provides an appropriate description of the releases and the receiving environment. In the confirmatory phase, higher tier models, i.e. models that are temporally and/or geographically explicit, might be suitable. Temporally explicit models might also be employed to predict the time course of PECs. Measured environmental concentrations provide the ultimate possibility to establish environmental exposure. Such data, in combination with appropriate modelling approaches can be used to extrapolate to other geographical regions and/or to derive field degradation rates.

7.4.2 Refining PEC_{oral}

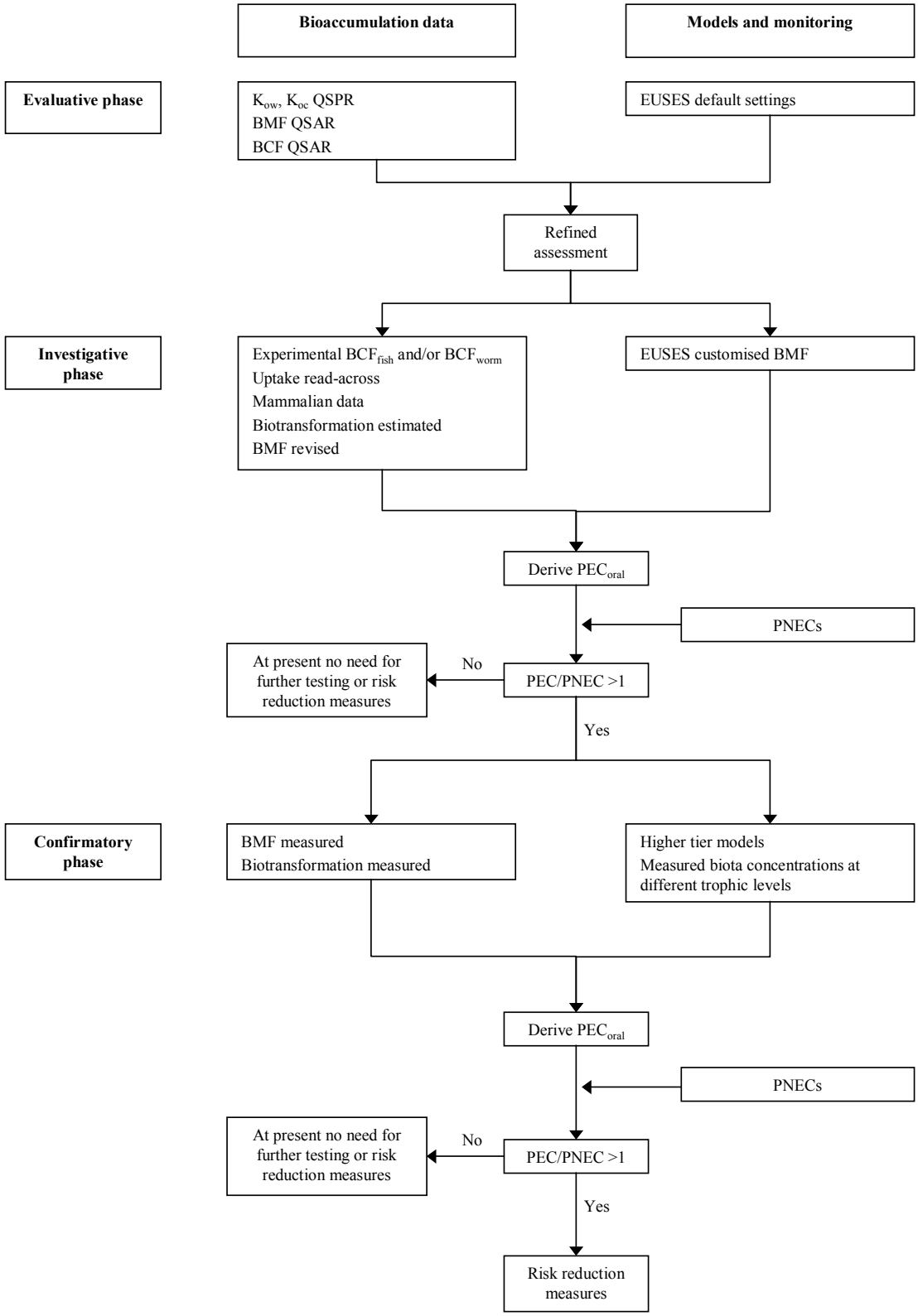
The approach to the assessment of food chain bioaccumulation is shown in Figure 16. It requires input information of the environmental concentrations in the relevant compartments and data on the properties that are relevant for the bioaccumulation behaviour. The environmental

concentrations are assessed following the strategy outlined in Section 7.4.1. The assessment of food chain bioaccumulation results in estimates of the concentrations in the food chain organisms, i.e. body residues. This data serves a dual purpose in the risk characterisation. First, the body residues can be compared with critical body burdens in the organism under consideration. Second, if the organism is consumed by a predator, its body residue data is used for calculating the predator's oral dose, which in turn is compared to the maximum tolerable dose for the predator.

At the investigative phase, experimental data on the BCF should be available. In addition, BMF estimates may be revised on the basis of additional, often non-standard information. This information (see Table 7) includes evidence of metabolism in the food chain, of susceptibility to chemical reactions, and of limited uptake that can be used to refine the model. This can be achieved by, for instance, read-across from one substance to another or by use of a model which allows for input of this information (e.g. a model which explicitly accounts for ADME). Some suggestions have been made in Table 7. For example, the tool to model bioaccumulation might be EUSES with revised BMF values.

In the confirmatory phase, experimental BMF values may be available from laboratory experiments (see Section 5.2.1.2) or from field observations (see Section 5.5.3). Such data can serve as input for higher tier bioaccumulation models. Additionally, concentrations in food chain organisms may be established in field monitoring campaigns. Such field-derived data may provide the ultimate evidence of whether or not food chain bioaccumulation occurs. An interaction between monitoring and modelling, including sensitivity and uncertainty analyses, will inform the risk assessor about the predictive value of the model and which strategy is most efficient for improving the accuracy and reducing the uncertainty of the assessment.

