Assessing the Health and Environmental Impacts in the Context of Socio-economic Analysis Under REACH

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Final Report

Part 2: THE PROPOSED LOGIC FRAMEWORK AND SUPPORTING CASE STUDIES

Prepared for
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ASSESSING THE HEALTH AND ENVIRONMENTAL IMPACTS IN THE CONTEXT OF SOCIO-ECONOMIC ANALYSIS UNDER REACH

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Part 2:
The Proposed Human Health Logic Framework

prepared for

European Commission

Directorate-General Environment

by

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1. INTRODUCTION TO THE PROPOSED LOGIC FRAMEWORK

1.1 Overview

This report is the second of two parts. It presents the proposed logic framework for assessing the human health and the environment impacts of restriction proposals and either refusing or granting authorisations under REACH.

While the framework is intended to be generic in nature and hence potentially of wide application, it is nonetheless being developed in light of the anticipated issues (e.g. with regard to data availability) that might arise when attempting to develop a SEA for substances being considered for Authorisation or Restriction under REACH.

This part also presents in Annexes two illustrative examples of the application of the logic framework using chemicals currently being considered for further risk management. These are substances which have both been identified as substances of very high concern according to the criteria set out in Article 57 of REACH and have therefore been included in the candidate list for authorisation and prioritised by ECHA for inclusion in Annex XIV of REACH.

- Tris(2-chloroethyl) phosphate (TCEP) is a chlorinated phosphate flame retardant used in a wide range of industrial applications because of its flame retardant properties and also has some applications as an intermediate. It is classified according to the Dangerous Substances Directive 67/548/EEC (DSD) as being a reproductive toxin Category 2 (R60). TCEP is also classified as a Carcinogen (Cat 3, R40), harmful (Xn, R22), and dangerous to the aquatic environment (N, R51/53). The focus of the case study is to assess the human health impacts of the continued use of TCEP.

- Hexabromocyclododecane (HBCDD) is a brominated flame retardant mainly in textile coatings (mainly for upholstered furniture) and polystyrene to help protect against fire damage. It has classified as a PBT, with concerns for aquatic and terrestrial toxicity, bioaccumulation potential and persistence. The focus of the HBCDD case study is to try and better describe what the potential impacts on the environment of continued HBCDD use are so that these may be balanced against the benefits derived from continued use in any authorised applications.

Part 1 to this report presents the output from the literature review to establish the types of data that could contribute to the dataset on which a SEA might be constructed and the conclusions from the Expert Workshop held early on in the study, together with a short summary of the research needs that have been identified throughout the study.

1.2 The ECHA Guidance on SEA as a Starting Point

ECHA (2008) has previously produced Guidance that addresses the overall SEA process in respect of its use for restrictions in accordance with Article 69 of REACH. The underlying principles and overall recommended process are discussed in Section 1.4 of the Guidance (the main stages are summarised in Figure 1.1 below). In brief, the process developed by ECHA comprises five stages:

- **Stage1**: Set the aims of the SEA (why is the SEA being developed)

- **Stage 2**: Set the scope of the SEA (what is the baseline and the proposed control scenario, what activities will be affected and how?)
  - Stage 2.1: Defining the necessary activities and organising the activities required
  - Stage 2.2: Definition of "baseline scenario" based on current and predicted future use of the substance in the absence of any regulatory changes
  - Step 2.3: Definition of the "proposed restriction" scenario, and
  - Step 2.4: Setting the scope of the SEA by defining time periods, geographical boundaries and types of impact to be considered

- **Stage 3**: Identify and assess the impacts (i.e. the changes in costs and benefits under the proposed control scenario compared to the baseline)
  - Stage 3.1: Identification of impacts based largely upon the data collected as part of the Annex XV dossier and through the collection of additional data (including through consultation with Member States, supply chains and other stakeholders), based upon the baseline and proposed restriction scenarios as defined in Stage 2
  - Stage 3.2: Collection of data on emissions, exposures and human and environmental risks relating to the substance of concern and the alternatives;
  - Stage 3.3: Assessment of impacts (human health and environmental impacts but also those relating to economics, social factors and trade, competition and economic development) in qualitative, semi-quantitative or quantitative terms through an iterative process
  - Step 3.4: Ensure consistency of analysis, including consideration of uncertainties

- **Stage 4**: Interpretation and conclusion drawing (bringing together information on cost, health, environment, social and other impacts)
  - Stage 4.1: Comparison of the different types of impact using appropriate SEA assessment tools
  - Stage 4.2: Assessment of distribution of impacts, to consider the different actors in supply chains, other industrial sectors and geographical issues regarding the distribution of health or environmental impacts
  - Stage 4.3: Conduct of an uncertainty analysis, possibly based on a sensitivity analysis of key assumptions, to establish the extent to which different assumptions or estimates might influence the conclusions drawn

- Stage 4.4: Decision as to whether a conclusion can be reached or if more data collection or analysis is first necessary (i.e. continuation of the iterative process), and

- **Stage 5:** Present the results (prepare a report that documents the results and assumptions used in the analysis).

The logic framework proposed here fits within Stages 2 to 4 of the above SEA process. The aim the framework developed for this study is not to re-invent a new approach but to provide further suggestions as to how health and environmental impacts in particular could be assessed within the overall SEA process for restrictions and authorisation. This includes recommending an iterative approach, based first on a qualitative assessment which would then be followed by a more quantitative assessment, where appropriate and of value to decision makers.

It is also important to note that the approach set out here is generic, and is applicable to assessments carried out in relation to both restrictions and authorisation.

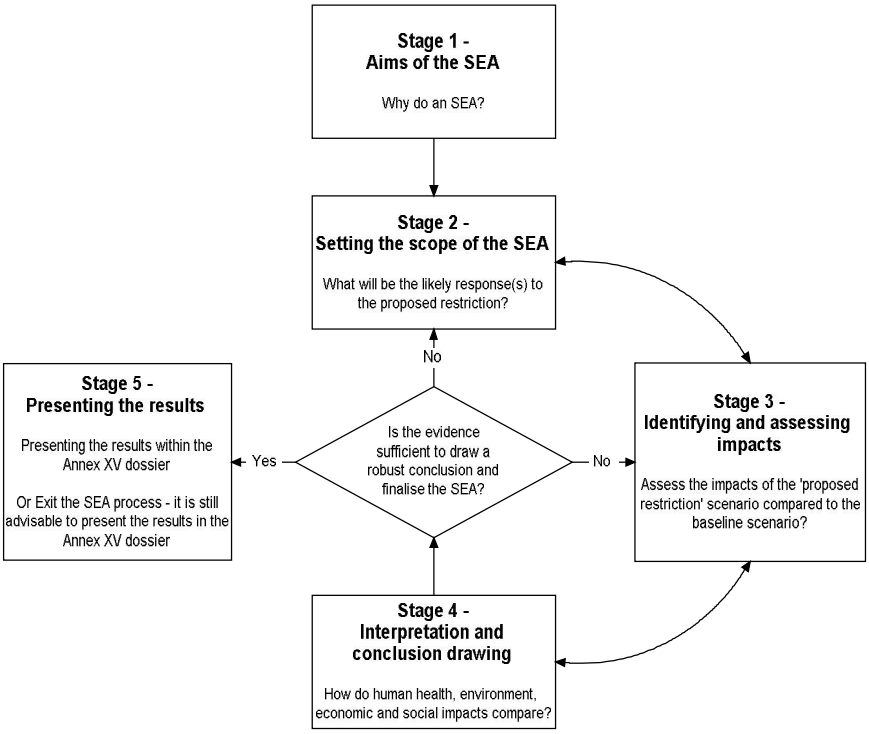


Figure 1.1: Overall Process for Preparing a SEA from the ECHA Guidance Document

1.3 Steps in the Logic Framework

The starting point for the logic framework is a clear description of the uses of the chemical being addressed, the principle associated risks or concerns identified in the risk assessment and other potential health and environmental concerns that may be of significance for a SEA (Step 1). This is then followed by the collation of more detailed information on the nature and severity of the potential health and environmental impacts or, in the case of substances with persistent (P) or very persistent (vP) and bioaccumulative (B) or very bioaccumulative (vB) properties, of the possible implications of these, so as to provide a qualitative to semi-quantitative indication of their potential significance (Step 2). Elements of the assessment may then become more quantitative depending on the availability of data, the limitations of those data, and the degree to which quantification may help decision makers understand the magnitude and severity of the impacts (Step 3).

In certain cases, it may be possible to progress to the monetary valuation of impacts, drawing on either readily available benefits transfer values or applying economic valuation methods (Step 4).

The final stage (Step 5) in the logic framework is then to undertake a comparative assessment of each of the individual changes considered in respect of human health and environmental impacts, and to also consider the overall impact (i.e. net effect) to allow conclusions to be drawn as to both the individual and overall (net) health and/or environmental effects.

These five main steps in the logic framework for assessing health and environmental impacts can be summarised as follows:

- **Step 1: Characterisation and scoping assessment** – using the available data to define the scope of the impact assessment to be carried out (linked to Stage 2 of the ECHA guidance;

- **Step 2: Qualitative to semi-quantitative assessment of impacts** – drawing data from the chemical safety assessment and other sources to provide a detailed description of potential impacts (Stage 3 in the ECHA guidance);

- **Step 3: Quantitative assessment of exposures and impact** – where feasible and appropriate, developing further quantitative data to support decision making. This may be at two levels: comparison against benchmarks or predictions of changes in the population or stock at risk; and quantification of the associated changes in impacts on that population or environmental stock; and

- **Step 4: Valuation of impacts** – estimating the economic value of the change in impacts using methods and units of measure appropriate to health or the environment (e.g. willingness to pay values, health care costs, market value of changes in productivity, etc.); and

- **Step 5**: **Comparative analysis –** analysing the changes in health or environmental effects and determining whether the net change is positive or negative.

Although the stages and general philosophy of the framework are the same for health and the environment, the detailed approaches and issues to be considered vary. For this reason, there are separate but parallel frameworks for Steps 2 to 4 for health and the environment to reflect these differences; these Steps are essentially expansions on Stage 3 as set out in the ECHA guidance.

Furthermore, in line with the ECHA guidance, the logic framework proposed here recognises that different issues may need to be considered with regard to changes in health and environmental effects. As defined here, these are:

- **Effects related to the chemical of concern**: these include both primary and secondary impacts:
  - ***primary impacts*** are those stemming from the risks of concern – i.e. the risks leading to the decision to propose restrictions or other properties (such as persistence and/or bioaccumulative potential) that have lead to the substance being placed on Annex XIV in the case of authorisation;
  - ***secondary impacts*** are those stemming from other relevant risk endpoints (e.g. respiratory sensitisation as an impact on workers in addition to potential carcinogenic effects) or from impacts that may arise from the primary impact (e.g. impacts on particular species may lead to food chain effects or wider effects on ecosystem services);

- **Effects arising from substitution** (in its broadest sense): these are the health or environmental impacts that may arise from a shift to the use of alternative substances, processes or technologies. They may arise across the lifecycle of a chemical or product's use and arise from changes in inputs, changes in process emissions or changes in usage requirements or changes in end waste products (composition or volume).

The framework focuses on assessing effects related to the chemical of concern. Some additional discussion is provided on assessing the effects arising from substitution, but reference should also be made to the ECHA Guidance on SEA for further discussion on assessing alternatives. However, Step 5 of this framework provides a discussion on how to bring together the outputs from the assessment of those effects associated with exposures from the chemical of concern and those likely to arise from a move to alternatives.

1.4 Organisation of This Document

Chapter 2 of this document provides an overview of Step 1 of the proposed Logic Framework for the impacts on health and the environment. Chapter 3 then presents the proposed framework for assessing health impacts, while Chapter 4 sets out the proposed framework for assessing environmental effects. Chapter 5 presents Step 5 and how to bring the information on health and environmental impacts together within an overall assessment.

2. STEP 1: CHARACTERISATION AND SCOPING – HEALTH AND THE ENVIRONMENT

2.1 Overview

The first step in the logic framework is essentially aimed at pulling together the basic information on usage of the chemical, the risks of concern and on alternatives so as to determine the likely scope of the health and environmental impact assessment work. It is effectively linked to Stage 2 of the overall SEA process as defined in the ECHA guidance.

At the end of this stage, the analyst should have detailed the following:

1) characterisation of the uses of concern;

2) description of the risks of health or environment effects associated with the chemical and/or other properties such as persistence or bioaccumulation in the environment that are the focus of the proposed restriction or of the authorisation application (i.e. the properties of the chemical that led to a substances being added to Annex XIV); and

3) whether there are likely to be health or environmental risks or other impacts arising from the use of alternatives (chemicals, processes or technologies) that should be included in the assessment to determine the net effects of restricting the use of the chemical.

This step of the assessment will draw on:

a) any Chemical Safety Assessment and exposure scenarios available for the substance (if available in the case of Restrictions);

b) an Annex XV dossier for a restriction or the identification of Substances of Very High Concern and other relevant documents if not included there, such as the assessment of alternative risk management options and any assessment of alternatives;

c) the analysis of alternatives carried out to support an authorisation application;

d) other supporting or relevant information collected for preparing other parts of the SEA, such as the number of users of the chemical and their location, any legislative drivers (e.g. safety or environmental) for the use of the chemical, etc.; and

e) any monitoring data, information on emissions, alternatives etc. available from public sources or collected through public consultations.

2.2 Characterisation of Uses

Basic data on use of the chemical are important to both identifying potential impacts and to understanding the potential significance of these impacts. The aim of this first stage is to provide a good description of the following aspects of use as a start to the health and environmental impact assessment:

- tonnages of the substance used in the application(s)/use(s) (or covered by a particular application for an authorisation) giving rise to the risks of concern;
- number of sites where the substance is used or the nature and number of downstream users covered by the application and the number of associated sites; and
- where relevant to consumer exposures or to environmental exposures, information on the size of the relevant markets for the products associated with the use.

These data should be available from the CSA for the chemical. Most of it will also be relevant to other aspects of the SEA, such as the analysis of the costs of complying with a proposed restriction or the benefits (calculated as avoided costs) to industry of a successful authorisation. However, it is important that these data are also recognised as being relevant to understanding the potential scope and scale of health and environmental impacts.

2.3 Characterisation of the Risks of Concern

The next task is to provide a description of the risks to health and the environment that are the focus of the proposed restriction or of the need for authorisation (i.e. the properties of the chemical that led to a substance being added to Annex XIV).

For each risk of concern (generally established within the context of the EU risk assessment process on the basis of RCRs), information should be gathered to characterise the nature and basis of the risk concerns. So, for example, if a risk assessment concluded that a chemical gives rise to cancer and poses risks to both workers and consumers, then these conclusions should provide the starting point for the subsequent stages of this assessment.

2.3.1 A Focus on Human Health Impacts

Key considerations at this point in determining the potential direct and indirect health impacts to include

i) **Risk Group**: this involves setting out whether the risk is to workers, consumers or man via the environment. As part of this step, further details on particular sub-groups at risk, for example workers undertaking particular activities or a

particularly vulnerable sub-group of the general population (e.g. infants, elderly, those with immunological impairment), should be identified;

ii) **Risk Characterisation Ratio** (RCR): this information is drawn directly from the risk assessment[1] to provide an indication of the level and severity of the primary risk associated with predicted exposures, i.e. the risks related to the key hazardous properties of the substance leading to restriction proposals or to entry onto Annex XIV;

iii) **Basis for Hazard Characterisation**: this relates to the nature of the available data concerning that primary hazard posed by the substance and whether it is based on: epidemiological or other human data; experimental data or computer models (e.g. SARs); or other theoretical or read-across approaches;

iv) **Basis for Exposure Characterisation**: this relates to the nature of the available exposure data and whether this was based on: hypothetical data, monitoring or other 'real' measurement data or model outputs supported by a mix of hypothetical and/or real data; and

v) **Identification of Secondary Risks**: RCRs are only likely to be available within the risk assessment for those risks that were judged of primary of concern. Reference should also be made to other hazard data presented in the Chemical Safety Report or for the exposure scenario on other potential hazards of secondary concern. Thus, while the critical risk of concern on which the RCR was based might be cancer, for example, the assessment process might have also identified other health effects (such as chronic respiratory effects, skin or respiratory sensitisation, or specific target organ toxicities) which are considered to be of less severity or concern than the cancer risk or which might only be anticipated to occur at exposures somewhat higher than those estimated for the primary concern. However, within the exposure scenarios to be considered in the SEA, it is possible that such secondary concerns might need to be considered to derive a complete quantification and valuation of the scale of the potential health burden.

The aim of Step 1 for health impacts is to identify, based on the balance of probability, which of the various health-related endpoints considered during the risk assessment process may potentially contribute to an assessment of the substance's overall impacts on human health.

Table 2.1 provides a checklist for the principle categories of data that potentially may be available from the Chemical Safety Report or other readily available sources and that might require consideration at this stage; further detail on the specific nature of the data available is presented under Step 2. The review process will require consideration of not only the DNEL used in the characterisation of RCRs but also the nature of the NOEALs (or other points of departure, PODs) for each of the toxic effects considered in the risk assessment, to establish the extent to which each of the

[1] Note: In some cases, risk may be characterised in terms of a Margin of Safety (MOS).

types of effect may be of significance within the range of exposures to be considered in the SEA.

Table 2.1: Checklist of Evidence on Health Effects		
Data from	**Type of study**	**Likelihood of availability**
Experimental studies	Acute toxicity; Irritation; Sensitization; Repeat dose toxicity; Mutagenicity; Carcinogenicity; Reproductive toxicity; Developmental toxicity	Dependent on tonnage of substance
	Toxicokinetics; Detailed immunotoxicity studies Detailed neurotoxicity studies; Mechanistic studies	Only likely to be available for highly studied substances or where undertaken to address specific concerns about the substance
Human studies that may be present	Cross-sectional; Cohort; Case-control; Group-level/ Ecological; Volunteer studies	Only likely to be available for highly studied substances or, for example, as a consequence of investigations on particular occupational sectors (i.e. job based studies) or population sub-groups

Figure 2.1 below provides an overview of the scoping assessment process in relation to human health concerns, and sets out the different types of information that should be taken into account.

2.3.2 A Focus on Environmental Impacts

When considering environmental impacts, the aim of Step 1 is to establish for relevant compartments the individual effect(s) that may be of significance to a SEA. This will involve establishing for which of the environmental compartments routinely considered in the risk assessment significant risks have been identified. A recent report (WCA, 2010) has suggested that the initial screening of environmental compartments may be based upon consideration of the RCRs produced by the risk assessment and that, for chemicals not defined as PBT or vPvB, only those with RCR >1 need be considered further.

Within the scope of this initial step, it is also necessary to identify which of the various endpoints considered during the risk assessment process could be of relevance to an assessment of the substance's overall impact on the environment. As for health, this should be based on a balance of probability approach informed by the findings of the risk assessment. Thus, in order to ensure the comprehensive identification of potential risks of concern, it will be necessary to consider not only the RCR values developed in the risk assessment but also to some extent the underlying basis for the Predicted No Effect Concentration (PNEC) on which the RCRs were based (i.e. to consider the nature of the available data on the no-observed-effect-concentration (NOEC) for the various test data available for the substance). It may also be important to consider whether any of the effects on human health might also be relevant to mammals (i.e. with regard to potential mechanisms of secondary poisoning).

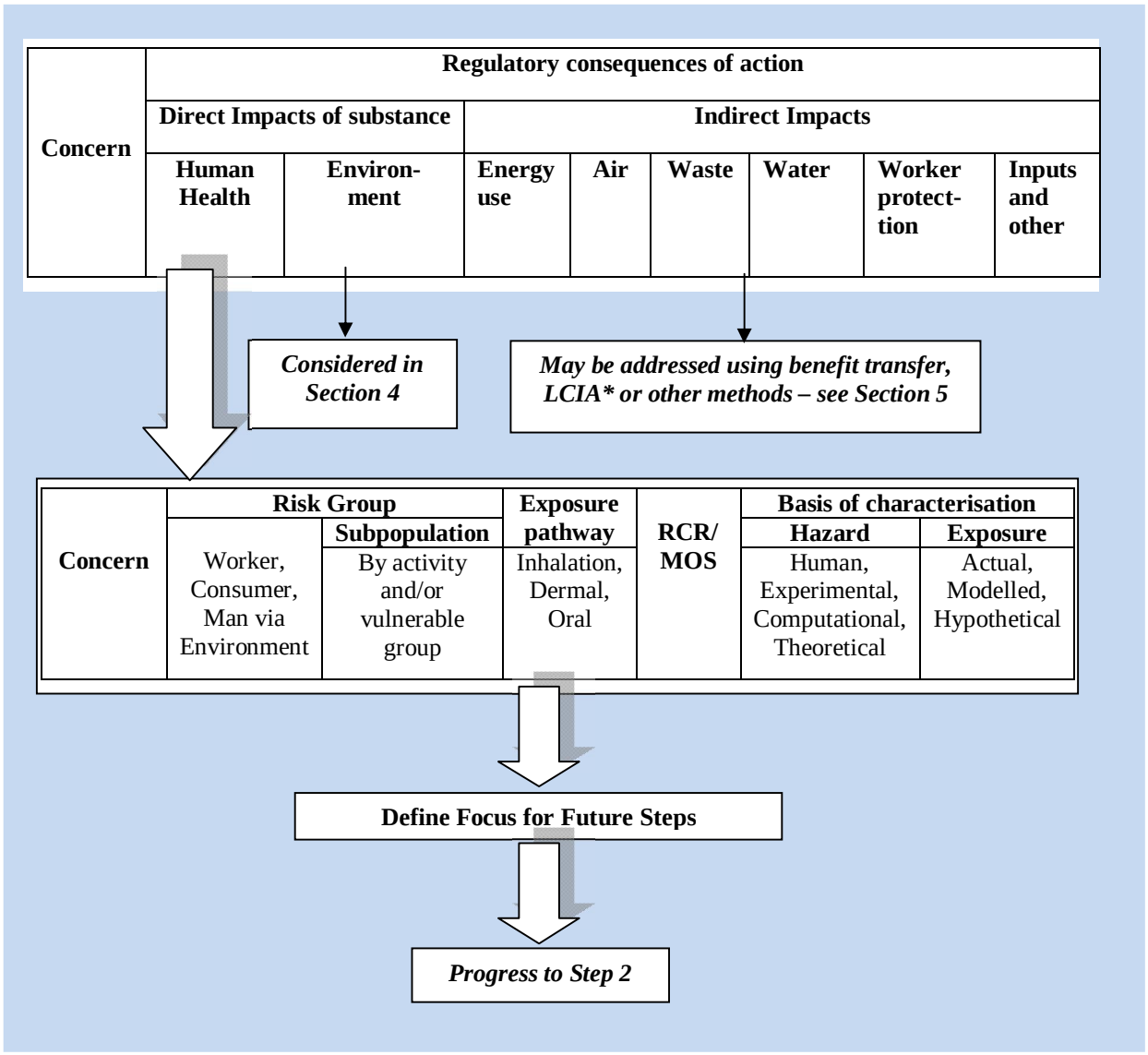


Figure 2.1: Step 1- Scoping Assessment for Human Health

Importantly, the magnitude of the RCR in excess of '1' should not on its own be used to form the basis for selecting or prioritising the effects that warrant further consideration. It will be essential to consider both the endpoint used to establish the PNEC in the risk assessment and to review any other hazardous effects identified for a given compartment during the risk assessment. In particular, the extent to which these other effects might potentially occur at concentrations of relevance to the proposed restrictions or authorisation scenarios should be determined, as these other toxic endpoints could be of socioeconomic importance in themselves or as an indicator or surrogate that would permit quantification or valuation of the impact of the substance on the environment.

In the case of substances – or their breakdown products - that display either PBT or vPvB properties, however, consideration needs to be given to the underlying data on

environmental fate and behaviour (including consideration of the implications for food webs), not just the substance's toxicity profile, and the relevance of the PBT or vPvB properties needs to be assessed for the scenarios under consideration. In particular, for substances with these properties, it would not be appropriate to rely solely on the RCR criteria. These proscriptions would also apply to substances considered as of 'equivalent concern' (for example, due to possession of endocrine disrupting activity).

Table 2.2 provides a checklist for the principle categories of data relevant when considering environmental impacts that potentially may be available from the Chemical Safety Report or other readily available sources and that might require consideration at this stage; further detail on the specific nature of the data available is presented under Step 2.

Table 2.2: Checklist of Evidence on Environmental Effects

Data on	Type of study	Likelihood of availability
Physicochemical Properties	Physical state; Melting/ freezing point; Boiling point; Relative density; Vapour pressure; Surface tension; Water solubility; Partition coefficient (at least octanol-water ratio); Flash-point; Flammability; Explosive properties; Self-ignition temperature; Oxidising properties; Granulometry (solids only)	Likely to be available (required for substances produced or marketed at 1 tonne/annum or above)
	Stability in organic solvents; Identity of degradation products; Dissociation constant; Viscosity	Dependent on tonnage
Experimental ecotoxicological studies	Aquatic toxicity (acute/chronic); Degradation; Fate and behaviour in the environment; Effects on terrestrial organisms (acute/chronic); Long-term toxicity to sediment organisms; Long-term or reproductive toxicity in birds	Dependent on tonnage
	Mammalian toxicity studies	From human health risk assessment (of potential relevance to secondary poisoning concerns)
Environmental observations	Observational reports; Population or ecosystem monitoring	Uncertain – may be studies on particular species or particular habitat-types/locations, that may be of relevance

Key considerations with regard to direct and indirect health impacts for substances classed as toxic to the environment (i.e. those fulfilling the T criterion under REACH but that may also have P or B properties) include:

i) **Environmental Compartment(s) at Risk:** this involves consideration of the RAR to determine for which compartments (air, soil or water (fresh or marine), etc) RCR values of greater than one were identified. For each compartment with a RCR greater than one, the data used in the risk assessment and on which the RCR was established should be reviewed to determine if there are particularly sub-groups of organisms or vulnerable life stages that could be at particular risk (e.g. birds, fish, bottom feeders, top predators, larval forms or young);

ii) **Rick Characterisation Ratios:** data underlying the RCRs for each compartment should be reviewed and summarised to provide an indication of the level and severity of the primary risks associated with environmental exposures;

iii) **Basis for Hazard Characterisation:** this involves reviewing the available data concerning the hazardous properties of the substance, including the expected toxicity of the substance based on its physiochemical properties and test or other data. In addition, the nature of the hazard data should be summarised, including clarification of whether it is based on experimental data, modelled data or read-across approaches;

iv) **Basis for Exposure Characterisation:** it will be important to provide information on the expected fate and behaviour of the substance based on its physiochemical properties. It will also be important to indicate whether the exposure data used in the risk assessment were based on hypothetical data, monitoring or other 'real' data, or were derived from model outputs (possibly supported by a mix of hypothetical or real data); and

v) **Identification of Secondary Risks:** Reference should be made to other data provided in the RA on other hazardous properties possessed by the substance and any consequent risks that might arising from use of the chemical (even if the RCR's for the scenarios considered were <1) and that are relevant to the restriction proposal or the continued use of the chemical. In addition, at this stage it is also essential to establish if the substance under consideration, even if not judged to be a PBT, possess any P, B, vPvB or other properties judged of 'equivalent concern', since the possession of such characteristics may significantly influence the nature of the approach taken in subsequent stages of the SEA. Thus, consideration of other potential concerns is an essential final element of this stage in order to identify and understand the full range of potential environmental impacts that might arise from use of the substance and to maximise the possibility of identifying endpoints suitable for detailed quantification and valuation.

In particular, for substances that meet the vP and vB criteria of REACH, but for which no particular toxic (T) concern has yet been defined, it will not be possible to determine what the environmental consequences (i.e. adverse effects) might be from the chemical's accumulation in the environment or within food chains over time. However, it may still be possible to examine the potential implications of on-going use in terms of concentration build-up in the environment, in particular species of concern, etc. Similarly, it may be possible to benchmark the chemical against other substances with these properties in order to provide an indication of their potential to give rise to concern.

Figure 2.2 sets out the range of issues to be addressed in the Step 1 Scoping Assessment for the Environment. Consideration of the range of issues should allow the analyst to identify those concerns that should be carried forward to the qualitative assessment to be undertaken under Step 2 (see Chapter 4).

2.3.3 Scoping the Impact Assessment

Once the above information has been collated, a decision will need to be made as to what impacts should be considered within the next steps of the assessment in more detail. This may include some but not all health effects, some but not all environmental effects or a combination of both health and environmental effects.
The decision as to what impacts should be assessed in more detail – including both primary and secondary effects - should be based on the strength of evidence supporting an association between the effect (e.g. a change in an experimental endpoint) and the substance under consideration and the relevance to humans or the environment. Figures 2.1 and 2.2 summarise the types of issues that should be considered within the Scoping Assessment.

Scoping the remainder of the assessment will require consideration of the following issues with regard to both the potential primary and secondary risks/impacts:

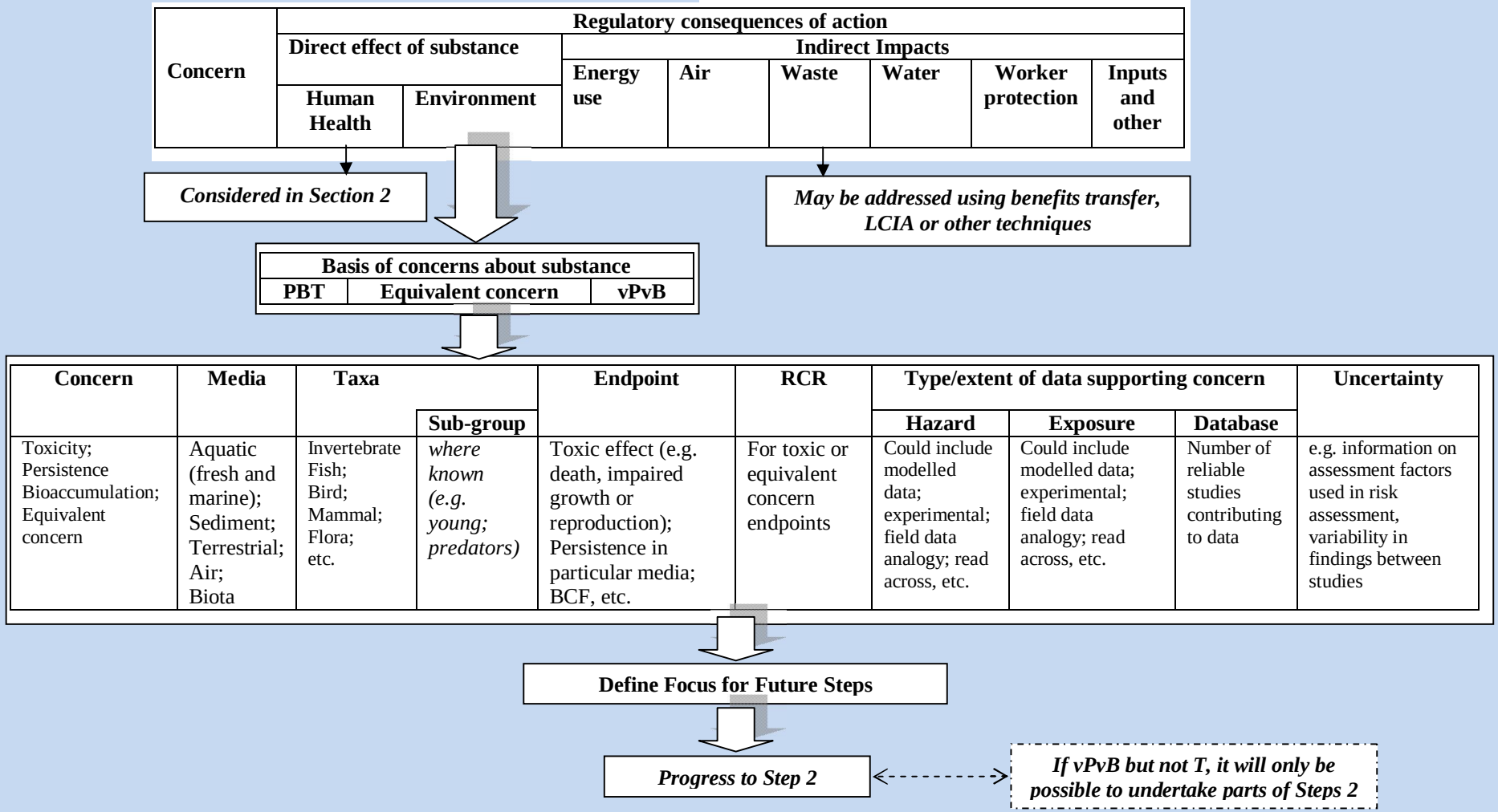
- the ability to clearly define a particular type of impact and its potential seriousness;

- the likelihood that the impact may occur given the tonnages being used and the confines of the exposure scenarios being considered;

- in the case of secondary impacts, the extent to which information on these effects or, particularly in the case of the environment, other properties (e.g. vPvB) of concern that may be important to the overall decision regarding a proposed restriction or an authorisation application; and

- in the case of alternatives, the potential health and environmental impacts identified from the analysis of alternatives as being significant enough to have an impact on the end decision.

Figure 2.2: Step 1 - Scoping Assessment for the Environment



Essentially, the aim is for analysts to apply a 'balance of probability' approach. The use of such an approach for decision making in the human and environmental risk assessment context has been widely discussed in the published literature (see for example Gee (2006 a, b), O'Brien (2002) and van der Sluijs (2007)).

For those risks/impacts that are considered to warrant further analysis, the next step is to develop a qualitative description of the likely severity of the effects and the magnitude of the population that may be affected (see Step 2) or the extent of environmental exposures.

3. ASSESSING HUMAN HEALTH IMPACTS - STEPS 2 TO 4

3.1 Overview

Following the Step 1 Scoping Assessment, the Logic Framework divides into three parallel streams, with one of these being specific to assessing the human health impacts arising from limits on the use of a chemical either due to restrictions or due to a refused authorisation. This part of the Logic Framework (LF) is presented here, with Chapter 4 covering the LF specific to environmental impacts and Chapter 5 discussing briefly the assessment of impacts from adoption of alternatives.

Within this human health LF, Step 2 is aimed at ensuring that there is a sufficiently detailed qualitative description of potential impacts to enable decision makers to act on the basis of this information alone, if necessary.

Where possible, it is recommended that those aspects of the assessment that can be are progressed to Step 3, with the aim of providing more quantitative information on the magnitude and severity of impacts. Thus, even though it is unlikely that the data required to carry out a fully quantitative assessment of all aspects will be available for many of the chemicals going through restrictions and authorisation, there may be elements that can be further quantified. For example, it should be possible to provide a comparison of the hazards/risks associated with the chemical of concern to those of other chemicals (i.e. carrying out a benchmarking analysis).

At the end of both Step 2 and Step 3 of the human health LF there are decision points; i.e. the analyst will need to decide whether or not there is sufficient information and certainty surrounding the conclusions from the work carried out to try and move to the next Step. If quantification under Step 3 has been possible, then a decision will need to be made at the end of this Step as to whether the assessment should move towards monetary valuation. If the decision is taken to stop the assessment at the end of either Step 2 or 3, then the assessment would move to Step 5; if monetary valuation as part of Step 4 is carried out, then the analysis would then naturally progress to Step 5. The overall process flow between the Steps is illustrated in Figure 3.1 below.

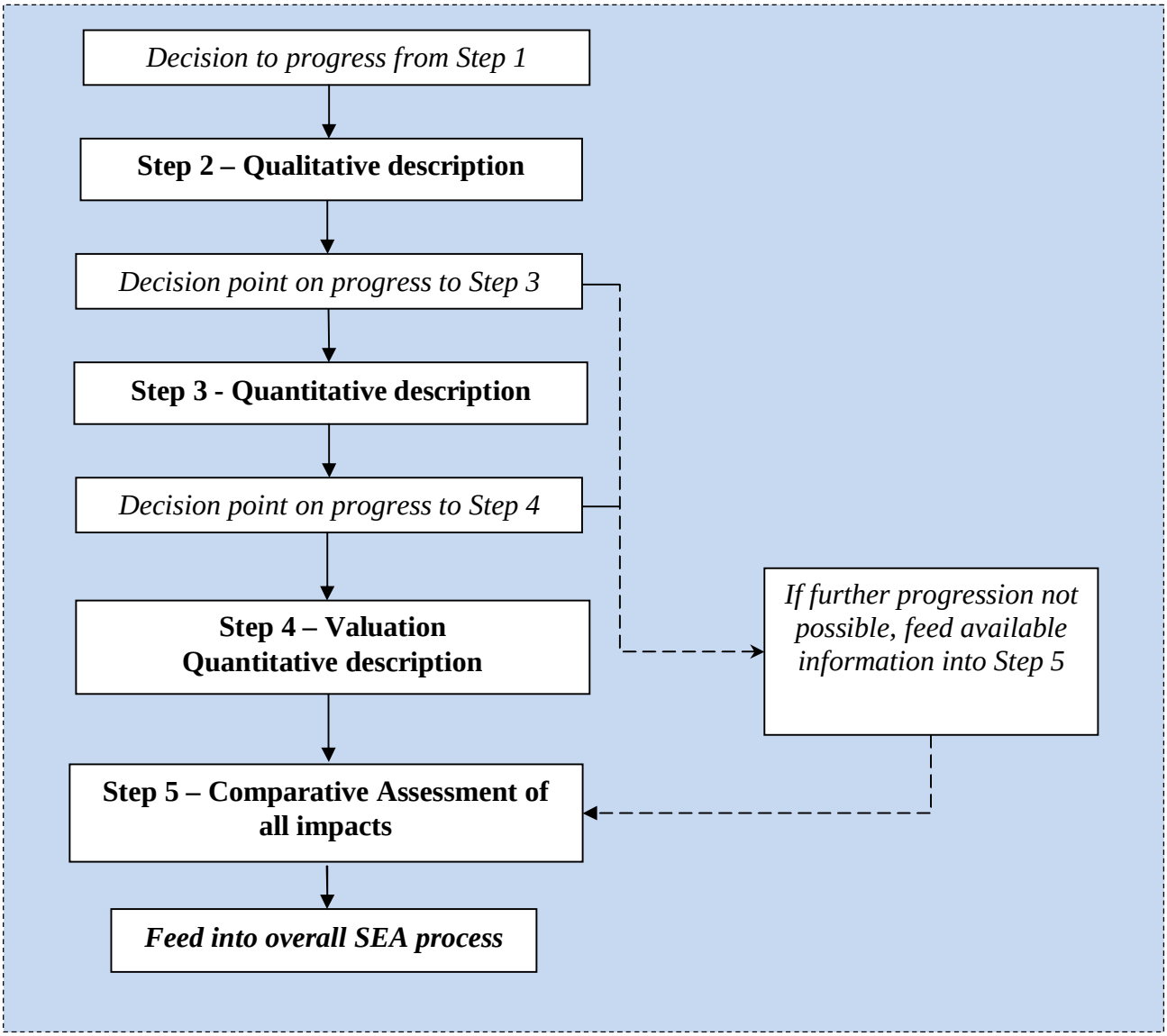


Figure 3.1: Summary of Steps 2 to 5 of Logic Framework for Human Health

3.2 Step 2: Qualitative to Semi-Quantitative Assessment of Human Health Impacts

3.2.1 Introduction

The aim of the qualitative assessment is to ensure that decision makers have a good understanding of the nature of the potential health impacts associated with continued use of the substance and hence the benefits that would be realised by reducing exposures. Where it is feasible to add some quantitative details on, e.g. the population (and sub-groups) exposed, the number of industry sites involved in the relevant activities, average tonnages used at the different sites, emission levels, human exposure data in terms duration and frequency, then this should also be provided at

this point in the assessment. This will help ensure that basic quantitative information is provided to decision makers in the event that the assessment does not move forward to Step 3.