Figure 16: Schematic for refining the assessment of PEC_{oral}



7.4.3 Refining PNEC

Figure 17 provides a schematic representation of the necessary elements in PNEC development and refinement proposed for chemicals categorised as PBTs or vPvBs. It illustrates how an increasingly predictive and more accurate PNEC could be derived using correspondingly reduced assessment or uncertainty factors for use within a less uncertain risk assessment.

In the evaluative (data-gathering) phase, collection and review of chronic ecotoxicological studies, mammalian data, and aquatic BCF information will provide the basic information necessary to enter a refined assessment. Modelling (e.g. EqP or QSAR) and read-across will provide additional screening level information, to determine the necessity of further study in non-aquatic (i.e. soil and sediment) compartments.

It is in the investigative phase that higher tier mammalian tests and avian studies are introduced to better define food chain PNECs, and sediment and/or soil chronic and bioaccumulation studies are initiated. At this point we can introduce the concept of estimating and using CBBs to evaluate life-cycle endpoints. Section 6.3.3 introduces the concept of CBBs and their use may be appropriate in a refined effects assessment of a PBT-type chemical. Figure 18 provides an illustrative example of the role CBBs can play within a risk assessment of a biomagnifying chemical.

CBBs may vary slightly from species to species within limits and are completely independent of habitat, phylum, feeding strategy, etc. It is generally expected that steady-state concentrations take some time to be reached especially for vPvB chemicals. In some cases they may never be reached if the lifetime of the animal is short. For biomagnifying chemicals, some increase of steady-state concentration is expected with the level in the food chain (as in Figure 18), although higher-level organisms may have more efficient mechanisms for detoxification and the degree of biomagnification would be reduced in this case. The aim of a CBB-based approach is to demonstrate whether or not the CBB would be reached in the environment using experimental knowledge of the CBB (at least for surrogate food chain species), background PECs and time to steady state.

CBBs[a] can be used within a risk assessment of a chemical categorised as PBT or vPvB to develop refined PNECs. Consideration of MOA brings a level of understanding of the mechanisms of toxicity to organisms (Escher and Hermens, 2002). Currently, this can be achieved with more confidence for MOA I (non-polar narcotic) and II (polar narcotic) chemicals; however, they may be used on MOA III (reactive) and IV (specifically acting) chemicals on a case-by-case basis.

[a] Within this report we refer to LBBs as being the internal body concentrations causing lethality and CBBs as being the internal body concentrations causing a specific sublethal effect of interest, e.g. effect on reproduction.

Figure 17: Schematic for refining the assessment of PNEC

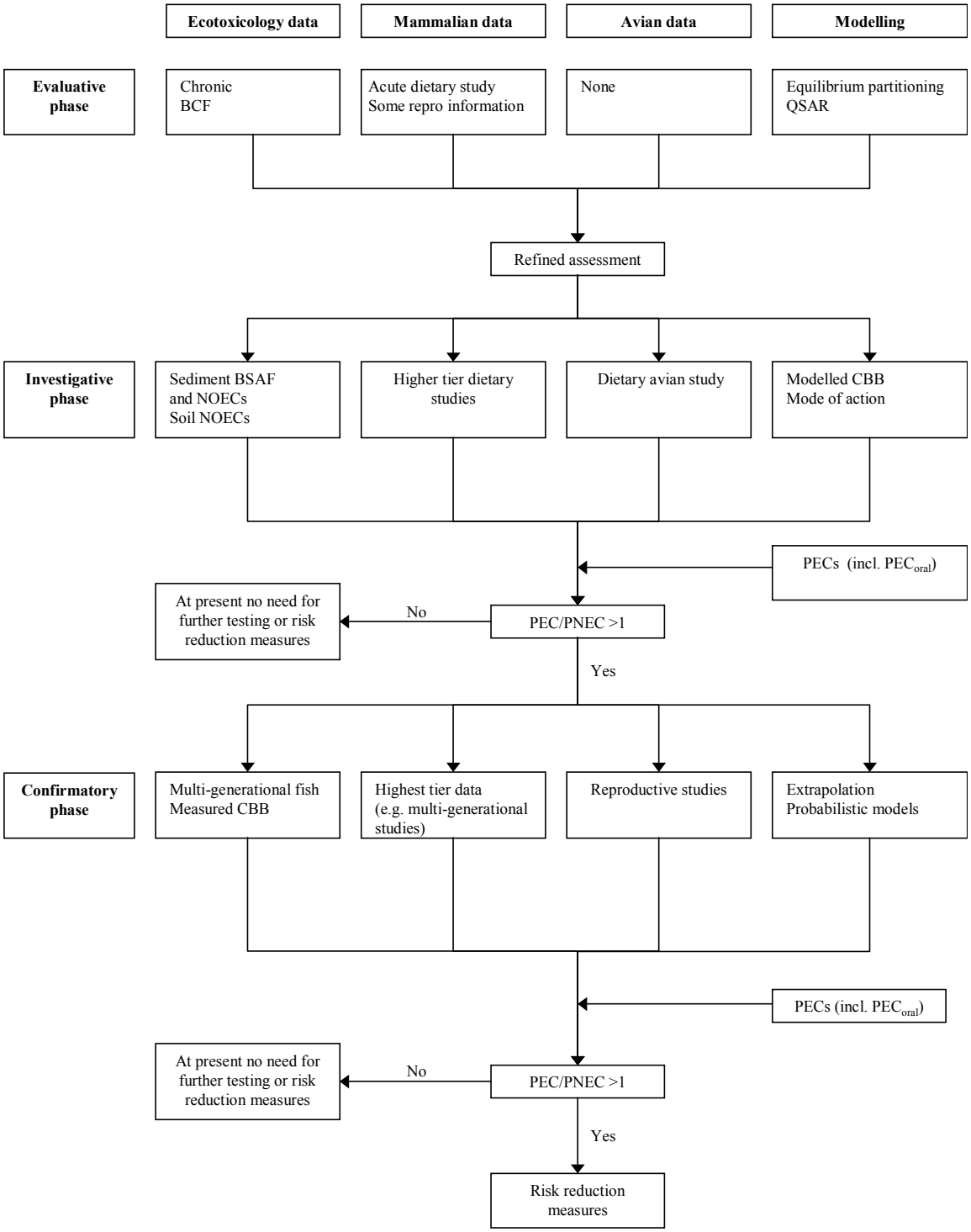
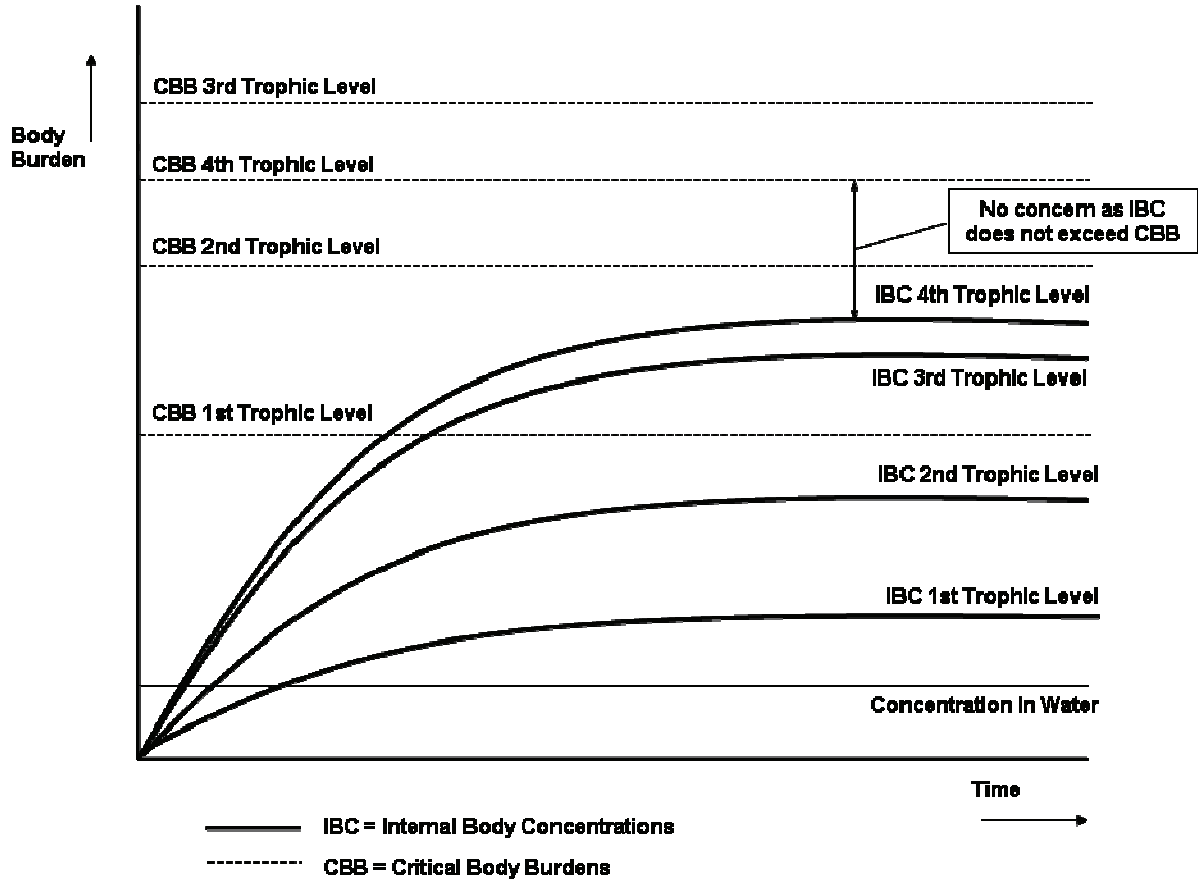