For each of the effects identified in Step 1 as warranting further consideration, there are essentially four possible stages to this Step:

i) Step 2a: Hazard characterisation;
ii) Step 2b: Exposure characterisation;
iii) Step 2c: Qualitative description of potential human health impacts;
iv) Step 2d: Benchmarking for human health;
v) Step 2e: Assessment of the potential for quantification of impacts.

Figure 3.2 overleaf illustrates the detailed stages involved in Step 2 of the human health logic framework.

3.2.2 Step 2a: Hazard Characterisation

For each of the risk issues identified in Step 1, the first stage in Step 2 is to characterise the basis (i.e. the type of hazard) on which the concern was identified and to establish if it is possible to define the nature of the expected health consequences to humans.

For example, some of the endpoints in experimental toxicity models that are used to identify the potential toxic (hazardous) properties of a chemical (e.g. some of the endpoints studied in rodent reproductive toxicity studies) do not provide a direct indication of potential health consequences for humans; in other words, there is no direct correlation between the findings for some toxicity endpoints and human health effects. Thus, it is unclear what possible human health impacts should be considered as being equivalent to a change in mating behaviour or minor variations in the numbers or sex distribution of rodent pups in litters.

In comparison, the implications of other toxic endpoints may be of obvious relevance to a potential human health effect, e.g. demonstration of an experimental carcinogenic potential would be interpreted as an indication that the substance could cause cancer in humans.

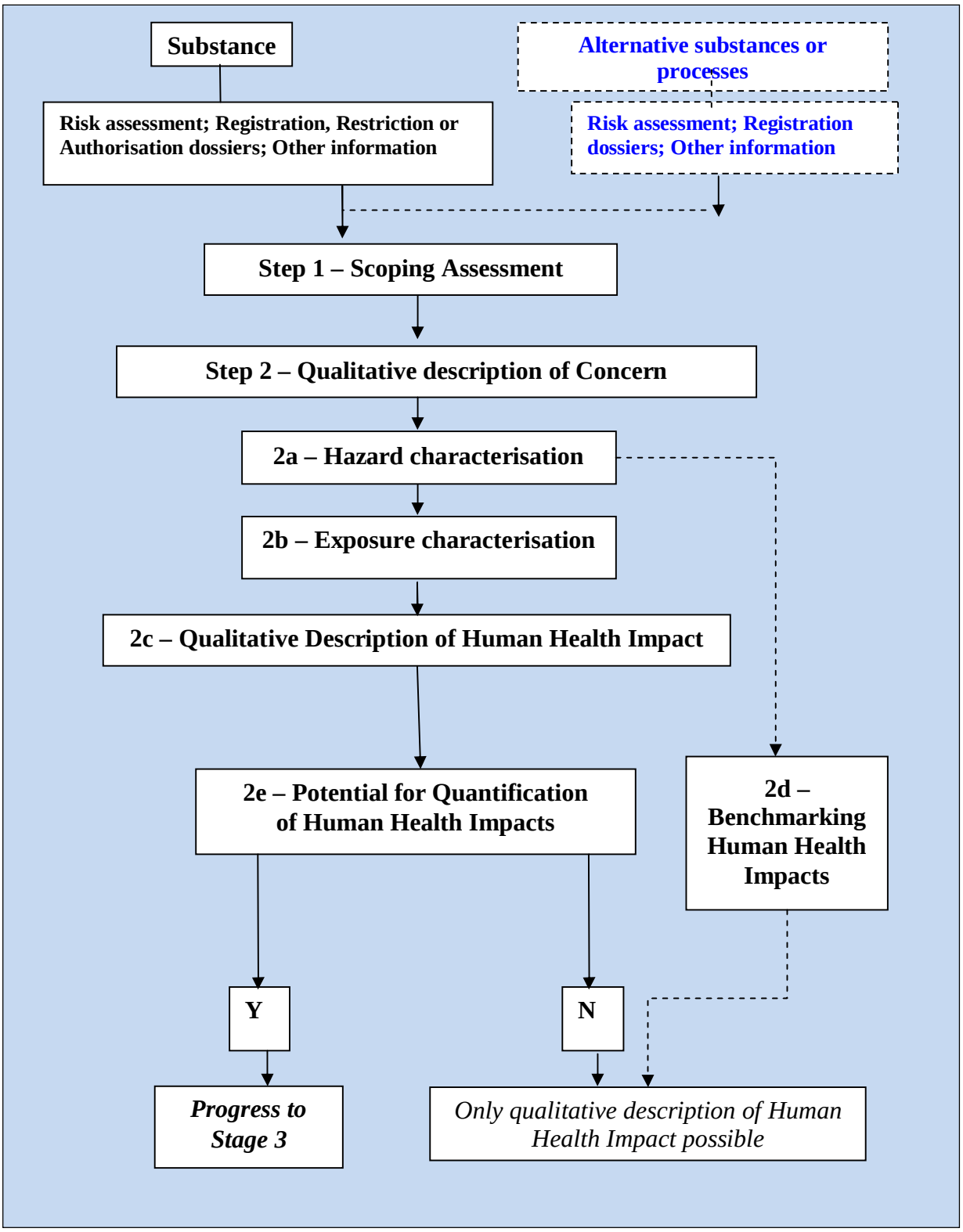


Figure 3.2: Step 2 of Logic Framework for Human Health

Table 3.1 has been prepared to provide a checklist for the types and level of hazard information that should be developed as a minimum under this Step.

Table 3.1: Checklist of Information on Hazard Potential to be Developed in Step 2a	
Reporting Headlines	**Data / Discussion Areas**
Human health endpoint	Acute toxicity, irritancy, sensitization, repeat dose toxicity, mutagenicity etc
Species/Model in which hazard was identified	Human, specific animal species, in vitro model, QSAR, etc
Detailed nature of effect	Detailed description of specific effect endpoint identified
Nature of point of departure (POD) on which DN(M)EL could be based)	Epidemiological – OR, AR, etc Experimental - NOAEL, LOAEL, BMDL, etc
Adequacy of dose-response characterisation	Do studies include suitable dose-response information to support extrapolation to human scenarios under consideration
Data integrity	Robustness of study design (e.g. compliance with standard regulatory study design), adequacy of group size, adequacy of reporting, identifiable uncertainties
Possible approaches to enable cross-species extrapolation (where relevant)	Linear extrapolation, BMD approach, simple physiological based extrapolation, complex PBPK modelling
Conclusion on possibility of extrapolation of identified effect to human health outcome	No, Possible, Yes

Based on a scientific assessment of the relevance to humans of the effect and the suitability and robustness of the dataset on which it is based, a conclusion should be reached as to the feasibility of developing an exposure characterisation (Step 2b) and a qualitative description of the health impacts (Step 2c). This should be based on consideration of the robustness of the available data.

For those hazard endpoints for which it is concluded that it is not possible to identify a corresponding specific human health effect, it will be inappropriate to attempt to provide an assessment of the direct human health impacts in either qualitative or quantitative terms, or to develop detailed descriptions of the exposure characteristics that may apply. However, in such instances it may still be appropriate to apply a benchmarking approach (or similar) approach, as set out under Step 2d.

For each hazard endpoint for which a human health effect can definitely or possibly be identified, a qualitative description of the envisaged health impact in terms of the nature of the effect (acute, chronic and/or death brought forward/fatality) should be developed. This should be combined with information on the possible economic consequences of the expected effects following the approach set out for Steps 2c and 2e. For effects where it is not possible to achieve this degree of characterisation, benchmarking approaches (Step 2d) may still provide value information of value to regulators.

3.2.3 Step 2b: Exposure Characterisation

In order to understand in qualitative terms the nature of the risks posed to different human populations for each of the health concerns carried forward from Step 2a, it is essential to characterise to some degree the level and frequency at which different population groups may be exposed to the chemical of concern. In some instances, the frequency of exposure may on its own act as a useful measure of exposure if the level (i.e. concentration) at which exposures occur is uncertain.

In particular, the aim under this Step should be to develop – for each combination of health risk and sub-population at risk – information on the following aspects of exposure:

a) **level of exposure**: assessed in terms of the relative exposure concentrations (high, medium or low compared to likely levels at which effects are likely to occur) for each exposure episode and for particular population groups. To help provide context for this, data should also be reported on the tonnages of the substance used in the applications of concern and any trends in use that may be relevant to understanding future exposures;

b) **duration of exposure**: assessed in qualitatively in terms of the anticipated length of each exposure episode for particular population groups (e.g. 15 minute periods, 3 hours, entire working day, etc.);

c) **frequency of exposure**: assessed in terms of the frequency at which exposure episodes might occur, where these might include 'continuous' (e.g. for man via the environment), daily (e.g. worker), daily, irregular (e.g. workers or consumer use of a particular product) or rare exposure events;

d) **data availability**: there is a need to understand the nature of the available data for the actual population(s) exposed. For example, are actual measured data available (most likely for workers)? Or are modelled or other estimates available (e.g. as outputs from an environmental fate and transport model)? Or, is there the potential to develop surrogate estimates of exposure (e.g. based on market data for particular consumer goods or concentrations in products)? Alternatively, it may be concluded that there is a strong likelihood that there are inadequate market or other data available to support the development of a robust estimate of populations exposed; and

e) **certainty**: as part of this qualitative assessment, the degree of certainty surrounding both the level of risk posed by the chemical and on exposure data should be assessed qualitatively.

Table 3.2 provides a checklist for the types of information that should be developed and reported on for each of the health risk concern/population group combinations considered, and where there are significant differences across these, to provide data on the significance of exposures in terms of the potential human health impacts.

Table 3.2: Checklist of Information on Exposure for Each Risk for Step 2b	
Reporting Headlines	**Data / Discussion Areas**
Group at risk	e.g. workers, consumers, man via the environment
Description of sub-group or vulnerability	e.g. workers performing a particular function for which high exposures are estimated or other indicator of vulnerable groups (e.g. women of child bearing age)
Level of exposure	Assessment of the extent, at least in qualitative terms (e.g. low, intermediate, high), it may be possible to categorise the concentrations to which particular population groups may be subject
Duration of each exposure episode	e.g. few minutes, few hours, continuous
Frequency of exposure	e.g. continuous, daily, irregular, rare
Certainty in exposure data	Based on consideration of the nature of the data (e.g. actual, modelled) and robustness of the measurement or modelling systems employed (e.g. low, medium or high)
Availability of data on populations exposed, number of sites at which exposures occur, or geographic distribution of exposures at or above levels of concern	Are actual data or estimates available, what is the potential for developing estimates using GIS, fate and transport models, market data on number of companies operating in a given sector, etc.
Tonnages associated with exposure	Carried forward from the Step 1 scoping exercise, including any information on trends in use which may be important to understanding future exposures

3.2.4 Step 2c: Qualitative Description of Potential Human Health Impact

For each of the endpoints that can be linked to human health consequences, information should be provided on the population groups and subgroups at risk (informed by the considerations in Step 2b) and of the nature of the anticipated health consequences (in terms of potential morbidity, mortality and economic consequences). As detailed and comprehensive a description as possible should be provided, with a checklist for the types of information that should be developed as part of this step set out in Table 3.3. Separate reporting would be required for each health endpoint and sub-group of the population considered.

Table 3.3: Checklist of Information on Health Impacts for Each Endpoint for Step 2c	
Reporting Headlines	**Data / Discussion Areas**
Group at risk:	e.g. workers, consumers
Description of sub-group or vulnerability	e.g. workers performing a particular function for which high exposures are estimated
Nature of Anticipated Effect in Humans: Description of Health Effect	
Morbidity:	
Duration of disease	e.g. acute versus chronic or short (<21 days), medium (< 3 months), long term(> 3 months)
Frequency of disease episodes	e.g. one-off, 3 times annually, etc.
Lag to recovery (time to full recovery)	e.g. Immediate, several years, no recovery likely
Mortality:	
Rapidity of fatality	Years lived after on-set (months, years)

Table 3.3: Checklist of Information on Health Impacts for Each Endpoint for Step 2c	
Reporting Headlines	**Data / Discussion Areas**
Latency of disease	Period before on-set
Survivorship probability	Either based on medical data (e.g. % surviving 5 years form diagnosis) or in qualitative terms (e.g. high – for non-lethal conditions; medium – where some deaths may occur, or low – for rapidly fatal cancers)
Economic Impacts of Disease:	
Medical treatment costs	Magnitude of hospital costs, out-patient treatment costs, medicines, etc.
Impacts on ability to work	Related to days off work, lost productivity at work, etc.
Impacts on ability to carry out normal day to day functions	Impacts on mobility, self-care, level of pain or discomfort, anxiety or depression
Impairment of earning potential	Impacts on cognitive functions (memory, concentration, IQ)
Implications for future health care requirements	Dependency

3.2.5 Step 2d: Human Health Benchmarking

The use of benchmarking data as a comparator for providing some quantitative data on human health impacts is likely to be important for many chemicals regulated under both the restrictions and authorisation process. In particular, it is likely to be the only means of providing a further assessment for substances linked to mutagenic and reproductive toxicity effects that are unsuited for further (quantitative) characterisation using the approaches discussed under Step 3 and beyond. This will also be the case for the majority of carcinogens, which are likely to be lacking sufficient data to create a dose-response function, and for a wide range of the potential morbidity effects that might be relevant to worker protection in particular.

Potential Benchmarking Tool

As discussed in detail in Part 1 of the Report, there is a range of potential tools available which could be used for benchmarking chemicals according to their physico-chemical properties. The key issue for this logic framework is the ability of the selected tool to rank chemicals in relation to their human toxicity potential, but to also take into account uncertainty (see also the discussion on benchmarking in relation to environmental concerns). One of the tools reviewed in the main report was SCRAM, the use of which is briefly illustrated here. This tool was designed to evaluate and score the toxicity, persistence and bioaccumulation potential of chemicals based on limited information (see Section 7 of the Part 1 report for further details) specifically in relation to the American Great Lakes. While not suggested as fully meeting requirements for REACH benchmarking, the model is readily available and addresses both environmental and human health concerns to some extent so was chosen to illustrate the basics of benchmarking.

The data needed by SCRAM in relation to human health are:

- General Toxicity: LOAEL or 90 d NOAEL;
- Reproductive Toxicity: LOAEL or 90 d NOAEL;
- Developmental Toxicity: LOAEL or 90 d NOAEL;
- Carcinogenicity; and
- Other Toxicity (mutagenicity, behavioural effects, immune system effects, endocrine effects).

The spreadsheet tool and associated guidance are available online from the US EPA website at http://www.epa.gov/greatlakes/toxteam/pbtrept/index.html. From the information above gathered, a final chemical score is determined together with a final uncertainty score. These two scores are then combined to give the final composite score thus allowing the ranking of the substance. Scores for 146 substances are available from the above USEPA website.

Use of Benchmark Scores

It is recommended that benchmark scores are provided for individual health effects and then at an aggregate level across health effects to act as comparators for providing a wider context for the human health impacts. In using these scores, the suggested benchmarking process would involve:

i) Identifying substances with a human health score above and below that calculated for the chemical of concern, i.e. appropriate benchmarks;

ii) Determine whether exposure routes for these other chemicals are likely to be similar to the exposure routes for the chemical of concern; and

iii) Decide whether the types of health effects are also likely to be comparable and have similar modes of action – in particular, whether they relate to effects of the same severity and with the same implications with regard to mobility, quality of life, etc.

3.2.6 Step 2e: Potential for Human Health Quantification of Impact

The final stage in Step 2 is to determine – **for each risk concern and population group considered of concern** - whether or not there is merit in moving to Step 3 and the development of further quantitative information on the potential health impacts.

This final step represents an important decision point in the overall process: analysts should decide:

i) whether it would be possible to quantify the likely health impacts of either the proposed restriction or a refused authorisation given the available toxicological

data, exposure information and availability of human morbidity/mortality information; and

ii) whether the data required to do so are both available and are sufficiently robust.

Depending on the nature of the data available from the risk assessment and other supporting sources, it may be possible to predict the number of disease cases (or other health impacts) that would occur in the absence of regulatory action and the extent to which these would be reduced from implementation of a proposed restriction or a refused authorisation.

If the most that can be derived from the risk assessment is a RCR (i.e. based on an estimate of exposures and definition of the POD such as a NOAEL or BMDL), then it will not be possible to move to Step 3; the impact assessment for that endpoint will stop following completion of Step 2c (or Step 2d, as appropriate).

This will most likely be the case where the risk assessment is based only on animal data and it has not been possible to attempt inter-species extrapolation from such data to a human-relevant dose-response function, or where the risk has been identified based on assessment of theoretical data (such as structure-activity-relationships (SARs) or read-across methods). Even in such instances, it may be possible to develop benchmark indicators (Step 2d) of the severity of the potential human health hazards relative to those associated with other regulatory chemicals to act as a proxy measure of severity of potential health impacts.

To reach a conclusion, the analyst will need to consider:

- the extent to which the hazard information underlying the concern can be translated to human health consequences;
- the robustness of the data underlying the risk assessment, particularly in relation to definition of NOAEL/LOAEL and the dose-response relationship;
- the robustness of the data available on exposure (i.e. the size and nature of the database on which estimates may be based and the degree of certainty surrounding both the hazard posed by the chemical and the exposure data); and
- the extent to which it may be possible to develop estimates of the size of population exposed at levels that might give rise to a risk of an adverse effect.

If the conclusion is that quantification of exposure is possible and that it is also possible to make a translation from the risk assessment outputs or underlying data to health impacts, then the analyst should progress to Step 3. In particular, where epidemiological data are available, dose-response data are available, or a human-relevant dose-response function can be extrapolated from the various experimental datasets available, then the assessment should proceed to Step 3.

Even if it is only possible to quantify the size of the exposed (or vulnerable) population, there is merit in doing this to provide this type of information to decision makers.

3.3 Step 3 – Quantitative Description of Human Health Impacts

3.3.1 Overview

The aim of this step is to provide an indication of the significance of the proposed risk reduction to the current levels of risk (and by inference the consequent change that would occur in the estimated health impacts). Quantification may be important in the context of restrictions to justifying them as the best risk management option. In the context of authorisation, it may be critical to determining whether or not the socio-economic benefits of continued use outweigh the risks, in this case, to human health; this may be particularly important against the background of on-going use of a chemical in other applications or in other supply chains.

Quantification in part or in full can be achieved through a number of different approaches, offering varying degrees of information on the change in health impacts:

- use of a simple physical indicator of change in risk as a proxy for impact; for example, change in usage, change in exposure levels and/or frequency, change in concentrations of a chemical in consumer products, or changes in emissions in the workplace or to the environment; or

- full quantification of the change in human health impact that may arise from the risk reduction measures under consideration.

Simple physical indicators should have been developed through the approaches set out in Steps 1 and 2 of this framework. Their use is therefore not discussed further as part of this Step.

Fuller quantification may be achieved through a number of different approaches depending upon the type of effect, types of exposure and population data available. All of these approaches, however, will need to draw on the outputs of exposure modelling and therefore require data on the size of exposed populations. Although collation of such data may be feasible in relation to worker exposures, it may be much more difficult for consumer exposures or exposures of man via the environment.

The outputs of a fully quantitative exercise would be predictions of the number of cases of a given disease (or diseases) that are attributable to exposure to the substance of concern under the baseline situation and estimates of the reduction in the number of cases from either a restriction or a refused authorisation.

Any such predictions of changes in the number of disease cases would need to be accompanied by information on the level and sources of uncertainty surrounding the estimates. It will also be important to undertake a sensitivity analysis to test the most important assumptions underlying the analysis and the degree to which changes in key assumptions would impact on the predicted change in health impacts (e.g. basing estimates on average values versus reasonable estimates versus worst case assumptions).

As data availability will determine the path that this more quantitative assessment of health effects might take, Step 3 has been broken down into four different stages (see Figure 3.3.

i) Step 3a: Detailed description of the baseline and the restriction scenario or the no-use scenario for authorisation;

ii) Step 3b: Use of experimental data (dose-response based quantification);

iii) Step 3c: Epidemiology based quantification; and

iv) Step 3d: Assessment of potential for valuation.

Table 3.4 provides a checklist for the various types of information that would have to be considered and reported on for each of the risks (and at risk groups) carried forward to this Step (drawing on the data identified in the previous Stages), possible methods of estimation and the likely nature of the resultant outputs. Estimates would need to assembled in turn for each risk of concern and exposed population combination identified in Step 2d. Ultimately, the health impact estimates for each risk would then need to be combined to provide information on the overall impacts.

Table 3.4: checklist of Information Needs, Approaches and Reporting Outputs

Reporting Headlines	Data / Discussion Areas and Outputs
Definition of Risk Management Scenarios	Baseline plus restriction options (e.g. banning from consumer use, establishing an OEL to protect workers)
Definition of characteristics of population considered at risk	Group (e.g. industry workers, professions, consumers) and subgroup (e.g. women of child of bearing age); estimate of population numbers; depending on methods to be employed , data on worker turnover rates may be required
Nature of health impact	Disease state (or other health impact) including information on nature of morbidity and/or mortality characteristics, latency etc.
Basis for extrapolation	Effect - epidemiological data; experimental data; read across; analogy; use of proxy estimate; etc. Exposure – measurements; modelled estimates; read-across from other datasets; etc
Method of impact estimation	Epidemiological techniques: such as derivation of attributable fraction and numbers, or use of prevalence data Experimentally-based: such as physiologically-based extrapolation from animal data using approaches such as linear extrapolation, BMD techniques LCIA models Others: use of proxy measures, read across or analogy, bench mark against other substances
Output	Depending on method used and nature of impact, number of new cases per year; number of deaths per year; changes in population incidence of a condition, etc.
Sensitivity analysis	Derivation of estimates based on worst case, realistic and mean/average value assumptions

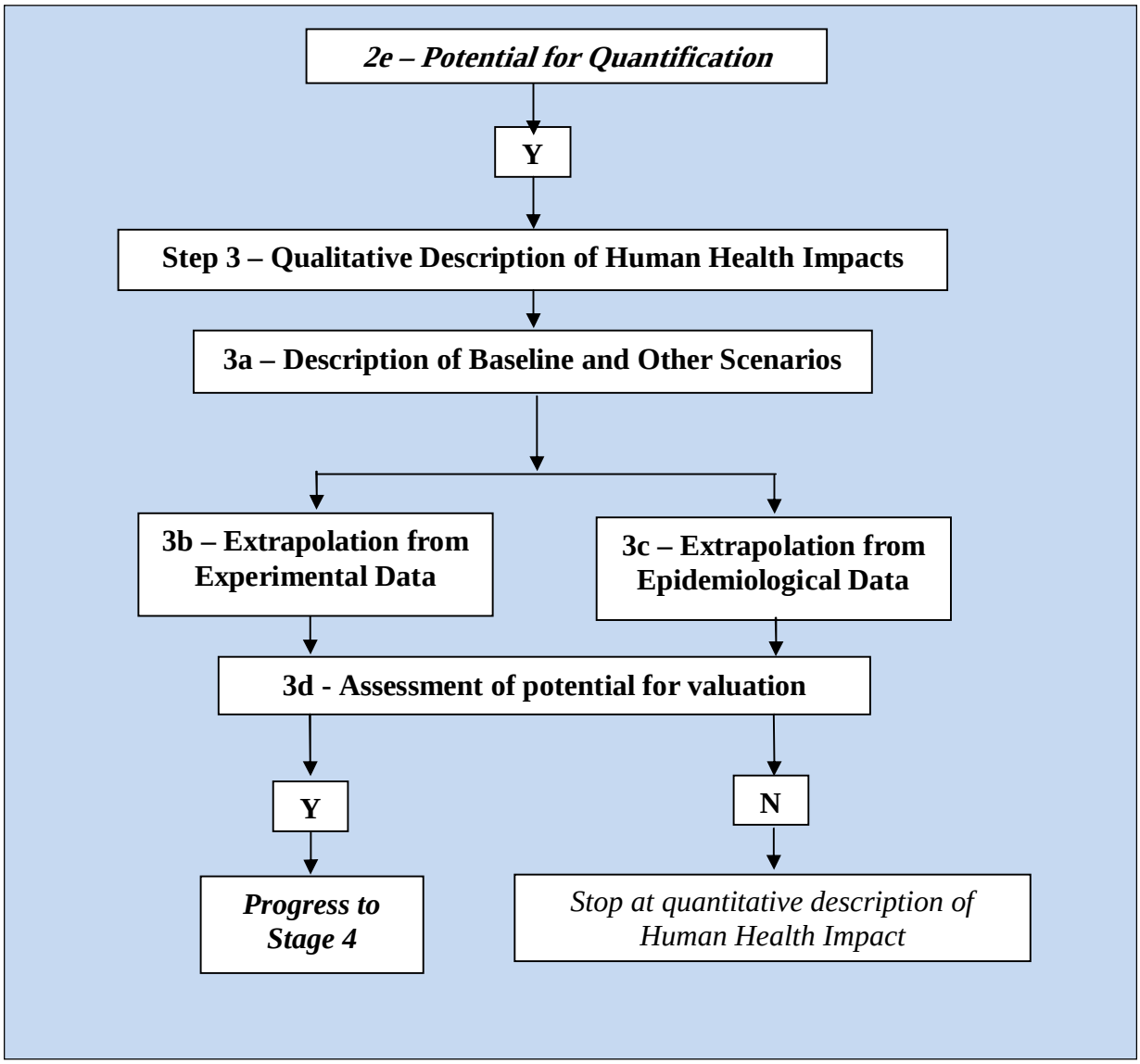


Figure 3.3: Step 3 of Logic Framework for Human Health

3.3.2 Step 3a – Baseline and Scenarios

As part of the work carried out more generally during Stage 2 of preparing a SEA according to the ECHA guidance (see Section 2.3), analysts will have defined the baseline for the assessment, as well as the restriction or authorisation scenarios.

The detail underlying the definitions of both the baseline and the scenario in relation to human health should be carried forward to this Step in the assessment. It is important that the baseline for both the cost and health impact assessment are consistent and based on the same assumptions. This includes assumptions on, for example, current uses and quantities used, future use, and trends in how the substance is used, including the number of sites using the substance of concern, the number of

workers involved in the processes, the number of units of a product placed on the market, etc.

3.3.3 Step 3b: Use of Experimental Data (Dose-response Based Quantification)

Within the context of REACH restrictions and authorisations, it is most likely that adequate dose-response data will only be available from experimental (non-human) studies; that is even if present epidemiological information may be limited in nature and unsuited for suited for the quantification of impacts due to a lack of dose-response data.

Where experimental data are available indicating an effect of a type suitable for extrapolation to humans (see Step 2), it may be possible to use the dose-response functions as the basis for quantifying changes in health impact. This is likely to be the case for substances where the concern is carcinogens or certain types of morbidity effects (e.g. asthma, dermatitis, specific organ toxicity). Dose-response functions have been developed, for example, by DG Employment's Scientific Committee on Occupational Exposure Limits (SCOEL) on the excess rates of cancer due to different worker exposure levels to some substances. Other potential sources are IARC documents and work undertaken by national authorities, including for example, Health Canada, and OSHA and the EPA in the US.

Where the dose-response function has been developed to reflect worker exposures, care will be required to ensure that its application to consumer exposure scenarios or man via the environment are also relevant (e.g. will be a need to consider the exposure route and exposure range and time periods to ensure these are relevant).

Extrapolation of experimental dose-response data to estimates of impacts in humans

In order to use animal data to develop dose-response functions that can be applied to estimates of potential human impacts, it is necessary to establish the position with regard to a number of aspects (several of which should have been clarified during Step 2):

1) Is the experimental effect of a type that could be extrapolated to humans;
2) What is the nature of the experimental effect (i.e. is it thought to be threshold or non-threshold in nature);
3) Does the experimental data contain sufficient data to allow derivation of a dose-response function (i.e. is response information for a reasonable number of study groups (i.e. dosages);
4) What is the appropriate approach to inter-species extrapolation of data (i.e. can simple allometric scaling be applied or is it possible to apply more sophisticated physiologically-based pharmacokinetic (PBPK) models); and
5) Are the routes of exposure used in the experimental study of relevance to human sources of exposure and - if not - is route-to-route extrapolation possible and appropriate for the effect considered;

As such the results of these considerations will inform on the possibility and appropriate method to achieve the inter-species extrapolation. Approaches to undertaking such an extrapolation will, however, essentially follow those detailed in the ECHA and is likely to draw on approaches such as linear extrapolation and benchmark dose (BMD) modelling. Unlike the situation with regard to the use of such techniques during risk assessment, for use within the SEA, additional assessment factors would not be applied to address the uncertainties implicit within such an extrapolation. An illustration of the extrapolation of rodent data to provide a dose-response function relevant to human impact estimation is given in Box 3.1.

Box 3.1: Estimation of worker renal cancer burden from TCEP based on experimental dose-response data

Several rodent studies have considered renal cancer induction by TCEP. Of these that of Takeda et al (1989) and therefore, the extra burden of cancers in treated mice (see Table below) was modelled against human equivalent doses (obtained using simple allometric scaling of 7) using the US EPA's BMD[1] program for multistage cancer.

Although subject to uncertainty due, for example to, inherent differences in susceptibility to tumours between species, the scale of effect seen in the mouse study (expressed as 'extra response seen above control' levels) was used without further application of assessment factors to infer what the possible additional 'risk' of renal cancer might be to humans as a result of a particular TCEP exposure.

Dataset from Takeda et al (1989) used in BMD modelling					
Mouse dose (mg/kg/day)	0	12	60	300	1500
Human equivalent dose (mg/kg/day)	0	1.71	8.57	42.86	214.29
No. Animals with tumours	2/50	0/49	2/49	5/47	41/50
No. Animals with tumours above control	0/50	0/49	0/49	3/47	39/50

The model used gave BMD and BMDL values of 56.6 and 40 mg/kg/day respectively. The BMD model was then used to derive estimates of the scale of effect that might be anticipated at any particular dose within the established response curve.

The conservative exposure estimates for workers derived in the risk assessment were first considered; these estimated worker exposures to range between 3.17 and 36.9 mg/kg bw/day across a number of exposure scenarios reflecting the different applications of this substance. This resulted in estimates of additional cancers (per 100,000) for each worker scenario. These were then converted to total cancer burdens per scenario based on the numbers of workers 'at risk'. From this, for the total worker population of about 307,000, an additional life-time burden of approximately 3700 additional kidney cancers was estimated. Given that this tumour type generally occurs later in life and the mechanism of this effect is probably non-mutagenic for TCEP, it was assumed that workers would need to have been exposed for much of their working life before tumours developed; a 40-year occupational exposure period was therefore assumed. On this basis, the annual cancer burden was estimated at 93 cases for the European worker population. When the process was repeated using more realistic exposure scenarios (i.e. with allowance for a lower dermal absorption and the influence of high efficiency protective equipment to reduce systemic exposure), a much lower cancer burden of the order of 0.05 extra cancer cases per year was estimated.

In order to apply the dose-response data, quantitative estimates on the population exposed will be required. Different sources of data and different approaches may be require to estimate exposed populations.

Estimating Worker Populations and Exposures

Potential data sources for estimating the number of workers exposed to a particular chemical include:

- company level data on numbers of workers involved in the activities or processes leading to exposures;
- at the national level (and potentially at the EU level), use of workforce data to develop estimates of the potential worker population exposed to a substance;
- use of job exposure matrices to develop information on the percentage of workers likely to be exposed at relevant exposure levels; and
- use of CAREX[2] and other similar data on exposure to carcinogens in different industries and extrapolation from this to the national level or the EU level.

In most cases, these data would need to be combined with information on actual workplace exposures. At the company level, in-house monitoring data may exist which could provide the basis for estimating the number of workers exposed at different rates. An alternative often used in occupational epidemiology, is use of job descriptions as a surrogate for extent of exposure. At the national level, data collected by regulatory authorities may be available to assist in detailing typical exposure rates; alternatively, information on national OELs or biologically-based exposure limits (in the absence of an EU-wide occupational standard) can be used to act as the basis for developing a worst-case scenario of worker exposures.

Predictions of Consumer Exposure

Quantifying the number of consumers that may be exposed at relevant concentrations is likely to be significantly more difficult than quantifying the number of workers exposed. In these cases, exposures will be determined by product types and the extent to which chemicals are released from products either deliberately or non-deliberately. Thus, estimating exposures requires information on:

- the types of products in which the chemical is used;
- the proportion of these products that incorporate the chemical of concern;
- market data on sales of the products in terms of number of units placed on the market across the EU;
- information on typical (and perhaps worst-case) usage of the product and whether consumers are likely to follow manufacturers' instructions regarding safe use (e.g. wear gloves, masks, etc.);
- frequency of use by the consumer, i.e. several times a day, once a day, once a month, once a year; and

[2] http://www.ttl.fi/en/chemical_safety/carex/Pages/default.aspx

- duration of use, i.e. whether for a few minutes, a few hours, all day, etc.

While some product types, such as textiles, paints, flooring materials and products, and building materials, are likely to be associated with a potential for exposures for the majority of the general population, other chemicals will be associated with much smaller sub-populations and, in some cases, use of the product may often be much less frequent, with lower durations (and thus lower levels of exposure).

It is likely that a range of statistical and other data sources may need to be called upon. This could include consumer behaviour studies and market surveys which try and describe typical consumers and their activities and profiles and provide estimates of the likely market for new products. It may also include the types of data which can be found on industry association websites with provide details of markets for different types of products, including the numbers of units sold.

Where data on numbers of units sold is unavailable, it may be possible to generate estimates by manipulating other data. For example, product sales data or a company's data on turnover in relation to a give product could be divided by the average cost of a product to develop a rough estimate of the corresponding number of units sold.

Of greatest difficulty may be developing estimates of exposures, where this requires making a series of assumptions regarding the conditions of use (e.g. room size, air flow through the room, duration of an activity; or, life of the product, frequency of use, length of time used on each occasion, clean-up methods, use of protective masks or gloves, etc.).

Box 3.2 provides an example of how consumer exposures were calculated for the use of cadmium-bearing brazing alloys in a recent study carried out for the European Commission (RPA, 2010). The example highlights the fact that developing such estimates can involve collation of a wide range of information and adoption of a range of assumptions. It also highlights the importance of clear reporting on all of the assumptions made in an analysis.

Box 3.2: Predicting consumer exposures from the use of cadmium-bearing brazing alloys

Cadmium-bearing brazing alloys have numerous applications. For consumers however, their main use is in model engineering. It is estimated that in the EU consumers use approximately 10 tonnes of alloys per year (containing up to 2.5 tonnes of cadmium). This is the cause of concern as the use of cadmium-bearing brazing fillers may result in exposure of the user to cadmium oxide fumes, which may cause adverse health effects.

To calculate the consumer exposure to cadmium–bearing brazing alloys (as in most predictions of consumer exposures) a number of estimates were developed based on various generic assumptions and default values. These included assumptions on workshop size, ventilation conditions, cadmium content of brazing fillers and quantities, and patterns of brazing filler used. In addition to these assumptions, the different short term (15 minute) and daily exposure estimating techniques were also based on a number of more specific assumptions (see below).

The equations used to estimate personal exposure over a short-term period of brazing activity and over the course of an 'activity day' are given below, respectively:

Box 3.2: Predicting consumer exposures from the use of cadmium-bearing brazing alloys

$A_S = (W_S/(V \times F))*D$,

where; A_S = short-term atmospheric level (mg/m^3), W_S = weight of cadmium released in 15 minutes, V = volume of immediate breathing zone (i.e. 0.134 m^3), F = adjustment for assumed air exchange rate in 15 minute exposure period (3 per 15 minutes) and D = nominal adjustment assuming to allow for dilution effect over 15 min period of operator breathing of non-contaminated (i.e. out of activity zone; nominal value of 0.5 assigned). A natural ventilation decay rate of 0.42 h^{-1} and a forced ventilation decay rate of 0.97 h^{-1} was also assumed.

The value thus derived (A_{SA}) was compared with the established UK 15-minute short-term exposure limit (STEL) for cadmium oxide fume, to provide information on the possible risk of acute effects.

$A_L = W_L/(V \times F)$,

where; A_L = resultant average atmospheric level (mg/m^3) over an eight hour activity period, W_L = weight of Cd released over course of all brazing activities during the activity day, V = volume of air in building where activities conducted (40 m^3 or 120 m^3 for a professional user) and F = adjustment for assumed number of air exchanges over period (6 per hour for 8 hours).

As with short-term estimates (above), the atmospheric level (A_L) thus derived was further adjusted to allow for the potential loss of particles from the atmosphere (A_{LA}); a nominal period of 4 hours in the air was assumed. The intake estimated to arise from this background level of exposure was based upon the equation:

$I_L = (A_{LA} \times R_L)/P$

where; I_L= intake arising from 8-hour exposure (in mg Cd), A_{LA} = estimated adjusted background atmospheric level (mg/m^3), R = respiratory volume in activity period (i.e. 6.67 m^3 per 8 hours) and P = proportion of inhaled material absorbed (25%).

The results showed that where personalised fume extraction is not used at close proximity to the brazing process user exposure can be extremely high. In short-term exposure scenarios, the STEL was exceeded every time and, as cadmium concentrations were so high under the majority of scenarios, it raised questions over the effectiveness of personal protective equipment. For the daily exposures scenario, where wall or personal fume extractors were in use, the exposure concentration was well below the 8 hour time weighted average (TWA); in scenarios assuming no ventilation or natural ventilation a significant proportion of the 8 hour TWA was accounted for (except for one example where it was exceeded).

Source: RPA (2010): Socio-Economic Impact of a Potential Update of the Restrictions on the Marketing and Use of Cadmium, Revised Final Report to the European Commission, DG Enterprise and Industry.

Modelling approaches, such as use of the ConsExpo model may assist in developing consumer exposure estimates (see Section 5.2 of the Part 1 report). It will be important in using such models to ensure that there is a good understanding of the potential exposure ranges for consumers and how these may link to the health endpoints of concern and dose-response data. It will be important to determine whether it is appropriate to extrapolate from worker exposure data to consumers; this may not, for example be justified, if exposures take place via a different route for which the mechanism of effect is no longer valid) or at significantly lower levels

unless it is considered appropriate to extrapolate to these lower levels from the available dose-response data (e.g. if non-threshold mechanisms are postulated or a definitive threshold of effect has not be shown).