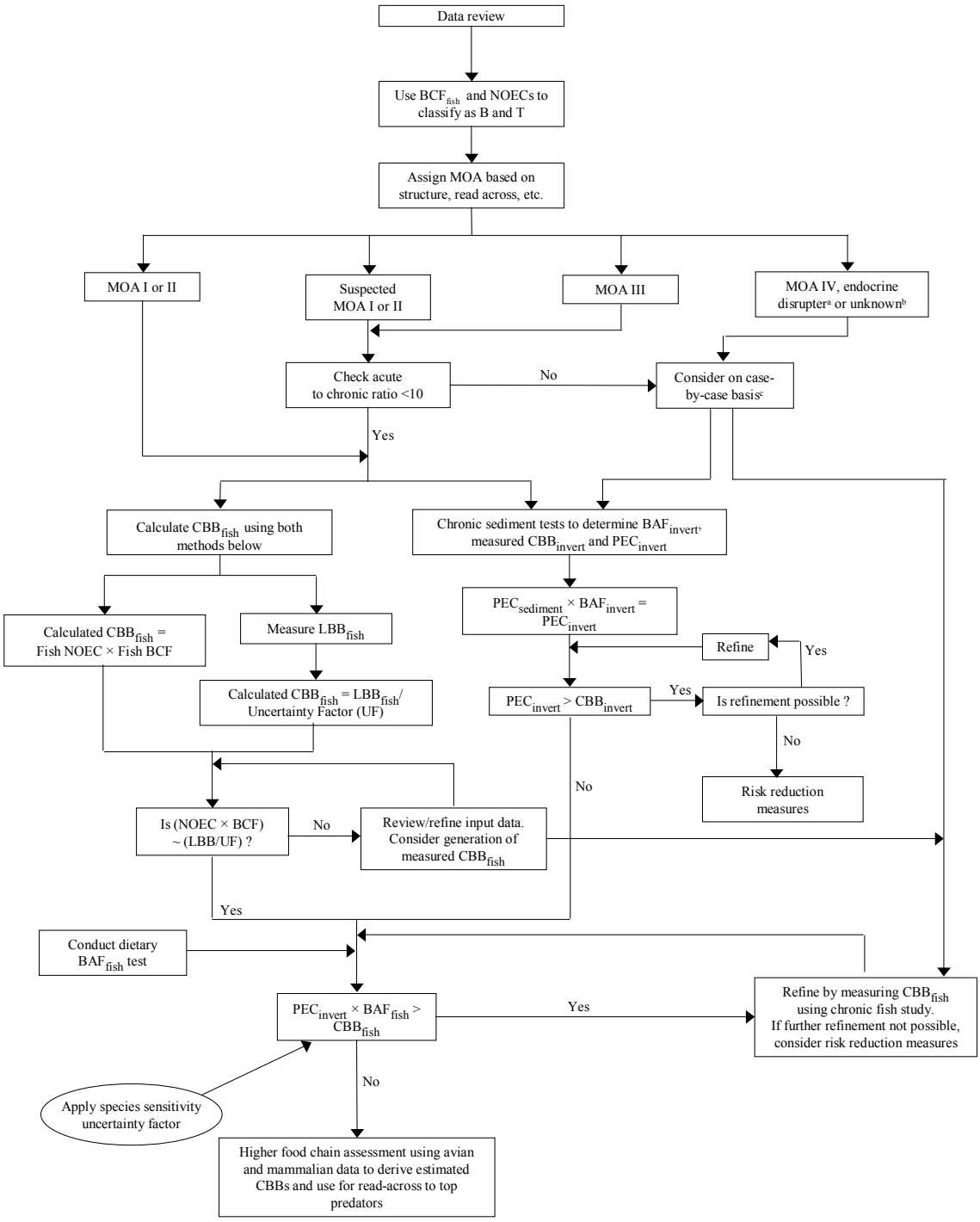
Figure 18: Illustration of the use of No Effect Body Burden data in the risk assessment of a biomagnifying chemical