Man Via the Environment

The principle routes of chemical exposure for man via the environment are:

- water used for drinking and recreational activities;
- indoor and outdoor air; and
- dietary intake.

These exposures will largely be determined by: the volume of releases; the regional/geographical distribution of emissions; and the environmental fate of the substance in question. For persistent and bioaccumulative substances used in large volumes, the assessment may need to consider the entire EU population. However, where emissions are associated with smaller volumes of use or with local sites, then it is likely to be more appropriate to focus on regional or local populations and determine the degree to which vulnerable groups within these are exposed at levels which may give rise to risks.

Where dose-response data are available, then an exposure-based approach to estimating health impacts from environmental emissions can be applied. This will require information on:

- emissions to different environmental media;
- monitoring or modelled data on concentrations of the substance in the environment;
- dietary surveys providing information on ingestion of a substance from different types of food; and
- potentially, if relevant, monitoring data on concentrations found in human blood or breast milk.

At the local level, models may not be required to generate estimates of populations exposed at levels giving rise to the risks of concern. It may be possible to develop estimates of the number of people at risk based on population data and mapping of environmental concentrations above levels which would trigger a concern.

At the regional or EU level, however, it is likely that some form of fugacity model would be required. The EUSES model provides the ability to do this type of modelling, as do other software based models such as those used in LCIA. The key issue with the latter is whether they apply health statistics (i.e. NOAELs and not EC50s for example) which are relevant to REACH risk assessments.

Use of Dose-Response Data

Table 3.5 below presents quantitative risk estimates (i.e. a simplified dose-response function) for lung cancer associated with occupational exposure to Cr (VI) compounds (SCOEL/SUM/86 final document). The values in the table are based on an analysis of 10 epidemiological studies and were derived using a linear no-threshold model (HSE, 2007).

Table 3.5: Example Dose-Response Data for Lung Cancer

Excess relative lung cancer risk per 1000 male workers	Exposure (Working Lifetime to a range of Cr VI compounds)
5-28	0.05 mg/m^3
2-14	0.025 mg/m^3
1-6	0.01 mg/m^3
0.5-3	0.005 mg/m^3
0.1-0.6	0.001 mg/m^3

This type of data can be combined with the predicted worst case or a 'reasonable' worst case inhalation exposure estimates based on actual monitoring data, to estimate the excess relative lung cancer risk per 1,000 workers (over a 45 year working life).

This can be done, for example, by converting the data to a more easily used unit of measure expressed in terms of *units of exposure*[3]. This type of translation is illustrated in Table 3.6. It is based on the observed data provided in Table 3.5 and the assumption that:

> *one year's exposure for 100 workers to 1 mg/m^3 is equivalent to one unit of exposure*

On this basis the associated cancer risk per unit exposure over 45 year working life can be derived as:

Units of exposure at 0.05 mg/m^3 = 0.05 x 45 = 2.25
Excess cancers per unit of exposure at 0.05 mg/m^3= 5 observed ÷ 2.25 units = 2.22
28 observed ÷ 2.25 units = 12.4

[3] This approach was developed by RPA for application to chemicals as it provides a more readily usable metric than risks expressed in terms of a lifetime (with a similar approach used in nuclear field). It makes it easier to compare risks to costs and to acceptable risk criteria (which are often expressed as an annual risk).

Table 3.6: Excess Risks for Lung Cancer				
Exposure Level (lifetime working)	**Units of Exposure* (over 45 years)**	**Observed Excess Cancers per 1000 workers**	**Excess Cancer Risk per Unit Exposure* (i.e. per 1000 workers)**	
			Low	**High**
0.05 mg/m^3	2.25	5 – 28	2.22	12.4
0.025 mg/m^3	1.125	2 – 14	1.78	12.4
0.01 mg/m^3	0.45	1 – 6	2.22	13.3
** 1 unit of exposure = exposure for 1000 workers at 1 mg/m^3 for one year*				

These figures would then be combined with predictions on the number of people exposed to different concentrations from the exposure assessment to estimate the annual excess cancer risk for the low and high excess cancer risk dose-response scenarios.

For example, if it is predicted that 3,000 workers are exposed at 0.025 mg/m^3, then the predicted excess cancers per year would be equal to between 5.34 and 37.2 (= 1.78 x 3 and = 12.4 x 3, respectively). Application of these excess cancer risk estimates per unit of exposure to consumers or man via the environment would need to be adjusted for differences in level, duration and frequency of exposure between these populations and workers.

3.3.4 Step 3c: Epidemiology Based Quantification

Epidemiological data may be available for chemicals which have been identified in the past as posing risks to human health. This is more likely to be the case for chemicals giving rise to concerns for workers, but may also be relevant for some carcinogens and sensitisers relevant to consumer exposures or to exposures of man via the environment. It may also be the case for some chemicals in respect of developmental effects (e.g. IQ related issues).

If adequate and relevant epidemiological information is available, then it may be possible to use metrics such as:

- relative risks (RR) or odds ratios (OR) (see Section 3.2 and Section 5 of the Part 1 report for more discussion on these and other epidemiological-based measures of risk) for specific population groups to estimate the attributable fraction (AF) of diseases associated with particular activities or types of exposures; or

- to use prevalence or incidence data (depending on the nature of the disease being considered) to predict the likely change in prevalence or incidence with changes in exposures (see Section 3.3 and section 5 of the Part 1 report).

Such data will exist for the more well studied carcinogens, and may also exist for a range of sensitisers and other morbidity endpoints in relation to workers. There may also be limited data for a few chemicals with regard to developmental effects (e.g. IQ related issues). These types of approaches are more generally used for estimating disease cases associated with worker exposures and for man via the environment.

Attributable Fractions

There are several different approaches applied in practice for estimating the attributable fraction of a disease for exposures to a given chemicals (see also Section 3.6 of the Part 1 report). One approach would be as follows.

1. Based on literature review identify the most recent risk estimates [in the form of relative risk ratios (RRs) or odds ratios ORs)] for a given cancer/disease type; this should ensure that the studies take account of length and intensity of exposures, exposures to other chemicals which may have a similar mode of action and confounding factors such as smoking, sex etc. Care should be taken to ensure that the studies demonstrate an exposure-response relationship.

2. Determine a relevant exposure period (REP) for the type of disease of concern, e.g. 20 to 40 years for cancers.

3. Develop estimates of levels of exposure on a national or regional basis using workforce data and data on the proportions of workers subject to exposure in different industry sectors (e.g. from CAREX). This will need to include allowances for the changing numbers of people ever employed for the sectors considered over the period and for employment turnover in the industries considered.

4. Use of the above data (e.g. by applying Levin's equation[4] or other similar approaches) to calculate the attributable fraction (AF) of cancers relevant to exposure to the chemical of concern. This should include some degree of sensitivity analysis, for example by developing estimates both for the RR or OR quoted by different studies, but also the confidence intervals surrounding these (with these reflecting the level of random error surrounding the RR or OR estimate).

5. The AF would then be multiplied by the number of cancer registrations or cancer deaths (in the Member State or EU) in a given year to derive the number of cases attributable to occupational or environmental exposures. It would be standard to give separate estimates for men and women.

Box 3.3 provides an example of the use of the above approach to calculate AFs for six cancers and occupational exposures for Great Britain from Phase 1 of a major study carried out for the UK Health and Safety Executive (Ruston, Hutchings and Brown, 2007). The resulting AF estimate could be carried forward to Step 4 and the derivation of either DALYs as a measure in the change in disease burden or for economic valuation.

[4] Levin's equation, as given in the HSE report (Rushton *et al*, 2007), is:
AF = Pr(E) * (RR - 1) / [1 + Pr(E) * (RR – 1)
where: Pr(E) = the proportion of the population exposed, and RR = the risk ratio

Box 3.3: Attributable Fractions Calculated for Various Occupational Carcinogens

The overall occupational AFs for six cancers were investigated in a study for the UK HSE, with estimates derived using an approach based on Levin's equation and data on odds and risk ratios. The study estimated that 6.0% of cancer deaths in men and 1.0% in women in GB are due to occupation when taking into account established carcinogens only (total deaths due to occupation over all cancer deaths). The estimates were 8.0% and 1.5% respectively for established plus uncertain carcinogens.

Cancer site:	Attributable Fraction			Attributable Deaths		Attributable Registrations	
	Male	Female	Total	Male	Female	Male	Female
Established carcinogens only (IARC Group 1 and 2A, strong human evidence)							
Bladder	1.3%	0.6%	1.0%	40	10	8	17
Leukaemia	0.3%	0.5%	0.2%	4	5	5	6
Lung	16.5%	4.5%	11.6%	3,137	599	3,509	680
Mesothelioma	85-90%	20-30%	74-80%	1,450	75	1,450[#]	75[#]
NMSC	11.8%	3.0%	8.4%	38	6	3,992	855
Sinonasal	34.1%	10.8%	23.4%	24	6	74	18
AFs for all six				6.0%	1.0%	5.4%	1.0%
Established + Uncertain carcinogens (IARC Group 1 and 2A, strong and suggestive human evidence)							
Bladder	11.6%	2.0%	8.3%	362	32	816	57
Leukaemia	2.7%	0.8%	1.7%	58	11	93	15
Lung	21.6%	5.5%	15.0%	4,106	728	4,594	826
Mesothelioma	98%*	90%*	97%*	1,650	270	1,650[#]	270[#]
NMSC	11.8%	3.0%	8.4%	38	6	3,992	855
Sinonasal	64.3%	18.4%	43.3%	45	11	140	31
Total				6259	1058	11284	2054
Total all cancers in GB				78,237	71,666	167,506	164,586
AFs for six cancers combined (out of all GB cancers)			4.9%	8.0%	1.5%	6.7%	1.2%

* Includes cases described as due to para-occupational or environmental exposure to asbestos.
[#] Taken as equal to attributable deaths for this short survival cancer.

Source: Ruston L, Hutchings, S and Brown T (2007): The burden of occupational cancer in Great Britain, Research Report RR595, for the UK Health and Safety Executive

Prevalence or Incidence Based Approaches

There is a considerable body of literature on the prevalence and incidence of many different types of disease for both worker and the general population (man via the environment).

A suggested approach for using such data to calculate the burden of occupational disease is as follows:

1. Obtain data on incidence rates (per million) from the literature, where available. Where not directly available, then some manipulation of data may be required:

a. calculation of incidence rates using proportion attributable to work where the diagnosis is generic; or
b. calculation of incidence rates from prevalence rates for occupational or generic disease using an estimated mean duration.

2. Estimate the proportion of cases that may be attributable to exposures to the substance of concern for the uses that would be affected by restrictions or authorisation.

3. Apply proportion from Step 2 to Step 1.

4. Use the incidence rate calculated in Step 3 to estimate the preventable number of disease cases for the EU workforce.

This type of approach requires several assumptions to be made by the analysts carrying out the work (see also the discussion below on consumer health), and thus is likely to be less reliable than an assessment based on relevant RR or OR ratios for different occupations or the use of dose-response functions.

Box 3.4 below provides an example of how this type of approach has been applied in the past in the context of REACH, in this case in relation to chronic obstructive pulmonary disease (COPD) and calculation of the incidence of occupational disease cases.

Box 3.4: Calculating the burden of chronic obstructive pulmonary disease in the EU

A study on the impact of REACH on occupational health by Pickvance et al (2005) underlined a methodology used to calculate the burden of diseases, with regards to occupational exposure. This method would firstly obtain incidence rates (per million) using different methods, obtain incidence rate of new cases of each occupational disease using incidence data were available, calculate the incidence rates using proportion attributable to work where the diagnosis is generic and calculate incidence rates from prevalence rates for occupational or generic disease using an estimated mean duration. The following example makes light, however, of the calculation of occupational disease burden when a limited amount of information is available (with reference to chronic obstructive pulmonary disease, COPD).

The reason that COPD was included within the report was because statistics calculated by The European Trade Union Bureau for Health and Safety suggested that 36% of occupational related respiratory diseases were related to chemicals exposure. A further reason for this was because there is a short time lag between exposure and effects.

The findings of the study stated that there was little firm data on occurrence levels of new cases of work-related COPD available. In the absence of this data the 'preferred' method used was to derive figures from population attributable risk (PAR).

PAR's from a range of previous studies failed to distinguish between different types of occupational respiratory disease (e.g. Asthma), and thus a conservative estimate of 15% was used in addition to another conservative estimate (derived from previous studies) that 5% of the adult population had COPD. From this, the prevalence of COPD attributable to work was calculated as 0.75%. The age of onset was established to be in the latter part of working life, with a mean duration of 10-20 years until the end of working life, so using a duration rate of 15 years an incidence rate of 0.05% per annum was calculated.

Box 3.4: Calculating the burden of chronic obstructive pulmonary disease in the EU

The table below shows the incidence of COPD, using data from the PAR method described above, and also includes incidence data derived from the European survey on working conditions and the European labour force survey (from EUROSTAT). The estimated incidence rate of 0.05% gave a work related incidence of COPD estimated (conservatively) at 500 people per million, per year, within the EU.

Incidence of COPD per million per year in the EU	
Source	**Incidence data**
Self-reporting (ELFS – 300K)	130
PAR method (Balmes – 15%)	500
ESCW (P = 3%, duration = 10 years)	3000
Estimate	500

Source: Adapted from: Pickvance S, Peters J & El-Arifi K (2005): The impacts of REACH on occupational health with a focus on respiratory and skin diseases, Final report.

3.3.5 Step 3d: Assessment of Potential for Valuation

At the end of this Step a decision needs to be made as to whether it would be both appropriate and feasible to progress to valuation of any predicted changes in the number of disease cases resulting from application of Steps 3b or 3c. This could be through using either:

- DALYs (or QALYs) in order to take into account chronic effects or benefits across multiple disease endpoints;
- use of willingness to pay estimates to place a value on the benefits from a reduction in the number of fatalities due to chemical exposures or changes in the number of disease cases; or
- monetary valuation of changes in the resource costs associated with illnesses, such health care-related costs, costs associated with lost productivity, costs from lost worker days, etc.

DALYs and QALYs are health utility measures and have been, in most cases, given a monetary value to justify interventions (see Section 6.3.2 of the Part 1 report). They can be particularly useful when comparing different health outcomes, for instance when use of an alternative substance may cause a different health effect to that of the substance of concern. In such instances, they can help to inform the decision as to the trade-off between different substances.

Other approaches to valuation include health care costs and loss of work days and productivity. Although these indicators are available at EU level, it needs to be acknowledged that they tend to underestimate the full value of the impacts. Because of this, WTP values to avoid an episode of a specific health outcome could also be considered (discussed below).

3.4 Step 4 – Valuation of Health Impacts

3.4.1 Introduction

If it has been possible at Step 3 to quantify the number of cases of different healthy effects that would be avoided through either restrictions or a refused authorisation, then there are two main options for the valuation of their socio-economic importance.

For example:

1) monetary valuation of the health benefits. This could either involve estimation of individuals' willingness to pay (WTP) to avoid a particular disease or may be limited to only the quantification of savings in health care costs and/or reductions in lost productivity (the extent to which WTP values are available that can be used validly within a benefits transfer based approach may be limited). If both WTP values are used and estimates are developed of savings in health care and other resource costs such as lost work time and lost productivity, then care is required to ensure that double-counting does not occur; this is because some WTP estimates may include elements related to lost work time / lost productivity, for example; or

2) the more generally available approach may be to value each disease case in terms of the associated reduction in DALYs, and to then multiply these across the number of cases avoided due to risk reduction. In addition, estimates of changes in DALYs, should be complemented by a further assessment of savings in health care costs and/or reductions in lost productivity where the data are available and this would not lead to double-counting.

Research is currently being carried out into the potential for translating DALYs into monetary values. It may be possible to draw on the outcomes of this research to place a standardised € per DALY figure on changes in health impacts. DALYs would appear to be preferred to QALYs in the context of ERACH as they take into account the fact that a year of life may not be equal depending on factors other than illness, such as age. In addition, they may be better at capturing impacts related to changes in health from, for example, neurological conditions which do not result in death but can account for a significant percentage of years lived with a disability (see also Section 6.3 of the Part 1 report).

The impacts with each disease would need to be valued individually, and totals should be provided for each disease and then across all diseases where relevant. See also the Annexes to the ECHA Guidance on SEA for further discussion of the use of both monetary valuation and DALYs (or QALYs).

Within this logic framework, it is not proposed that MS Authorities and authorisation applicants would undertake original studies to develop the disability weights used to determine DALYs lost for different disease types or original WTP valuation studies. Instead it is assumed that the most appropriate level for such work to be carried out

would be at the EU level with the aim of developing transferable DALY estimates, VOSLs and VOLYs, and morbidity-based WTP values specific to the types of health impacts likely to arise from the types of chemicals subject to restriction and authorisation.

However, there are a range of available data sources which can act as 'look-up' tables in the case of DALYs (see Section 6.3 of the Part 1 report) or benefits transfer values in the case of WTP estimates (see Section 6.4 of the Part 1 report). There will also be a role though for the generation of estimates of the economic costs associated with one case of a disease using actual health care estimates or wage and other productivity data.

Based on the above, there are four components to this step (see Figure 3.4):

i) Step 4a: Valuation of change in the number of disease cases in terms of DALYs, and comparison to WHO data on the EU disease burdens or to WTP valuations;

ii) Step 4b: Calculation of the savings in medical costs, productivity losses, administrative costs etc. associated with a reduction in the number of disease cases;

iii) Step 4c: Calculation of the savings set out in Step 4b plus estimation of the willingness to pay associated with the reduction in disease cases using available benefits transfer estimates; and

iv) Step 4d: Aggregation of estimates and a check for double counting where valuation has been carried out using multiple approaches.

Table 3.7 provides a checklist for the types of information that would have to be considered and reported on in Step 4, drawing on data derived during Stages 3a, b or c and other information in the literature on the appropriate values that should be attached to particular health conditions.

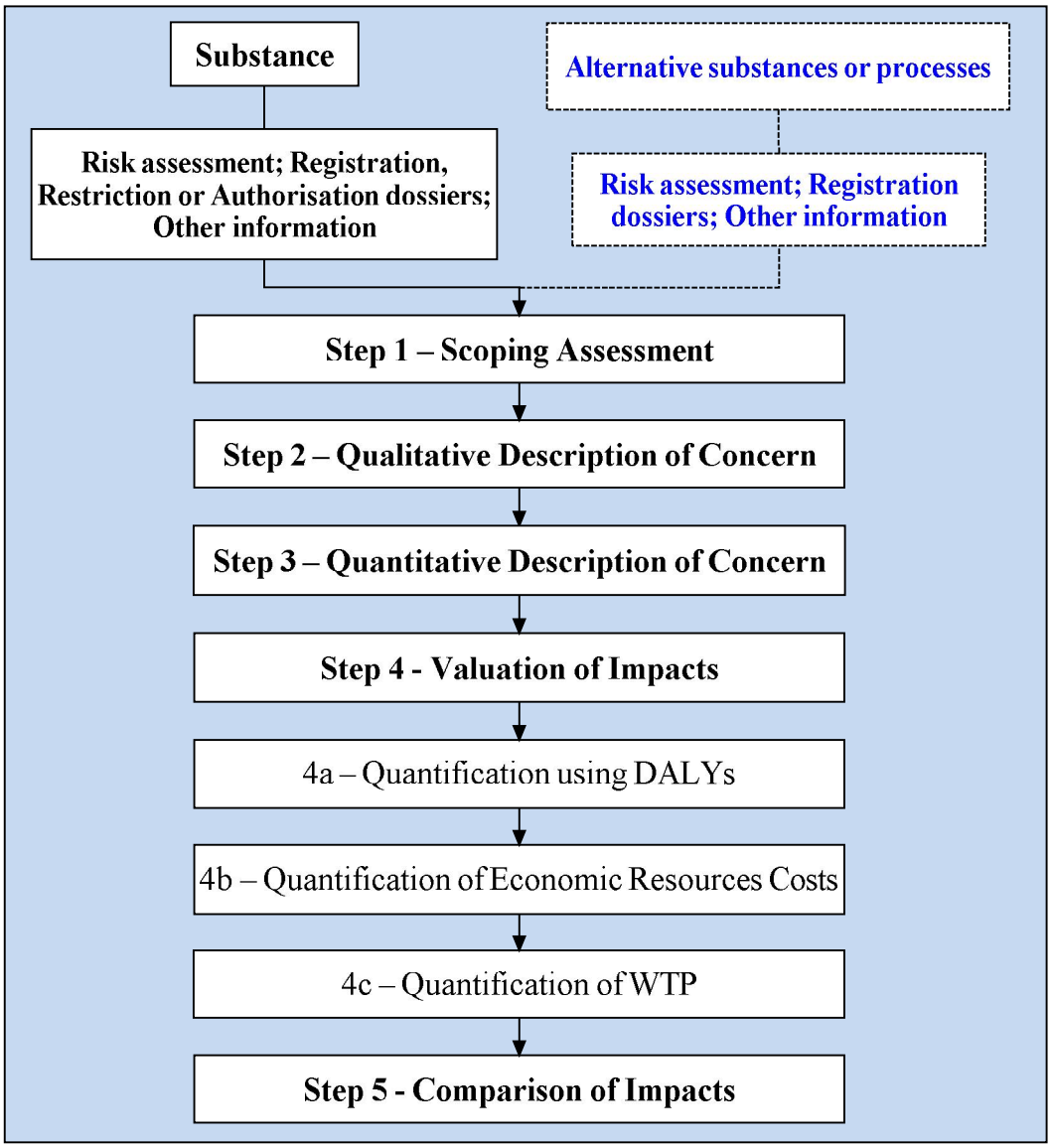


Figure 3.4: Step 4 of Logic Framework for Human Health

Table 3.7: Examples of Information Needs, Approaches and Reporting Outputs for Step 4	
Reporting Headlines	**Data / Discussion Areas and Outputs**
Health Impact	Number of cases (or deaths) avoided
Basis for estimation	DALY, QALY, WTP etc.
Method of quantification	Assignment of economic values to overall change in DALY or other economic metric
Output	Annual costs avoided
Sensitivity analysis	Derivation of estimates based on worst case, realistic and mean/average value assumptions

3.4.2 Step 4a: Quantification Using DALYs

Calculation of Reduction in DALYs

Table 3.8 sets out the number of DALYs associated with one case of illness for 49 non-communicable diseases, representative for the world in 1990 as given in Huijbregt *et al* (2005)[5]. Applying equal weightings for the importance of 1 year of life lost for all ages and no discounting for future damages, a DALY is the sum of years of life lost (YLL) and years of life disabled (YLD) caused by disease type:

$$DALY = YLL + YLD$$

Huijbregt et al (2005) identify a number of issues that should be taken into account when interpreting these values.

1. The DALYs given in Table 3.8 are based on world averages. Thus, for developed regions or countries, the DALYs gained or lost may be lower than those given in the Table, as medicine is more advanced than the world average. Hence in the context of REACH, the values may overestimate the benefits of banning or authorising the substance.

2. The DALYs below are calculated without applying age-specific weighting and without discounting future health damages, which may overestimate the number of DALYs gained or lost.

3. The use of YLDs includes subjective judgments on the weighting of health disabilities. For cancer diseases, DALYs and years of life lost differ by up to a factor of 1.2, indicating that the inclusion of years of life disabled does not have a large influence on the DALY outcomes. The situation is different for a number of non-cancer diseases, such as for musculoskeletal, neuropsychiatric and sense-organ diseases. For these disease types, the years of life disabled has a dominant contribution to the number of DALYs. As health-preference measurements tend to be rather stable across groups of individuals and regions of the world (Hofstetter and Hammitt, 2002, in Huijbregt M A.J. *et al*, 2005), it is expected that the influence of subjective judgment in years of life disabled estimates on the DALY outcomes will be small. This highlights the adequacy of using DALYs for morbidity cases or non-fatal illnesses as opposed to fatal health outcomes as the values are likely to be less subjective.

Last and not least, when applying DALYs, the population exposure and probability of occurrence are as follows:

[5] Mark A.J. Huijbregts, Linda J.A. Rombouts, Ad M.J. Ragasand Dik van de Meent (2005): Human-Toxicological Effect and Damage Factors of Carcinogenic and Noncarcinogenic Chemicals for Life Cycle Impact Assessment, Integrated Environmental Assessment and Management — Volume 1, Number 3—pp. 181–244.

*Damage (as DALY caused by a number of diseases) = Npop * ΣDALYe * Re*

where *Npop* is the total population number, *DALYe* is the DALY for disease type *e*, and *Re* is the probability of occurrence of disease type *e* in the human population.

Table 3.8: Average DALYS for Different Disease Types

Disease type	YLL	YLD	DALY
Cancer			
Mouth and oropharynx cancer	5.7	0.5	6.2
Oesophagus cancer	17.6	0.4	17.9
Stomach cancer	12	0.6	13.6
Colon and rectum cancer	8	0.8	8.8
Liver cancer	22.1	0.4	22.5
Pancreas cancer	15.9	0.3	16.2
Trachea, bronchus and lung cancer	16.2	0.3	16.5
Melanoma and other skin cancer	6.1	0.2	6.3
Breast cancer	7.2	0.3	7.6
Cervix uteri cancer	11.7	0.3	12.0
Corpus uteri cancer	3.7	0.4	4.0
Ovary cancer	13	0.3	13.3
Prostate cancer	3.3	0.5	3.9
Bladder cancer	4.6	0.4	5.0
Lymphomas and multiple myeloma	13.9	0.3	14.2
Leukemia	28	0.3	28.3
Cancer average	*11.0*	*0.5*	*11.5*
Neuropsychiatric conditions			
Bipolar disorder	0.1	0.7	0.8
Schizophrenia	1.9	23.4	25.3
Epilepsy	0.5	0.3	0.8
Dementia	1.3	5	6.2
Parkinson's disease	1.8	4.7	6.5
Multiple sclerosis	6.5	13.2	19.7
Obsessive-compulsive disorder	0	0.2	0.2
Panic disorder	0	0.1	0.1
Sense-organ diseases			
Glaucoma	0.3	5.6	5.9
Cataract	0.1	1.0	1.1
Cardiovascular diseases			
Rheumatic heart disease	19.2	1.3	20.5
Ischemic heart disease	8.5	0.7	9.2
Cerebrovascular heart disease	19.2	1.3	20.5
Inflammatory heart disease	5	0.5	5.5
Respiratory diseases			
Chronic obstructive pulmonary disease	5	3.2	8.2
Asthma	0.1	0.4	0.6
Diabetes mellitus	1.3	0.9	2.2
Digestive diseases			

Table 3.8: Average DALYS for Different Disease Types			
Disease type	**YLL**	**YLD**	**DALY**
Peptic ulcer	0.6	0.3	1.0
Liver cirrhosis	17	2.6	19.5
Genitourinary diseases			
Nephritis and nephrosis	11.6	0.8	12.4
Benign prostate hypertrophy	0.04	0.3	0.4
Musculoskeletal diseases			
Rheumatoid arthritis	0.1	1.4	1.5
Osteoarthritis	0	2.7	2.7
Congenital anomalies			
Abdominal wall defect	45	0	45
Anencephaly	80	0	80
Anorectal atresia	16	0.2	16.2
Cleft lip	80	0	80
Cleft palate	2.6	3.6	6.2
Renal agenesis	5.8	7.8	13.6
Down's syndrome	19.5	36.4	55.9
Congenital heart anomalies	18.5	20.1	38.6
Spina bifida	32	37.9	69.9
Noncancer average	*1.7*	*1.0*	*2.7*

Key: Shading denotes diseases which may be caused by chemical exposures but there is conflicting evidence (e.g. a cleft palate) or for which there are known chemical causes (e.g. Down's syndrome)
Sources: Huijbregts M, Rombouts L, Ragasand A, and van de Meent D (2005): Human-Toxicological Effect and Damage Factors of Carcinogenic and Noncarcinogenic Chemicals for Life Cycle Impact Assessment, Integrated Environmental Assessment and Management — Volume 1, Number 3—pp. 181–244.
(Labreche etl al, 2010)
(Goldman, 2010), (Tanner et al, 2009)
(Stamper et al, 2009)
(HSE, 2006)
(HSE, 2004)
(Hodgson et al, 2006), (Soderland et al, 2010)
(Bianchi et al, 2000), (Bonnot et al, 2001), (Kallen et al, 2007)
(Blatter et al, 1997), (Shaw et al, 1999)

Although many of the above diseases are not known to be related to chemical exposures. However, it may be possible for a trained clinician to make an expert judgement on the degree to which the type of disease caused by a particular chemical exposure may be similar to one of the diseases listed above. For example, it may be possible for a clinician to link a peptic ulcer to a chemically induced irritation of the gastro intestinal tract. However, all of the diseases given in shaded cells have either been linked (although not proven) to chemical exposures or are known to result from certain chemical exposures.

Comparison to Data on Disease Burdens

Data are available from the World Health Organisation (WHO) on both the attributable number of deaths due to different risk factors and the attributable number of standard DALYs due to different disease risk factors. These can be found at:

http://www.who.int/healthinfo/global_burden_disease/risk_factors/en/index.html

In addition, the WHO provides regional estimates of the burden of disease in terms of mortality, incidence, prevalence, and years of life lost and DALYs by age, sex and cause (with the latest year for which these are available being 2004). This includes data for DALYs for end-points such as respiratory illnesses which are directly relevant to chemical exposures.

These WHO data for Europe could be compared to the change in the number of DALYs associated with reductions in exposures to the chemical of concern to provide an indication of their relative significance.

Comparison to WTP Values

The translation of DALYs or QALYs to monetary values is discussed in the ECHA Guidance on SEA, and further guidance on this is expected soon from the EuroQuol study being carried out for the European Commission.

An alternative approach to trying to directly convert DALYs to monetary values is to see if there are WTP values that cover a similar type of disease and which may provide a proxy valuation. In other words, WTP values for avoidance of a respiratory illness over a year (see also Section 3.4.4 below) could be used as a proxy for the value of reducing the number of DALYs lost due to a particular chemically-induced respiratory disease.

3.4.3 Step 4b: Quantification of Economic Resource Costs of a Disease Case

There are two components to the resource costs of an illness. The first is the actual costs of the illness (COI), which are the easiest to measure. Estimation of these costs is based either on the actual expenditures associated with an illness, or on the expected frequency of the use of different health services required for treatment of an illness. Part of these costs may be incurred by the individual directly and others through public or private medical care (including insurance).

The second component of resource costs is that of lost earnings and/or time. The costs of lost earnings are typically valued at the after-tax wage rate (for the work time lost), and at the opportunity cost of lost leisure time. Typically the latter is between one half and one third of the after-tax wage. Complications arise when a worker can work but is not performing at his/her full capacity or has to move to a change which is less productive. In such cases, an estimate of the productivity loss should be included in the valuation of lost time. When an individual is off work due to an occupational

illness or is unable to continue in a higher paid job, they may also experience a loss of income. (Note that because these estimates only include a measure of resource costs, they will underestimate the full cost of an illness because they do not provide a measure of an individual's full WTP to avoid an illness).

Total resource costs are then estimated as the sum of:

- actual expenditures (e.g. medicines, doctor and hospital bills) per day's illness; plus
- the value of lost earnings and leisure time per day's illness;
- multiplied by the number of days sick times the number of cases of the illness.

Data on medical and other costs will need to be collected from national or private health care services. The ECHA Guidance on SEA and Restrictions provides some standard valuations as used in CAFÉ for (2003 prices):

- Respiratory and cardiac hospital admissions: €2134 per admission; and
- Consultations with primary care physicians: €57 per consultation.

Other illustrative cost of illness estimates are given in Table 3.9 at the end of this section. Some of the values are fairly old and not all are from EU studies. However, they are illustrative of the types of data that can be found from searches on the internet.

Data on the number of days associated with different types of illnesses will also need to be collected from reference to either medical studies, health care services or, in the case of workers, some of the statistical data published by health and safety authorities.

For example, the UK Health and Safety Executive's Economic Analysis Unit provides standardised appraisal values for use in HSE impact assessments (see http://www.hse.gov.uk/economics/eauappraisal.htm for links to a range of resources). This includes estimates for the value of both resource costs and lost output (productivity losses). In this case, resource costs include administration, recruitment and medical treatment costs. Lost output is calculated as "equal to the labour cost that is normally incurred in employing the absent worker, plus any sick pay". Table 3.10 presents the UK HSE figures, including estimates of the intangible or human costs of an illness (i.e. an individual's willingness to pay to avoid an illness – see below).

Table 3.10: UK HSE Economic Analysis Unit Appraisal Values for 2006				
	Resource costs	**Lost output**	**Human cost (WTP)**	**Total**
Fatality	£900	£520,700	£991,200	**£1,500,000**
Major injury	£5,800	£16,200	£18,400	**£40,500**
Other reportable injury (O3D)*	£500	£2,600	£ 2,700	**£5,800**
Minor injury	£50	£100	£200	**£350**
Average case of ill health	£800	£2,700	£6,700	**£10,100**
* Under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995 (RIDDOR) O3D refers to those injuries which keep an employee off normal work for more than 3 days; see http://www.hse.gov.uk/pubns/priced/l73.pdf				

An example illustrating how cost-of-illness estimates have been derived in the context of EU policy making is given in Box 3.5, based on work carried out by the University of Sheffield to feed into the impact assessments on the introduction of REACH.

Box 3.5: Calculating the cost of chronic obstructive pulmonary disease in the EU

As discussed in Box 3.4, the study by Pickvance et al (2005) developed a methodology to quantify the costs of chronic obstructive pulmonary disease (COPD). The analysis of costs in this case was divided into three categories, covering health service costs, productivity costs and the value of health-related quality of life that has been lost to the individual. Due to absence of primary data, both health service costs and productivity costs were established from reviews of literature.

In the study, health care costs accounted for the resources used to treat COPD. A significant amount of relevant previous literature was found, providing estimates for numerous EU Member States. Health care costs included the following resource items; inpatient, outpatient, emergency room and general practitioner visits, medication use and laboratory tests. Final estimates of health care costs for COPD between Member States ranged between €530 (in France) and €3238 (in Spain).

Productivity costs relate to the value of production lost due to the death, disability or ill-health of an individual. In this study, ideally, it was noted that costs would be based upon the assessment of 5 categories of work-related disability. However the study was constrained by a lack of published detail and as mentioned above relied upon a review of literature. The literature from which information was sourced had used the traditional human capital approach (which estimates productivity cost of illness based on the predicted remaining lifetime earnings in the absence of occupational disease) in some cases and the friction cost method (which recognises that society will restore the same production levels following a period of adaption) in others. To provide results for both the human capital and friction cost methods, the original human capital approach data was converted to equate to friction costs and vice versa; data from the literature was also adapted to describe costs for individuals of working age. Excluding the costs for Italy, which was identified as an extreme outlier within the study, costs ranged between €833-2886 for the human capital approach and €297-1030 for the frictional cost approach.

Health related quality of life costs for occupational COPD were calculated by the multiplication of an estimated utility decrement over an assumed duration of symptoms and by the value of a QALY. The estimated utility decrement ranged between 0.05 and 2 and the assumed duration was between 20 and 30 years. The study then converted the QALY threshold of £20,000-£30,000 set by the UK National Institute for Health and Clinical Excellence into Euro's giving €28 000- €43 000. Utility effects were then discounted at 3.5% per annum and the annual health related quality of life cost was estimated to be between €2 100-€163 000 (€1 400-€8 600 per annum). The final cost impact summary for COPD can be seen in the table given below.

Box 3.5: Calculating the cost of chronic obstructive pulmonary disease in the EU

Cost impact summary of COPD (€)

Disease	Health service costs	Productivity costs*		Health related quality of life costs	Aggregate annual costs	Mid-point of cost estimates
		Human capital approach	Friction cost approach			
COPD	530-3228	833-2866	297-1030	1400-8600	2337-13651	7994

The study concludes that the best present estimate for COPD cost is defined as the mid-point of the estimated range of the cumulative cost estimate (€ 7994 per case). Despite a relatively wide range of available literature, the study noted that there remained a significant source of uncertainty due to a high level of divergence in the cost estimates from different EU Member States. It is also of note that many necessary assumptions may also have decreased accuracy.

Pickvance S, Peters J & El-Arifi K (2005): The impacts of REACH on occupational health with a focus on respiratory and skin diseases, Final report.

3.4.4 Step 4c: Quantification of WTP to Avoid a Disease Case

A wide range of studies have been undertaken to develop estimates of individuals' willingness to pay to avoid different illnesses or death either due to workplace exposures or to environmental exposures to pollutants. These past studies can be drawn upon using benefits transfer techniques to provide an indication of the 'human costs' associated with illnesses/diseases stemming from chemical exposures (see also Annex B of the ECHA Guidance on SEA and Restrictions for further discussion).

Although a wide range of existing studies are reported on below, it is unlikely that WTP valuations will be available for many of the health effects likely to be the focus of REACH restriction or authorisation decisions. As a result (and as may also be the case for developing estimates of DALYs), the advice of clinical experts or medics may be required to make a link between the available WTP studies and a particular health effect. For example, it may be possible to link a particular type of health effect to a 'restricted activity day' (see Table 3.12 below), to enable the valuation of the benefits of avoiding a day's illness. Alternatively, it may be possible to make such links based on information on the numbers of DALYs associated with different health impacts; where two different diseases would result in the same number of DALYs, then one may be able to assume that an individual's WTP to avoid a case of each disease would be similar.

However, where such assumptions are made, it will be important that the basis for them is clearly explained and that the uncertainty arising from the assumptions is highlighted.

Existing Valuations

The SEA Guidance for preparing a Restrictions dossier provides unit costs for mortality and morbidity linked to exposure to pollution. The figures quoted in the

Guidance for mortality due to chemicals exposure are given in Table 3.11 below, in 2003 price levels (they therefore need to be adjusted to current prices). Table 3.12 provides unit cost estimates for different types of acute morbidity effects (again in 2003 prices). Note that the ECHA Guidance also stresses that before these unit cost figures are used that checks are made to see if the values have been superseded by more recent studies.

Interestingly, one reviewer of this framework noted that it may not be appropriate to use VOLYs to value changes in the number of cancer cases. This is because the cancers are caused by a direct exposure to a substance. This is different from the air pollution context where VOLYs have been promoted as death is generally due to other factors than air pollution, with pollution instead affecting the timing of a person's death rather than being the main cause[6].

Table 3.11: Reference Values for Chemicals and Mortality (2003 prices)

	Central value	**Sensitivity value**
Value of a statistical life	€ 1,052,000	€ 2,258,000
Value of a life year lost	€ 55,800	€ 125,200
Source: NewExt, 2003		

Table 3.12: Unit Cost Estimates for Acute Morbidity Effects (2003 prices)

Effect	**Value**
Restricted activity day	€89 per day
Minor restricted activity day	€41 per day
Symptom day	€41 per day
* average value for working adult *Source:* Ready et al, 2004 according to CAFÉ, 2005	

The ECHA Guidance also provides estimates for chronic effects on morbidity, drawn from US studies which are related to the most severe definition of chronic bronchitis. Based on these, but adjusted to a case of "average severity" by the scalar estimated by Krupnick and Cropper (1992) the following benefit transfer values have been derived in the context of chemicals by ECHA (see the Guidance for further discussion):

- Low range estimate: €120,000
- Central range estimate: €190,000
- High range estimate: €250,000

See also the ECHA Guidance for further discussion on the validity of using these estimates; in particular before these unit cost figures are used that checks are made to see if the values have been superseded by more recent studies.