The main reason why MOA III and IV must be considered separately from MOA I or II substances is the risk that specific modes of action may lead to serious effects at the population level for species that have not been examined in the course of the study (e.g. development of male sexual structures in female dog whelks, *Nucella lapillus* (Gibbs and Bryan, 1986; Bryan *et al*, 1987)). Conversely, MOA I and II substances will, by definition, not lead to unexpected effects occurring in a compartment or species that was not assessed. The use of the body burden approach in *in vivo* studies will provide supporting evidence of mode of action of the substance in question while providing a critical endpoint (internal NOEC) that is, in principle, independent of log K_{ow}.

A proposed schematic for using the data collected in the evaluative and investigative phases, and also provided in the confirmatory phase, is shown in Figure 19. As with previous schematics given in the report, this is not intended to be prescriptive, but proposes a possible process that may be followed which incorporates CBBs to arrive at a more refined assessment of effects within the food chain.

Figure 19: Proposed schematic for estimating critical body burden



[a] Either confirmed ED or suspected ED based on, for example, structural alerts

[b] Could include vPvBs that have shown no effect in acute tests

[c] Both of the routes below could be used, but they are still regarded as being highly theoretical

Existing data should be used where possible to help confirm the CBBs. The simplest case will be the use of long-term ecotoxicity tests in conjunction with the BCF value providing a long-term CBB. However, these data must be reviewed critically to be sure that both the long-term fish study and the BCF test reached equilibrium concentration. A fish BAF study may be more appropriate in such a case. Such supplementary work may also help to provide more concrete information for vPvBs where NOECs > 0.01 mg/l are found.

The next step is to use the data and any literature or model information to determine the MOA of the substance. MOA can be determined on the basis of structure (Verhaar *et al*, 1992). Data from conventional studies (including acute to chronic ratio (ACR), etc.) are used to provide supplementary evidence that there is no change in MOA from acute to chronic effects and that endpoints are predictable. For example, an ACR for MOA I substances has been estimated by Di Toro *et al* (2000) as being approximately 5. Other information published by Roex *et al* (2000) places ACRs for MOA I substances at 2.6 (with a standard deviation of 1.6 and for MOA II substances at 9.8 (SD 11.8)). ACRs for other MOAs and for metals were substantially higher. It should be noted that for purposes of a PBT risk assessment the term acute is used loosely as in some cases acute toxicity may not reached due to the slow uptake of certain chemicals. In such cases subacute or dietary route data should be used in an attempt to determine an EC_{50} (or LBB).

Currently LBB tests appear to be more predictive and reproducible than CBB tests. As a consequence, on confirmation of MOA I or II, a CBB_{fish} is estimated using LBB_{fish} and an appropriate uncertainty factor. At first sight it may seem as though use of an LBB derived using acute data to help determine a CBB-based PNEC is a retrograde step but in fact the method is robust based on the following principles:

- The MOA is known so accurate predictions of long-term toxicity can be drawn, even from short term data provided that the quality of those data is high;
- the LBB is an alternative metric for EC/LC_{50} but is not complicated by external factors such as water concentration;
- the risk that toxicity in untested species occurs at significantly lower levels than those determined within the risk assessment is negligible.

The data are not used as stand alone values but in conjunction with all other data collected prior to and during the risk assessment. The amount of data needed depends upon the level of confidence the assessor has in the available data. For instance, for fish, an acute and chronic test and BCF/BAF may provide sufficient confidence not to perform a specific CBB study for fish provided that the endpoints were measured at equilibrium, ACRs were low and values from invertebrate data support the fish data.

Once the acute CBB_{fish} has been determined this can be converted to a conservative chronic CBB_{fish} using an appropriate uncertainty factor. For example, based on the ACRs of approximately 5 observed by Di Toro *et al* (2000) and Roex *et al* (2000), applying a factor of 10 would be conservative. If the CBB has not been exceeded at this trophic level, then BAF_{fish} data can be used along with data on CBB_{fish} and PEC_{invert} to determine if the CBB_{fish} will be exceeded.

Invertebrate data incorporating reproduction endpoints need to be provided for several species and trophic levels. For instance, as a minimum, ecotoxicity and body burden or bioaccumulation data on crustaceans and oligochaetes should be available to generate invertebrate BAFs and CBBs, which can be compared with knowledge of the sediment PEC to determine if the CBB_{invert} will be exceeded. Other sediment dwelling or benthic species such as molluscs could also be tested. The relative increase in uptake by marine organisms due to salinity induced increase of log K_{ow} (ECETOC, 2001) can be predicted. All the above can be used in the investigative level.

There is currently no clear understanding of sensitivity differences between species for either standard toxicity tests or CBB studies. However, an advantage of using CBBs rather than standard toxicity tests is that the toxicity level in the organism does not vary with the K_{ow} of the substance and is independent of the quantity of substance in the water, sediment or soil. This already removes many of the factors that reduce the predictability of the chronic toxicity results. While it is recognised that the CBB method is not ideal, various attempts have been made to arrive at whole-body CBB values that are identical between species, and improvements have been made by using lipid normalisation with some degree of success (Di Toro *et al*, 2000). Theoretically, there is no reason why lipid-normalised CBBs should differ at all between species for substances with MOA I or II. In the absence of species sensitivity data, confidence limits associated with species sensitivity distributions based on CBBs could be used in an attempt to describe the uncertainty.

Any suggestion that the data do not completely fit within the predictable parameters (i.e ACR and CBB) of MOA I or II leads to the refinement of the $PEC_{sediment}$, BAF_{invert} or CBB_{invert} using life-cycle tests (confirmatory phase). If refinement cannot be achieved, then risk reduction measures need to be considered. When CBB_{fish} is exceeded, refinement is possible through generation of measured chronic CBBs using an appropriately designed multi-generational study. As a major goal of a risk assessment of chemicals categorised as PBTs is to protect populations, a multi-generation test on fish will be used to determine the LOEC for parents and offspring alike. This should be highly predictive when used in conjunction with sets of multi-generation invertebrate studies. The data obtained could be used in conjunction with population dynamics models. Forbes *et al* (2001) had already demonstrated both analytically and by simulation, that for populations with multiplication rates close to one (steady state), effects of toxicants at the population level are likely to be less than or equal to effects on individual life-cycle traits. This suggests, at least, that risk assessments based on the latter should be protective of population-level impacts.

Whether or not a fish multi-generation test is performed, a secondary poisoning assessment should be carried out using avian and mammalian studies as surrogate data for predatory birds and top mammalian predators such as seals and polar bears. If biomagnification in the food chain is expected, or if the PNEC exceeds the PEC at the highest tier, risk reduction measures will need to be recommended.

A multiple-tier approach to using CBBs in risk assessment could provide:

- In the first tier, a screening level PNEC based on LBB calculated from acute data (evaluative phase data);
- in the second tier, the CBB can be estimated from acute CBB with application of an assessment factor (providing the MOA has previously been ascertained). This can be supported by invertebrate chronic ecotoxicity with invertebrate BAF data and fish ELS NOECs and fish BCF (investigative phase data);
- in the third tier, the CBB and potential population effects can be measured from a fish full life-cycle study (confirmatory phase data);
- in the confirmatory phase, in addition to the possibility of developing CBBs, other data can be collected to further refine traditional PNECs. Extrapolation between species (e.g. the use of mammalian and avian data as surrogates for higher trophic levels such as marine mammals) can provide a more robust assessment of food chain effects. Probabilistic models can also be introduced to provide more ecologically relevant PNECs.

The purpose of these tiered processes in the development of either traditional PNECs or CBBs is to provide more ecologically relevant information focusing on sensitive and population endpoints while reducing uncertainty. The Task Force believes that the use of these refined techniques will contribute to a better prediction of the fate and effects of persistent, bioaccumulative and toxic chemicals within the environment.

8. ADVANCES IN RISK ASSESSMENT

Research activities which improve a) our understanding of the behaviour and effects of chemicals, b) our ability to obtain data relevant for assessing difficult to test substances, or c) our tools for modelling the environmental fate and bioaccumulation, contribute to improving the risk assessment of chemicals. They result in more accurate and less uncertain estimates of the risk of all (i.e. both PBT and non-PBT) chemicals.

Recognising that food chain bioaccumulation is the culmination of multiple physiological processes in multiple organisms of the food chain, it is insufficient to assess bioaccumulation on the basis of a chemical's hydrophobicity alone. Rather than estimating bioaccumulation potential solely on the basis of log K_{ow}, the modulation of bioaccumulation by common physiological processes must be taken into account. A research initiative launched by the Health and Environmental Sciences Institute (HESI) is addressing the questions of whether and, if so, how information available about absorption, distribution, metabolism and excretion can be employed in evaluating a chemical's potential to accumulate in organisms and, ultimately, in the food chain. Approaches under investigation are: improvement of existing bioaccumulation models; re-application of pharmaceutical models; development of *in vitro* systems; *in vivo* invertebrate and vertebrate tests; passive sampling devices; and population-level monitoring of wildlife, humans and food.

A Cefic LRI (www.cefic-lri.org) project is addressing the question of whether there is reality in the concept that biodegradability can be related to food chain bioaccumulation as some chemicals may be universally degradable, others selectively so and yet others degradable to a very limited degree. The information generated in this project could help to refine the assessment of food chain bioaccumulation.

Bioavailability and the limitations of current testing for degradability have been reviewed (ECETOC, 2003a). The necessity for improved laboratory tests for assessing biodegradation of low bioavailability chemicals at environmentally realistic concentrations has been highlighted. Cefic LRI is planning a research programme to develop advanced biodegradation tests, which should offer improved environmental realism. The results of this initiative should be suitable for integration in the strategy proposed by ECETOC (2003a) to assess the biotic aspects of persistence.

Ecological risk assessment should be viewed in the context of relevance at the ecosystem level. As such, effects assessment can benefit by the development of models and methods to determine changes at the population level. Techniques to measure and evaluate CBBs, building on the work noted in Section 6.3.3 and Chapter 7, would provide a more realistic assessment of life-cycle

effects on organisms throughout the food chain. The strategy proposed should be tested with a number of appropriate case studies.

In summary, significant advances in risk assessment methodology can be achieved via ongoing and future research efforts. The results of these efforts will help to increase the accuracy of the risk estimation and reduce its uncertainty.