Additional estimates from other studies carried out in the US and the EU are provided in the Part I report and in Table 3.13 below. Again many of these are for the US and therefore can only be considered indicative of values that might be held by the EU population.

[6] Personal communication, Mike Holland, 2010.

3.4.5 Step 4d: Aggregation and Checking for Double-counting

If more than one valuation approach has been used, for example, the estimate of the resource costs under Step 4b and the use of WTP estimates under Step 4c, then it will be necessary to develop aggregate estimates of the environmental benefits of reduced chemical exposures. However, care should always be taken to ensure that individual estimates are reported separately in the SEA prior to aggregation; in other words, the estimate value of damages associated with each environmental impact carried forward to Step 5 should be reported on its own, prior to be combined with other damage estimates to develop an indication of total environmental impacts.

It will also be important to check that there is no double counting between WTP estimates and either market based valuations or revealed preferences valuations.

1) If the assessment has included the use of WTP–based estimates, estimates of savings in health care and estimates of other resource costs such as lost work time and lost productivity, then care is required to ensure that double-counting does not occur; this is because some WTP estimates may include elements related to lost work time / lost productivity; or

2) If estimates of changes in DALYs have been developed, then care should be taken to ensure that any resource cost estimates also included in the analysis do not lead to double counting, for example, where lost productivity forms an element of the number of DALYs per disease case.

The approach to developing estimates of aggregate health benefits will depend on the approach being adopted more generally for the SEA. See also Step 5.

Table 3.9: Various Cost of Illness Estimates from Literature			
Illness	**Source**	**Estimate**	**Comments**
COI of Parkinson's disease	Winter *et al*, 2010	Mean total costs varied from €2,620-€9,820 per person	2009? Carried out over 6 European countries. Per patient, per 6 months.
Total COI (for direct costs and costs of care) for dementia for EU 27	Wimo *et al*, 2009	€160.3 billion	Doesn't include productivity costs, not per patient. Time span unclear.
Cost per person with dementia for each WHO region of Europe	World Alzheimer Report, Alzheimer's Disease International, 2010	Western Europe: €29,830 ; Central Europe: €12,770; Eastern Europe: €7,600	Only Europe figures presented here. US$ 2009
COI of cases of depression	Luppa *et al*, 2007 (literature review)	Estimates for direct costs ranged from €750 - €1,900; €1,520 – 2,800 for morbidity costs	US$2006. Wide range of estimates due to perceived lack of methodological similarity of studies reviewed. Unclear if wider productivity costs etc taken into account.
COI of depression for Europe per annum	Sobocki *et al*, 2006	€118 billion (in 2004)	1% of Europe's GDP
'Health and disability costs' of employees with depression	Druss *et al*, 2000	€5,700 annually per employee	US$1999. Not clear how 'health and disability costs' defined – e.g. whether it includes loss of productivity
COI of panic disorder	Batelaan *et al*, 2007	€10,269. Sub-threshold panic disorder cost estimated at €6,384	€2006. Includes healthcare etc and productivity costs.
Indirect cost of ischemic heart disease to employers	Guico-Pabia *et al*, 2001	€210 per employee	$US2000
Total EU-wide cost of cardiovascular disease	Leal, 2008	€189 billion in	€2006
Total EU-wide cost of cerebrovascular disease	Leal, 2008	€37 billion +	€2006. Leal figures are from a PPT and fairly unspecific/unexplained.
Average EU COI per capita of Cardiovascular disease	Leal, 2008	€223	€2006. Leal figures are from a PPT and fairly unspecific/unexplained.
Direct cost of COPD (Netherlands)	Vestbo, citing Pauwels and Rabe (2004)	€665, per patient, per year	2003?
Social cost of COPD (UK)	Vestbo, citing Britton (2003)	€1,192	2003?
Cost of COPD exacerbation	Vestbo, citing Rutten-Van Molken	Mild: €86; Moderate: €579; Severe: €4,007	2003?

Table 3.9: Various Cost of Illness Estimates from Literature			
Illness	**Source**	**Estimate**	**Comments**
(Netherlands and Belgium)	and Oostenbrink (2004)		
Lifetime loss of earnings due to care of child with spina bifida	Tilford *et al* (2008)	€209,450	$2002. Based on carers working on average 7.5 – 11.3 hours less per week, using a 3% discount rate
Life time medical cost of spina bifida	Case & Canfield (2009)	€768,270	$2008
Cost (COI) per new case of abdominal wall defects	Enviros, EFTEC, DEFRA, 2004 (Waitzman *et al*, 1995)	€212,473	£2003. US study, intangible costs excluded, direct and indirect costs including lost productivity included.
COI per new case of neural tube defects	Enviros, EFTEC, DEFRA, 2004 (Waitzman *et al*, 1995)	€353,160 - €605,830	£2003. Intangible costs excluded, direct and indirect costs including lost productivity included.
COI for Asthma (Denmark)	DEPA 2004 (Serup-Hansen *et al*)	€269	Kr2004. Based on cost of individual asthma attach.
COI for headache (Denmark)	DEPA 2004 (Serup-Hansen *et al*)	€48	Kr2004. Headache defined as "two painful and splitting headaches during the day. Each period of headache will last 2 hours".
COI for contact allergy (Denmark)	DEPA 2004 (Serup-Hansen *et al*)	€39,015	Kr2004. Cost of allergy for rest of lifetime, based on assumption that average allergy contracted at of of 40 with a yearly discount factor of 3%.
COI for lung cancer (Denmark)	DEPA 2004 (Serup-Hansen *et al*)	€1,304,970	Kr2004. Based on Markov model of disease course. Assumed average age of patient at first occurrence is 50 with a yearly discount factor of 3%.
COI for non-melanoma skin cancer	DEPA 2004 (Serup-Hansen *et al)*	€33,633	Kr2004. Estimate made on basis of patients being cured within a year.
COI for gastrointestinal illness associated with exposure to polluted recreational coast waters	Remoundou and Koundouri, 2009 (citing Dwight *et al*, 2005)	€32	€2005. Dwight *et al*, 2005 study covered US.
COI for acute respiratory disease associated with exposure to polluted recreational coast	Remoundou and Koundouri, 2009 (citing Dwight *et al*, 2005)	€67	€2005. Dwight *et al*, 2005 study covered US.

Table 3.9: Various Cost of Illness Estimates from Literature			
Illness	**Source**	**Estimate**	**Comments**
waters			
COI for ear ailment associated with exposure to polluted recreational coast waters	Remoundou and Koundouri, 2009 (citing Dwight *et al*, 2005)	€33	€2005. Dwight *et al*, 2005 study covered US.
COI for eye ailment associated with exposure to polluted recreational coast waters	Remoundou and Koundouri, 2009 (citing Dwight *et al*, 2005)	€24	€2005. Dwight *et al*, 2005 study covered US.
Cost to society saved (in terms of COI) from preventing an individual contracting occupational asthma	Health and Safety Executive, 2003	€61,732	£2003. Working on a 10 year time span, combining loss of income and medical treatment.
COI for visit to emergency room due to respiratory illness	AEA Technology, 2005 (citing Ready *et al*, 2004)	€717	€2003.
Direct and Indirect costs of per employee-day absence	AEA Technology, 2005	€253	1998? Based on figures from the UK CBI (1998). Unclear whether figures updated to 2005 currency.

Table 3.13: Willingness to Pay Estimates for Various Health Effects			
Measure	**Source**	**Estimate**	**Comment**
WTP for various reliefs of dementia, surveying both patients and carers (also spouses)	Koenig and Zweifel, 2004	Stabilisation (condition not worsening): patients – €6,760, carers – €60,750; Cure: patients - €18,100, carers - €102,650; No burden (relief of carer): patient - €19360, carer - €30,880.	Mean for caregivers is strongly influenced by one respondent who was willing to pay US$ 2.8 mn. for stabilization or cure. Koenig and Zweifel suggest another reason patient figures are lower are due to 'protest zeroes' and refusals to pay.
WTP for various reliefs of dementia, surveying both patients and carers (also spouses), in terms of percentage of wealth	Koenig and Zweifel, 2004	Stabilisation: patients – 14%, carers – 24%; Cure: patients – 22%, carers – 31%; No Burden: patients – 22%, carers – 18%.	2003? Recommended as more accurate of actual WTP preferences, but harder to determine an appropriate monetary value from.

Table 3.13: Willingness to Pay Estimates for Various Health Effects			
Measure	**Source**	**Estimate**	**Comment**
WTP of carers of relatives suffering from dementia for a reduction of burden level from 'moderate' to 'low'	Koenig and Wettstein, 2002	€1,675 per annum	2001. Qualitative values of 'moderate' and 'low' are fairly subjective and only give an indicator of the *potential* social benefit from reducing cases of dementia.
WTP for a 'magic pill' cure to depression	Morey *et al*, 2006	€680 per month	$2005. Study notes wide range of responses depending on individual's background and preference ($305 - $1700).
WTP for a six month treatment to cure depression	Unutzer *et al*, 2003	€270±187 per month	Also estimated as 9% of household income. Assumed $2002.
WTP to avoid additional angina	Chestnut *et al*, 1988 (for EPA)	$40 per episode, $42 per month to avoid 4-8 additional episodes that month. Mean WTP derived from avertive expenditure was $36 per episode.	$1987? As such an old report perhaps not most appropriate source, though gives a lot of information and clear.
WTP to avoid myocardial infarction	Yasunaga *et al*, 2006	€7,560	$2005?
Mean WTP estimates for ischemic heart disease	University of Chicago, Frank and Sunstein (2000) (citing EPA Regulatory Impact Analysis, Ozone and Particulates (1998))	age <65: $20,600; converted to €14,680 for 2010	$1990. Conversion to €1990 obviously not possible so conversions are based on current exchange rate.
Mean WTP estimates for respiratory related health endpoints	As above	Hospital admiss. For all resp. illness, all ages: $12,700; Chronic bronchitis: $260,000; Asthma: $32; Emergency visits for asthma: $9,000; Shortness of breath: $5.30; Acute respiratory systems: $18; COPD age >65: $15,900;	$1990. Conversion to €1990 obviously not possible so conversions are based on current exchange rate (November 2010). Based on report on effects ozone regulation.
WTP (CV) of leukaemia and lung cancer	Enviros, EFTEC, DEFRA, 2004 (Adapted from Pearce, 2000, original study by Aimola, 1998)	Lung cancer: €77,000; Leukaemia: €812,00	Italian study adapted for use in UK

Table 3.13: Willingness to Pay Estimates for Various Health Effects			
Measure	**Source**	**Estimate**	**Comment**
WTP for extra months of life due to reduction in air pollution	Remoundou and Koundouri, 2009 (citing Chilton, 2004)	One month extended life expectancy: €139 Three month extended life expectancy: €157 Six month extended life expectancy: €187	€2009. Original Chilton study covered UK.
Mean WTP estimate to avoid breathing discomfort	Chilton, 2004.	€50	£2003.
Mean WTP for a case of poor respiratory health	AEA Technology, 2005 (citing Ready *et al*, 2004)	€468	€2004. Bases on a survey describing a scenario of 3 days in followed by 5 days in bed
WTP of emergency room visit due to respiratory illness	AEA Technology, 2005 (citing Ready *et al*, 2004)	€242 to avoid visit to emergency room, given oxygen and medicine, followed by 5 days in bed.	€2003. From a 5 country pooled study.
WTP to avoid an additional day of asthma attacks after 14 days of attacks	AEA Technology, 2005 (citing Ready *et al*, 2004)	€15 central value	€2003. Value derived from responses for adult non-asthmatics, adult asthmatics and if the respondents children were to have an attack.

Table 3.13: VOLY Estimates			
Measure	**Source**	**Estimate**	**Comment**
VOLY	AEA Technology, 2005	€52,000	€2000
VOLY (mean estimate based on WTP)	University of Chicago, Frank and Sunstein (2000) (citing EPA Regulatory Impact Analysis, Ozone and Particulates (1998))	€79,849	$1990. Conversion to €1990 obviously not possible so conversions are based on current exchange rate (November 2010). Based on report on effects ozone regulation.

Table 3.13: IQ loss impact estimates			
Measure	**Source**	**Estimate**	**Comment**
Estimate in loss of wages due to 1 point drop in IQ (in this instance from mercury poisoning)	NESCAUM, 2005	€18,910	$2000. Based on a baseline average lifetime earning of $691,830 (from Grosse, 2003) and a proportional effect of 1 IQ point being estimated at 2.39%.

Table 3.13: IQ loss impact estimates			
Measure	**Source**	**Estimate**	**Comment**
Cost of education provided for those with an IQ <70	NESCAUM, 2005	€8939 per annum. Educational cost estimate of 1 IQ point is €332	$2000. Educational costs per IQ point estimated by probability of an IQ lower than 70 from a 1 point drop in mean IQ multiplied by value for educational costs.

Table 3.13: QALY Estimates			
Measure	**Source**	**Estimate**	**Comment**
QALY	University of Sheffield, 2005	€28,000-43,000	£2005 Based on UK National Institute for Health and Clinical Excellence threshold of £20,000-30,000.
Cost per QALY of screening for lung cancer	Kyle *et al*, 2006	Best case scenario cost of €32,219	$2006.

Table 3.13: DALY Estimates			
Measure	**Source**	**Estimate**	**Comment**
Average DALY estimate for the UK	WWF, 2003	€94,836	€2003.

4. ASSESSING ENVIRONMENTAL IMPACTS - STEPS 2 TO 4

4.1 Overview

As for human health, the aim of Steps 2 and 3 is to provide an assessment of the environmental impacts arising from limits on the use of a chemical either due to restrictions under REACH or due to a refused authorisation. Step 2 is aimed at ensuring that there is a sufficiently detailed qualitative description of each of the potential impacts, while Step 3 is intended to provide more quantitative information on the magnitude and severity of each impact.

More so than for human health, it is likely that difficulties will be encountered when attempting to carry out a fully quantitative assessment for many of the chemicals going through restrictions or authorisation because of likely limitations in the amount of data available. A further confounding factor when attempting to characterise potential environmental impacts are the difficulties in determining environmental consequences based upon experimental data and the potentially large degree of uncertainty that may surround such predictions.

Ideally, one would wish to extrapolate from experimental data to specific ecotoxicological impacts, this objective is difficult to achieve and any estimates are likely to be subject to a high degree of uncertainty (Calow and Fobes, 2003). This is due to the current low level of basic scientific understanding of the relationships between structure and function in ecosystems and of the statistical distribution of toxicity end-points in relation to outcomes in natural communities (Forbes and Forbes, 1993). For example, while ecotoxicity studies may inform on the degree and extent of toxicity to particular experimental species and there are techniques by which such data can be used to model estimates of the proportion of species that may be affected within an environmental compartment at a particular level of exposure (discussed further below), the proportion of species in any given ecosystem that can be adversely impacted without significantly affecting the ecosystem's sustainability is currently unknown.

As a result, it is likely that for many assessments the emphasis will be to ensure that as complete a set of information as possible is provided on environmental effects in Step 2. Thus, if the analysis stops at this point, decision makers would then at least have as much information as possible on possible impacts with which to assist in reaching a conclusion on a restriction proposal or an authorisation application.

If the assessment can progress to Step 3, the analyst will again need to decide whether or not there is sufficient information and certainty surrounding the conclusions from the work to rely on the quantitative data generated in this step. If quantification has been possible, then a decision will need to be made at the end of Step 3 as to whether the assessment could move further towards monetary valuation.

If a decision is taken to stop the assessment after Steps 2 or 3, then the next stage would be to move to Step 5; if Step 4 is carried out, then the analysis would naturally progress to Step 5.

Importantly, in order to fully characterise the potential environmental consequences that might arise from the use of a substance, it is essential to consider not just the exposure and toxic profile of the substance but also it's potential for bioaccumulation or persistence within the environment. These properties may significantly influence the nature of the overall risk posed and the approach that needs to be taken to characterise the associated potential environmental impacts. It is also important to appreciate that substances may be broken down within the environment by a wide range of chemical and/or biochemical processes (such as hydrolysis, oxidation, photo-degradation or enzyme systems). While in many instances such chemical changes may result in its biological inactivation (i.e. detoxification), it can in some instances result in the generation of a more toxic metabolite or degradation products. Also, even if the substance is itself readily broken down by physical or biological processes within the environment, it is possible that some of the breakdown products arising might themselves have undesirable properties such as toxicity, persistent or bioaccumulation, or other properties of equivalent concern, that might also warrant consideration within the SEA; an example is illustrated in Box 4.1. Such concerns are likely to have been highlighted within the risk assessment process but attention should be given at this stage of the assessment to ensure that all such potential concerns are captured and are assessed for their relevance.

Box 4.1: Example of potential consequences of environmental breakdown of a substance

The pesticide 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT) occurs as a mixture of *p,p*- and *o,p*-isomers and is a highly effective insect neurotoxin. It is highly stable within the environment where it is very toxic to fish and has been shown to affect egg-shell formation in birds. DDT is also toxic in mammals to the liver, kidneys, immune and reproductive systems. Although very stable in the abiotic environment it is be metabolised by biota through dehydrocholrination to 2,2-bis-(p-chlorophenyl)-1,1-dichloroethylene (DDE) or by reductive dechlorination to 2,2,-bis-(*p*-chlorophenyl)-1,1,-dichloroethane (DDD). These metabolites have similar physicochemical properties to the parent molecule. However, DDE is substantially more environmental stable than DDT.

Of particular note are the differences in endocrine activities shown by these various forms. While *o,p*-DDT is oestrogenic, this activity is not shared with its *p,p*-form. However, *p,p*-DDE is a relatively potent anti-androgen while *DDD* is toxic to the adrenal gland.

Thus, in the case of DDT, the complete risks profile could not be captured solely on the basis of considering the properties of the parent substance.

4.2 Step 2: Qualitative Assessment of Environmental Impacts

4.2.1 Introduction

As noted above, the aim of the qualitative assessment is to ensure that decision makers have a good understanding of the nature of the potential environmental impacts associated with continued use of the substance and hence the benefits that would be realised by reducing exposures. The primary toxic effects of concern, together with other secondary effects, issues relating to persistence and bioaccumulation potential and properties suggesting the substance is of 'equivalent concern' that were considered at Step 1 to warrant further consideration should each be considered in turn at this time. In addition, the overall extent of risk posed by the substance should be considered.

Where feasible, quantitative details on, e.g. the ecosystem compartments exposed, the number of industry sites involved in the relevant activities, average tonnages used at the different sites, emission data, etc. should also be provided. This ensures that some basic quantitative information is provided to decision makers even when an assessment does not move forward to Step 3.

For each of the effects/concerns identified in Step 1 as warranting further consideration, there are four assessment stages:

i) Step 2a: Hazard characterisation;
ii) Step 2b: Exposure characterisation;
iii) Step 2c: Qualitative description of potential impacts;
iv) Step 2d: Benchmarking of environmental hazard; and
v) Step 2e: Assessment of the potential for quantification of impacts.

Figure 4.1, overleaf, illustrates the assessment process for Step 2.

4.2.2 Step 2a: Hazard Characterisation

The first stage in Step 2 is to characterise, in qualitative terms, the nature of the hazard that is associated with each risk of concern that was identified in Step 1 to warrant further detailed consideration. As such, while in most instances the concern may relate to the parent substance, in some cases consideration may need to also be given to a metabolite, degradation or other transformation product that gives rise to environmental concerns.