GLOSSARY

Acute toxicity:	The harmful properties of a substance that are demonstrated within a short period of exposure (hours, for e.g. algae, to days, for e.g. crustaceans and fish).
Assessment factor:	A factor applied to effect data point(s) to predict a safe concentration of that substance in the environment.
Bioaccumulation:	The net result of uptake, distribution and elimination of a substance due to all routes of exposure.
Bioaccumulation factor (BAF):	The ratio of the steady-state concentration of a substance in an organism due to all routes of exposure versus the concentration of the substance in water.
Bioavailability:	The ability of a substance to interact with the biosystem of an organism. Systemic bioavailability will depend on the chemical or physical reactivity of the substance and its ability to be absorbed through the gastrointestinal tract, respiratory surface or skin. It may be locally bioavailable at all these sites. [aa]
Bioconcentration:	The net result of uptake, distribution and elimination of a substance due to water-borne exposure.
Bioconcentration factor (BCF):	The ratio of the steady-state concentration of a substance in an organism due to water-borne exposure versus the concentration of the substance in water.
Biomagnification:	The accumulation and transfer of substances via the food web (e.g. *algae* → invertebrate → fish → mammal) due to ingestion, resulting in an increase of the internal concentration in organisms at the succeeding trophic levels.
Chronic toxicity:	The harmful properties of a substance that are demonstrated only after long-term exposure in relation to the life of the test organism.
Complex substance:	Mixtures comprising a complex mix of individual substances with different water solubility and other physico-chemical properties. In most cases, they can be characterised as a homologous series of substances with a certain range of carbon chain length/number or degree of substitution. These materials are frequently referred to as 'multi-component substances'.
Critical body burden (CBB):	The term critical body burden is used in this report to encompass the various terms used by different authors, including critical body/tissue residues, residue-based toxicity, internal effect

[a] From van Leeuwen and Hermens (1996)

	concentration, etc. It is also used generally here to refer to body burdens that may relate to the 'highest tissue level having no effect' (equating to a NOEC) as well as the 'lowest level causing some significant effect' (equating to a LOEC).
EC_{50} value (median lethal concentration):	A statistically derived concentration that, over a defined period of exposure, is expected to cause a specified toxic effect in 50% of the test population.
Endocrine disrupter:	An exogenous substance that causes adverse effects in an intact organism, or its progeny, subsequent to changes in endocrine function.
Equilibrium partitioning theory:	The theory is based on the assumption that soil or sediment toxicity expressed in terms of the freely dissolved chemical concentration in pore water is the same as aquatic toxicity (Di Toro *et al*, 1991).
Existing chemicals:	Chemicals listed in the EINECS (EU legislation).
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 micro-organisms) 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. [a]
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.[a]
LC_{50} value (median lethal concentration):	A statistically derived concentration that, over a defined period of exposure, is expected to cause 50% mortality in the test population.
Local scale:	A specific concept in EC Environmental Risk Assessment, which defines a specific or local release site. Further details may be found in the TGD.
Lowest observed effect concentration (LOEC):	The lowest test concentration at which the substance is observed to have a statistically significant and unequivocal effect on the test species.
Model:	A formal representation of some component of the world or a mathematical function with parameters that can be adjusted so that

[a] From van Leeuwen and Hermens (1996)

	the function closely describes a set of empirical data. A mathematical or mechanistic model is usually based on biological, chemical or physical mechanisms, and its parameters have real world interpretations. By contrast, statistical or empirical models are curve-fitted to data where the mathematical function used is selected for its numerical properties. Extrapolation from mechanistic models (e.g. Pharmacokinetic equations) usually carries higher confidence than extrapolation using empirical models (e.g. the logistic extrapolation models). A model that can describe the temporal change of a system variable under the influence of an arbitrary 'external force' is called a *dynamic* model. To turn a mass balance model into a dynamic model, theories are needed to relate the internal processes to the state of the system, expressed e.g. in terms of concentrations. The elements required to build dynamic models are called process models.[a]
Mode of action (MoA):	A common set of physiological and behavioural signs that characterise a type of adverse biological response.
Mode of action (Type I) - non-polar narcotic substances:	Narcosis (or baseline) toxicity is believed to be the result of reversible and non-specific disturbance of membrane integrity and function resulting from the partitioning of the chemical into biological membranes (Escher and Hermens, 2002). Because the effects are not specific to particular chemical structures, this can be considered the minimum (or baseline) toxicity that any chemical will display, if it is not obscured by greater toxicity through other modes of action. This MOA is therefore displayed by chemicals that are 'inert' in terms of chemical or biochemical reactivity, and by interactions with specific biological receptors.
Mode of action (Type II) - polar narcotic substances:	This group consists of more polar but essentially non-reactive substances such as substituted phenols and anilines which ionise to some extent depending on pH and display slightly greater toxicity (external concentration) than would be predicted by 'baseline' toxicity QSARs. They are often characterised as possessing hydrogen bond donor acidity.
Mode of action (Type III) - reactive substances:	Reactive substances are considered as a group that includes diverse modes of action resulting from non-selective reactions with biomolecular structures and consequently displaying enhanced toxicity (lower CBBs) compared with baseline narcotics (Verhaar *et al*, 1992). The group also includes chemicals that are metabolically

[a] From van Leeuwen and Hermens (1996)

	activated into reactive substances. Of particular importance are electrophilic substances that react with amino, hydroxy and sulphydryl groups within proteins and DNA (Hermens, 1990), such as certain carbonyls, epoxides, nitriles, hydrazines, acid anhydrides and aldehydes. Acute toxicity QSARs have been developed for several classes of reactive electrophiles (reviewed by Hermens, 1990), but for epoxides and reactive alkyl halides these include a second descriptor, such as the reaction rate constant with 4-nitrobenzylpyridine, in addition to K_{ow}.
Mode of action (Type IV) - specifically acting (receptor-active) substances:	Specifically acting chemicals are those that react with particular enzymes or receptors, such as organo-phosphorus esters which inhibit acetylcholinesterase, DDT which interacts with sodium channel receptors in neurons, etc. Internal concentrations in an organism provide a better basis for assessing the intrinsic toxicity of a given compound than external concentrations (see ref 26-29 in Escher and Hermens, 2002).
Monitoring:	A long-term and standardised measurement, observation, evaluation and reporting of the environment in order to define status, trends and mass flows (loads).
New chemicals:	In the EU, those produced since 18th September 1981. They are not listed on the EINECS.
No observed effect concentration (NOEC):	The highest tested concentration below the LOEC where the stated effect was not observed. The NOEC is usually associated with chronic effects.
Predicted environmental concentration (PEC):	The concentration of a chemical in the environment, predicted on the basis of available information on certain of its properties, its use and discharge patterns and the quantities involved. [a]
PEC_{local}:	In the EU TGD, the PEC predicted for the vicinity of a point source e.g. a production or formulation site, or a sewage treatment works.
$PEC_{regional}$:	In the EU TGD, the PEC averaged over a standard European region of 200 km × 200 km, with twice the average European population density and production capacity.
Predicted no effect concentration (PNEC):	The environmental concentration that is regarded as a level below which the balance of probability is such that an unacceptable effect will not occur.

[a] From van Leeuwen and Hermens (1996)

Probabilistic:	The characterisation of a property by a distribution function (incorporating distribution shape, standard deviation, mean, median, and other statistical descriptors) rather than by a single value.
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. [a]
Receiving water:	Surface water (e.g. in a stream, river or lake) that has received a discharged waste, or is about to receive such a waste (e.g. just upstream or up-current from the discharge point). [a]
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. [a]
Risk management:	A decision making process that entails the consideration of political, social, economic and engineering information together with risk-related information in order to develop, analyse and compare the regulatory options and select the appropriate regulatory response to a potential health or environmental hazard.[a]
Secondary poisoning:	The product of trophic transfer and toxicity.
Speciation:	Determination of the exact chemical form or compound in which an element occurs in a sample, for example whether arsenic occurs in the form of trivalent or pentavalent ions or as part of an organic molecule, and the quantitative distribution of the different chemical forms that may co-exist.[a]
Steady state:	The non-equilibrium state of a system in which matter flows in and out at equal rates so that all of the components remain at constant concentrations (dynamic equilibrium). In a chemical reaction, a component is in a steady state if the rate at which the component is being synthesised (produced) is equal to the rate at which it is being degraded (used). In multi-media exposure models and bioaccumulation models it is the state at which the competing rates of input/uptake and output/elimination are equal. An apparent steady

[a] From van Leeuwen and Hermens (1996)

	state is reached when the concentration of a chemical remains essentially constant over time. Bioconcentration factors are usually measured at steady state.[a]
Surveillance:	A more continuous process than, for example a survey, addressing a specific measurement or observation, with the goal of environmental quality reporting (e.g. compliance with standards and quality objectives) and/or operational activity reporting (e.g. early warning and detection of pollution).
Survey:	A sampling programme of finite duration, and for a specific purpose, such as intensive field study or an exploratory campaign to infer semi-empirical relationships and establish tentative theories.
TGD:	EU Technical Guidance Document in support of risk assessment for new and existing chemicals.
Toxic mechanism:	The crucial biochemical process(es) and/or xenobiotic-biological interaction(s) underlying a given mode of action.
Toxicity:	The inherent property of a substance to cause adverse biological effects at specific concentrations.
Worst-case assumptions:	The most adverse environmental circumstances or the highest possible release parameters. Combining these necessarily results in an unrealistic overall worst-case estimation, which is extremely unlikely to occur.

[a] From van Leeuwen and Hermens (1996)

ABBREVIATIONS

ACHS	Advisory committee on hazardous substances
ADME	Absorption, distribution, metabolism, excretion
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BMF	Biomagnification factor
CBB	Critical body burden
CCBB	Chronic critical body burden
CMR	Carcinogenic, mutagenic or reprotoxic
COMMPS	Combined monitoring-based and modelling-based priority setting
CSF	Chemicals stakeholder forum
CSTEE	Scientific committee on toxicity, ecotoxicity and environment
CTV	Critical toxicity value
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DOM	Dissolved organic matter
DSL	Domestic substances list
DT_{50}	Half-life or disappearance time: time needed for reducing the concentration of a substance in a medium by 50% of its initial value.
DYNAMEC	Dynamic selection and prioritisation mechanism for hazardous substances.
EC_{50}	Acute toxicity expressed as the concentration that induces an effect in 50% of the exposed population
EDC	Endocrine disrupting chemical
EDMVS	Endocrine disruptor methods validation subcommittee
EEV	Estimated exposure value
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of Notified Chemical Substances
ELS	Early life stage test (fish)
EMAP	Environmental monitoring and assessment programme
ENEV	Estimated no effects value
EqP	Equilibrium partitioning
EQS	Environmental quality standard
ERA	Environmental risk assessment
EUSES	European Unified System for the Evaluation of Substances
H	Henry's law constant
HCB	Hexachlorobenzene
HCH	Hexachlorohexane
IPCS	International programme on chemical safety

K_{aw}	Air-water partition coefficient
K_{ow} or P_{ow}	Octanol-water partition coefficient
LBB	Lethal body burden
LC_{50}	Lethal concentration that kills 50% of the exposed population
LOEC	Lowest observed effect concentration
LRTP	Long-range transport potential
MATC	Maximum acceptable toxicant concentration
MOA	Mode of action
NOEC	No observed effect concentration
OPPTS	Office of prevention, pesticides and toxic substances (US-EPA)
OSPAR	Oslo-Paris commission
PAH	Polynuclear aromatic hydrocarbon
PBiT	Persistent, bioaccumulative and inherently toxic
PBT	Persistent, bioaccumulative and toxic
PBTK	Physiology-based toxicokinetic
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzodioxin
PEC	Predicted environmental concentration
PNEC	Predicted no effect concentration
POM	Particulate organic matter
POP	Persistent organic pollutant
p,p'-DDT	1,1,1-trichloro-2,2-bis-(4-chlorophenyl)-ethane
QSAR	Quantitative structure-activity relationship
QSBR	Quantitative structure-biodegradability relationship
QSPR	Quantitative structure-property relationship
REACH	Registration, evaluation and authorisation of chemicals
SOMS	Strategy on management of substances
t½	Half-life
TBT	Tributyltin
TGD	Technical guidance document
TSMP	Toxic substances management policy
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environment Programme
vPvB	Very persistent, very bioaccumulative
WFD	Water Framework Directive
WWTP	Wastewater treatment plant

APPENDIX A: UNCERTAINTY AND DECISION SUPPORT TOOLS

In this report uncertainty is discussed in the context of the fate and effects of a substance. It is important that uncertainty is properly identified and that tools are applied that help to make decisions in the presence of that uncertainty.

Uncertainty is usually indirectly related to the quality and quantity of available information. Thus, as the availability of good quality information and databases increases, uncertainty will tend to decrease. To help unbiased and near optimal decisions to be made, a degree of formalisation of this process is needed.

It is also necessary to address how issues of uncertainty (i.e. lack of information) within a tiered risk assessment framework may be taken into account. With recent transfers of technology from other fields, e.g. medicine (Sox *et al,* 1988), new approaches are beginning to be developed.

- *Probabilistic description of uncertainty:* There are two types of variables, discrete (e.g. the outcome of a carcinogenicity test with a yes/no answer) or continuous (e.g. an exposure concentration). In both cases, uncertainty can be quantified either using probability functions (e.g. in the carcinogenicity test, if a chemical is positive, there might still be a probability of 0.05 (5%) that that chemical is not a carcinogen in humans, i.e. the positive result was obtained by chance), or probability curves.
- *Decision trees:* These formalise and extend the notion of a flow chart. Decision trees can accommodate 'probabilistic nodes', where the outcome depends on the value taken by a random variable. A fundamental characteristic of decision trees is that they end with decisions ('leaves') to which a value is associated. This value integrates all the uncertainties incurred along the path leading from the tree root to the leaf. A decision tree, even for part of the risk assessment process, can aid transparency (about probabilities, test performances, utilities and values) as well as help to identify where opinions of stakeholders (e.g. regulators) may differ or converge.

By coupling a *probabilistic description of uncertainty* together with *decision tree analysis* a consistent approach is obtained to making decisions, based on uncertainty.

A formal decision analysis for devising a test strategy thus comprises:

- Building a decision tree;
- assigning prior probabilities on the state of the test;
- characterising the performance of the tests proposed;
- constructing a utility function that reflects the user's needs and concerns;

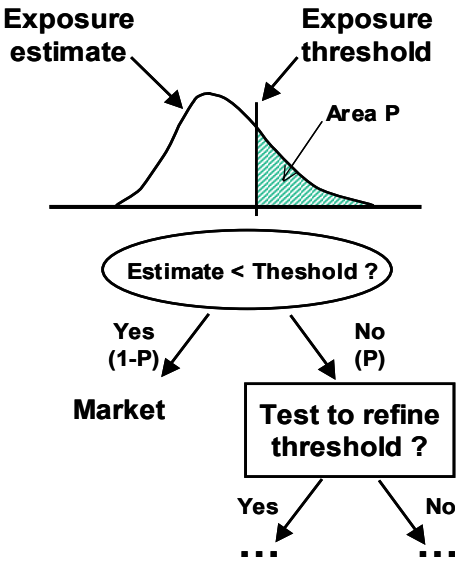
- evaluating the (expected) utility of each terminal node of the tree and choose the set of decisions that lead to the maximum expected utility.

That framework should be kept in mind, as it highlights some important aspects of decision making. However, implementing it *a priori* for the whole set of available tests and PBT risk assessment would obviously be unrealistic. Fortunately, the process can be split into local subquestions (e.g. on the various endpoints, or on risk versus toxicity assessment). The decision framework then becomes a sequence of limited decisions to be made, each of which can be assisted by decision analysis. For each one a partial utility can be evaluated. The overall result might not be the very optimum achievable, but should be close if the questions asked are relatively independent.

Example: Exposure assessment

The issue of addressing environmental exposure is addressed in Figure A.1.

Figure A.1: A decision tree illustrating a continuous variable (an exposure estimate)



This shows a probabilistic node corresponding to the question 'is exposure lower than a threshold?' That threshold could come from a 'threshold of toxicological concern' (TTC) approach, or from previously conducted tests. Exposure estimates, either estimated *a priori* or measured, are likely to be affected by uncertainty. That uncertainty can be described by a probability distribution with some probability, *P*, that the actual exposure exceeds the threshold. The outcome of the probabilistic node is therefore 'yes, exposure is lower' with probability (1 -

P), and 'no' with probability *P*. Further decision node or endpoints (direction of further testing, or no further tests) can be constructed.

A risk estimate can be treated in exactly the same way. The threshold in that case would be an acceptability ('*de minimis*') level for risk.

There are some outstanding issues that require further development.

Building a database: Probabilities (such as for test performances) could be updated with experimental data or improved QSAR. This may occur with increasing data generation resulting from REACH.

How far do we have to go in formal decision analysis? Obviously it is inadvisable to allow the trees to become too complex. The approach described gives tools and concepts to facilitate decision making and discussion about it. The trees can be used sequentially and 'pruned' if required, which can reduce the computational burden.

The role of uncertainty factors: Uncertainty factors are typically used to move the threshold of concern to a lower (conservative) value. Unfortunately, they hide the fact that the thresholds themselves are affected by uncertainty because they are derived from toxicity studies. The case can be made that in Figure A.1 two distributions should be presented: one for exposure and one for threshold. Yet, even then a probability of exceeding the threshold can still be derived and the computation of expected utility can proceed as previously.

Model uncertainty: Lack of knowledge, potential errors in experiments, variability between and within species can be conveniently handled by probability distributions. There can also be uncertainty about the structure of models themselves (exposure, dose response, or QSAR models) that are harder to deal with and often neglected. This can be a problem and the source of very large uncertainty when extrapolating outside the domain of the model. Recent publications in the field of risk assessment do suggest ways to deal with this issue (Bailer *et al,* 2005).

Weight of evidence: There is a strong connection between the issue of uncertainty and the 'weight of evidence' approach. Indeed, weight of evidence is a decision making move, often by an expert able to integrate all aspects of uncertainty (about data quality, model uncertainty, etc.). The weight associated to each fact discussed is simply the subjective probability of that fact being 'true'. The tools developed for Bayesian model averaging (Bailer *et al,* 2005) can also be applied here, but another interesting direction of investigation is 'meta-analysis'. Meta-analysis has been developed by epidemiologists to formalise the problem of weighting evidence in their field (i.e. seemingly incoherent epidemiological study results), and has developed into quite sophisticated concepts and techniques (Smith *et al,* 1995; Piegorsch, 1998; Piegorsch *et al,* 1998).

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ACKNOWLEDGEMENT

The Task Force would like to acknowledge the contributions of Dr. T. Aldenberg (RIVM, the Netherlands), Dr. M. McLachlan (Stockholm University, Sweden) and Dr. F. Bois (INERIS, France).

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