Ecotoxicological Considerations

Within the risk assessment process, ecotoxicological risk is ultimately assessed in terms of the RCR for each environmental compartment (i.e. media) considered. This is however based on the predicted no effect concentration (PNEC) derived from the most sensitive endpoint only, which in turn may be estimated through application of assessment factors from an effect value obtained using either multispecies approaches

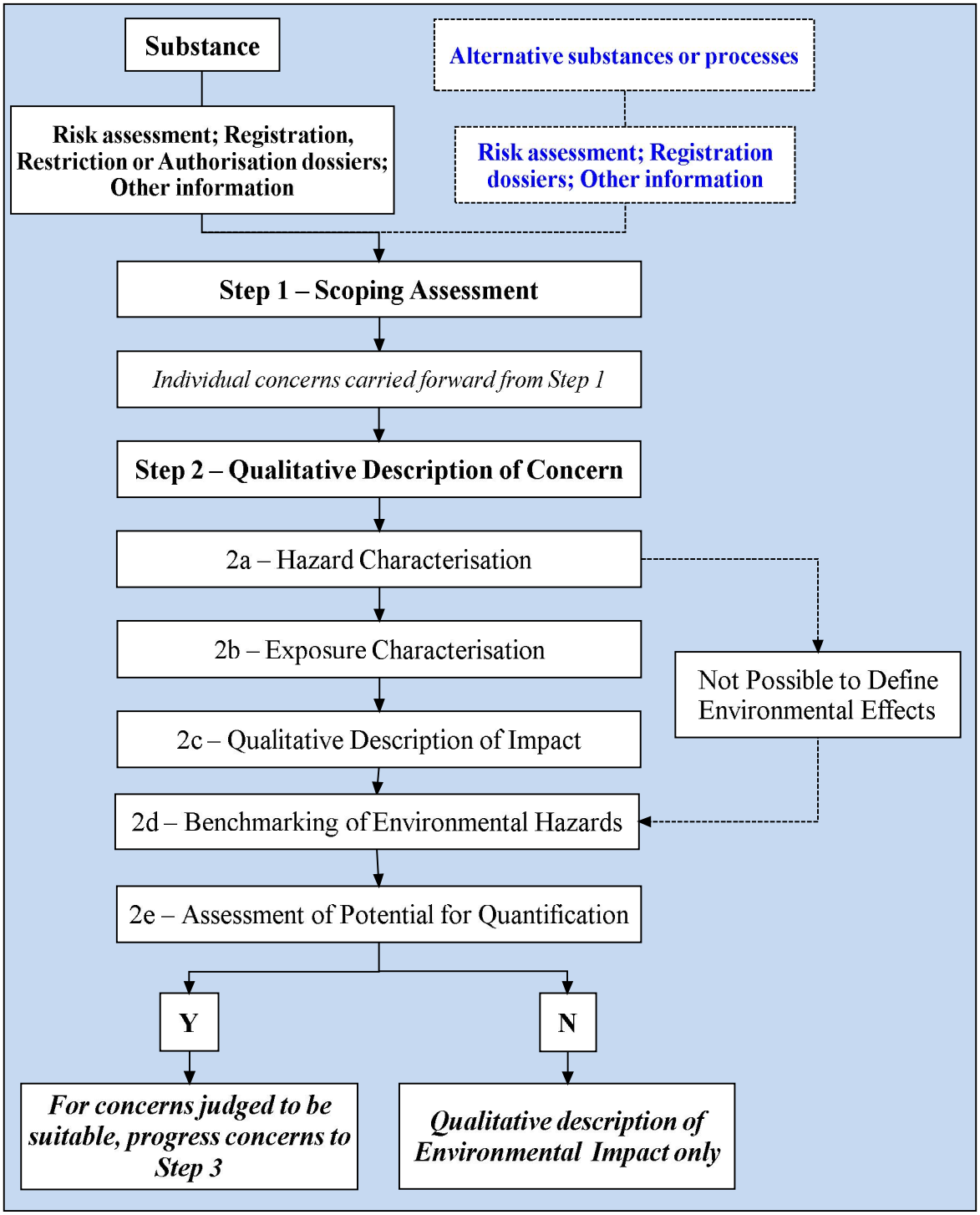


Figure 4.1: Assessment Process for Step 2

(such as species sensitivity distribution (SSD) models or on the basis of data from a single (most sensitive) species. However, the resulting RCR does not, in itself, indicate what the critical endpoint was, nor does it inform on the dose-response characteristics for the effect or the taxa that are considered to be at risk. It is therefore necessary, in Step 2a, to review the underlying detailed information in the risk assessment (together with any other relevant sources that may have also been identified) to fully characterise in qualitative or semi-qualitative terms the nature of this endpoint.

Also, each of the other (less sensitive) effects which were identified in the course of the risk assessment (i.e. other endpoints in that species or effects in other species) need to be considered as they may be relevant to understanding the full range of environmental impacts arising from the use of a chemical. The available toxicology data for all endpoints for which the RCR for the environment is greater than 1[7] should therefore be reviewed.

Ideally, the relevance of the experimental Point of Departure (POD) value for each effect (endpoint) should be considered in order to prepare for the next step, i.e. quantification of impacts (Step 3). In this respect, the nature of the data used to establish the environmental concentrations at which a particular effect may occur should be considered in detail.

In other words, while the risk assessment may utilise information on the NOEC and LOAEC only (which are dependent on the spacing of concentration levels used in the test design and the intrinsic variability of the end point which will determine the discriminatory ability), it may be worthwhile considering whether it would be possible to derive another more useful metric of effect to indicate the link between concentration and effect; for example, data may also be available on the EC_5, EC_{10}, EC_{25}, etc (or these may be calculable from the available data), which would facilitate the development of a dose-response function.

Other Considerations

In addition to consideration of the data on the ecotoxicity of the substance, its persistence and bioaccumulative potential will also need to be established, with Step 2 focusing on identifying which environmental media or type of biota are at risk from bioaccumulation of the substance. For example:

- if the substance has been shown to bioaccumulate in fish, then concerns would focus in the subsequent steps of the SEA on establishing the potential for adverse consequences to fisheries or may focus attention on the need to also consider higher predators or particular cornerstone or valued species; or

[7] i.e. the predicted concentration in the environment (PEC) would be greater than the predicted no effect concentration (PNEC).

- if the substance was suspected of having a high persistence in sewage sludge, then a particular focus might be on the extent to which this might impact on the ability to dispose of contaminated sludge to land.

In practice, actual quantitative data on the substance's persistence and bioaccumulation potential should be readily available from the risk assessment.

Similar attention also needs to be given to information gathering on any other effects considered of 'equivalent concern' under REACH. For example, evidence relating to the potential endocrine disrupting properties of the substance should be considered. Particular attention should be given to defining the strength of evidence for such effects, the hormone systems affected and the extent to which the dose-response characteristics are definable. Also, the possible pathophysiological consequences of such effects and the taxal groups at potential risk should be considered. This is important since different taxa may have significant differences in endocrine systems and, indeed, the same hormone may control different physiological processes in different species.

Types of Data to be Examined

In conducting Step 2a , it is likely that a number of different types of information may be drawn on, the majority of which are likely to be available from within the information dataset used for the risk assessment; Table 4.1 summarises the types of experimental data that may be available; the extent to which a particular data type will be available for a given substance is to a large part dependent on the substances production/market tonnage (REACH testing requirements for different tonnage bands is discussed further in Part 1 of this report).

Table 4.2 sets out the type of information that should be gathered and reported on for **each** identified aspect of risk that is considered out under Step 2a.

Table 4.1: Types of experimental information that may be considered

Data Type	Endpoint
Physicochemical Properties	State of the substance at 20 °C and 101,3 kPa Melting/freezing point Boiling point Relative density Vapour pressure Surface tension Water solubility Partition coefficient n-octanol/water Flash-point Flammability Explosive properties Self-ignition temperature Oxidising properties Granulometry Stability in organic solvents and identity of relevant degradation products Dissociation constant Viscosity

Table 4.1: Types of experimental information that may be considered	
Data Type	**Endpoint**
Aquatic toxicity	Short-term toxicity testing on invertebrates (preferred species Daphnia) Growth inhibition study aquatic plants (algae preferred) Short-term toxicity testing on fish Activated sludge respiration inhibition testing Long-term toxicity testing on invertebrates (preferred species Daphnia) Long-term toxicity testing on fish: Fish early-life stage (FELS) toxicity test Fish short-term toxicity test on embryo and sac-fry stages Fish, juvenile growth test
Degradation	Biotic Ready biodegradability Simulation testing on ultimate degradation in surface water Soil simulation testing (for substances with a high potential for adsorption to soil) Sediment simulation testing (for substances with a high potential for adsorption to sediment) Abiotic Hydrolysis as a function of pH. Identification of degradation products
Fate and behaviour in the environment	Adsorption/desorption screening Bioaccumulation in aquatic species, preferably fish Further information on adsorption/desorption Further information on the environmental fate and behaviour of the substance and/or degradation products
Effects on terrestrial organisms	Short-term toxicity to invertebrates Effects on soil micro-organisms Short-term toxicity to plants Long-term toxicity testing on invertebrates Long-term toxicity testing on plants
Effects on sediment organisms	Long-term toxicity to sediment organisms
Toxicity to birds	Long-term or reproductive toxicity to birds

Table 4.2: Example of Required Information on Hazard Potential in Step 2a	
Reporting Headlines	**Data / Discussion Areas**
Toxicity test endpoint	E.g. due to acute or chronic exposures and specific nature of response seen (e.g. death, growth impairment, loss of fecundity)
Persistence and bioaccumulation potential	E.g. abiotic degradation time, Kow, BCF.
Species/model in which effect identified	One or more species that were used to characterise the specific toxic or bioaccumulative properties
Environmental compartment in which toxic effect identified	Compartment for which concern was identified (based on type of species/model which identified effect)
Nature of point of departure (POD) for toxic effects	E.g. experimental EC10, EC5, NOAEC
Adequacy of dose-response characterisation for toxic effects	Do the available studies adequately inform on dose-response relationships for that effect so as to allow extrapolation to environmentally-relevant scenarios
Data integrity	Robustness of study design (e.g. compliance with standard regulatory study design), adequacy of group size, identification of uncertainties
Conclusion of suitability for further consideration	No, Possibly, Yes

4.2.3 Step 2b: Assessment of Exposure Data

The second stage in Step 2 is to describe the nature of the exposure information available for the different uses subject either to the restriction proposal or to authorisation. In particular, the focus should be to characterise the range of exposures that might realistically be anticipated to occur under each scenario that is of relevance to the individual hazards considered in Step 2a. Subsequently, a judgement can be reached as to the extent of any environmental impacts that might be expected to arise and an understanding of the degree of uncertainty surrounding such predictions can also be established. In order to achieve this, it is necessary to provide descriptions of the following for each of the effect scenarios under consideration:

- **Media and nature of concern:** an overview of the environmental compartment(s) (and biota group) to which concern relates and nature of the identified risks (e.g. toxicity (including endpoint of concern), bioaccumulation and persistence) for each;

- **Level and frequency of exposure:** this is assessed in subjective terms so as to indicate the likely extent of exposure (e.g. as might be indicated by consideration of some indicator such as the magnitude of predicted RCR) and the nature and anticipated pattern of emissions, for example the number of potential sources, whether exposure is likely to be continuous (e.g. arising from ongoing industrial emissions or emissions from products in use), occasional (e.g. due to yearly spreading of sludge to land) or a rare event (e.g. only at decommissioning or disposal at end of life). Data should also be provided on the tonnages associated with different exposures;

- **Data availability:** this relates to the nature of the available data on environmental concentrations, such as whether actual environmental monitoring data are available or whether there is modelling data available (e.g. output from an environmental fate and transport model) or if there is the potential to develop such estimates (e.g. based on industry data for production and use of the chemical). Alternatively, it might be concluded that there is a strong likelihood that there are inadequate exposure, market or other data to enable development of more quantitative estimates of environmental concentrations; and

- **Certainty:** an indication should be given as to the sources and level of certainty surrounding the exposure data.

Reporting headlines for each of these aspects are given in Table 4.3.

Table 4.3: Example Information on Exposure Data to be developed in Step 2b	
Reporting Headlines	**Data / Discussion Areas**
Media and nature of concern	E.g. aquatic toxicity, terrestrial toxicity, persistence &/or bioaccumulation, endocrine disruption
Species at risk	E.g. invertebrates, fish, birds, mammals, flora, etc.
Level of Exposure	Assessment of the extent of exposure for particular environmental media or target organisms, at least in qualitative terms (low, medium, high)
Frequency of Exposure	E.g. continuous, daily, irregular, rare, etc.
Nature of Exposure	Point source(s) or diffuse
Data Availability	Are actual data or estimates available? What is the potential for developing predictions of exposures, for example using GIS, fate and transport models, data on the number of companies using the substance, etc.
Certainty in Exposure Data	Based on consideration of the nature of the data (e.g. actual monitoring data, modelled data, combination of monitoring and modelling) and the likely robustness of the data
Tonnages associated with exposure	Carried forward from the Step 1 scoping exercise

One obvious source of exposure estimates would be those from the existing risk assessment for the substance, without further modification. However, it must be remembered that these are likely to have been generated using the standard models for national, continental and local predicted concentrations (PECs) and will therefore constitute 'reasonable worst-case' estimates. That is, they will have incorporated, at various stages in the processes, assessment factors (of various magnitudes depending on data availability) in line with the risk assessment technical guidance; the potential influence that such assessment factors may have is illustrated in Box 4.2 in relation to the impact of river flow assumptions on freshwater exposure estimates.

As a consequence, the exposure estimates used in the risk assessment may not necessarily be ideal for use in a SEA. As a result, it may also be important to derive more 'realistic' alternatives based on revised and more use specific assumptions. These 'realistic' exposure estimates should be provided for **each** environmental compartment relevant to the risk endpoints identified in Step 2a as being important to understanding the potential environmental impacts.

Based on an assessment of the outputs from Stages 2a and 2b and applying 'weight of evidence' considerations, a conclusion should be reached regarding the suitability of each of the identified hazards for development of a detailed qualitative description of the possible environmental impacts in Stage 2c.

Where it is not possible to describe environmental effects and exposures in detail, the assessment should move to Step 2d and the use of benchmarking methods.

BOX 4.2: Implications of Use of Exposure Estimates based on the Approaches utilised in Risk Assessment

The following example considers the impact of assumptions on river flow and illustrates how changes to the assessment factors used or assumptions can significantly influence resultant estimates of freshwater exposures.

For a risk assessment, dilution factors are calculated using the equation:

$$DILUTION = \frac{EFFLUENTlocal_{stp} + FLOW}{EFFLUENTlocal_{stp}}$$

where:

DILUTION = Dilution Factor (no units);
$EFFLUENTlocal_{stp}$ = Effluent flow of local sewage treatment plant (m^3/day); and
FLOW = Flow rate of receiving water body (e.g. river) (m^3/day).

The guidance requires that a lowest-flow rate (or 10th-percentile of average annual flow rate) is used. Where only average flows are available, the flow should be estimated as one-third this average. As such, the exposure estimates carried forward in the risk assessment may be based on one of three different assumptions, depending upon the data available, and none of these assumptions may reflect the actual flows that may occur in a receiving water body.

For example, flow rates recorded in the UK National River Flow Archive for the **River Thames** in 2008[1] are used here to illustrate how use of default and actual figures may result in significantly divergent estimates of exposures at particular sites. If no information is available regarding the flow rate of a receiving water, a dilution factor of 10 is applied. However, in the case of the Thames there are data and, assuming that the flow rate at the point of discharge is the same as that at the measurement site, a more accurate dilution factor may be calculated as:

1/3 Average flow = 27.5 m^3/s or 2,380,176 m^3/day

This results in a dilution factor (Dilution) = (5,000 + 2,380,176)/5,000 = 477.

However, the lowest flow rate = 16.6 m^3/s = 1,434,240 m^3/day, which would result in a dilution factor = Dilution = (5,000 + 1,434,240)/5,000 = 288.

When $EFFLUENTlocal_{stp}$ is not known, the guidance requires a figure of 5,000 (m^3/day) to be used. However, actual effluent may be much less than 5,000 (m^3/day). For example, if the actual $EFFLUENTlocal_{stp}$ were 1000 (m^3/day), the dilution factor would be almost five times greater than those shown.

In some instances, the actual dilution factor is known to be greater than 1,000 but the guidance states that the maximum dilution factor that may be used is limited to 1,000. Hence, depending upon the availability of information, the dilution factor used in the risk assessment for a site might be selected from a range varying by a factor of 100.

Importantly, no estimates are required for risk assessment purposes based on an approximation of the actual flow rate (or range of flow rates). As a consequence, during characterisation of risk, 'worst-case' estimates may be multiplied together, with this multiplication of precautionary assumptions (assessment factors) potentially repeated at several stages during the assessment process before a RCR is generated. Thus, depending on the criteria adopted, assessments of exposure may easily vary by several orders of magnitude. The use of multiple worse-case assumptions is therefore inappropriate in an SEA where realistic or average estimates for real life are required.

4.2.4 Step 2c: Qualitative Description of Environmental Impact

The next stage is to attempt to develop a detailed qualitative assessment of the potential environmental consequences that might arise from continued use of the chemical of concern. This should be carried out for each of the environmental compartments and risks that were identified from Steps 2a and 2b as being of relevance and as having sufficient information.

In the case of substances that exhibit persistence and/or bioaccumulation properties, the potential influence of these on the magnitude and distribution of potential environmental impacts should be considered. For example, such properties could impact on the geographic extent of impacts (e.g. as a result of transmission through the environment to remote regions) or may lead to variations in anticipated exposure levels, and hence risk of increased adverse impact, over time.

In many instances it is likely to be extremely difficult to extrapolate with any degree of certainty from an identified hazardous property to the definition of a specific environmental consequence. Research is underway on developing methods for carrying out such extrapolations (e.g. using the approaches being developed under the EDCAT project referred to in Part 1 of the report, or through use of novel markers of effects, '-omic technologies' or on the basis of mesocosm-type studies) but these methods are not sufficiently developed in the short to medium term.

In some cases though (for example where there is a lot of information on impacts across a number of different species or where the concerns include, for example, the potential for bioaccumulation), it may be possible to describe to some extent the potential ecosystems that may be at risk, or to identify particular species or trophic levels as being at particular risk. For example, if a substance is shown to partition to the aquatic environment, has a significant bioaccumulative potential and is highly toxic to freshwater fish, a potential risk to freshwater top predators (e.g. rainbow trout) could theoretically be envisaged.

Similarly, if a substance possesses key properties that are similar to another substance for which there is existing evidence of adverse environmental impacts, then it might also be possible to infer similar impacts from the continued use of the substance under assessment (i.e. through drawing on approaches such as 'read-across' and 'analogy', or using benchmarking or risk ranking methods – see also Step 2d). This may be particularly useful in the case of a substance for which a particular toxic effect of concern has yet to be defined, or is as yet insufficiently characterised, to allow estimates of impact to be made.

Ecosystem Services Based Approach to Identifying Potential Impacts

For substances for which toxic properties of concern have been described, the aim should be to link in qualitative terms the toxic effects with potential impacts on ecosystem services, to the greatest degree possible. For example, an adverse effect on top predator fish species might be associated with adverse impacts on natural and

commercial fisheries. Although this type of approach is still rather new, there is increased interest in its application and may become increasingly valuable to chemical risk management.

The identification of potential impacts on ecosystem services should be based on how continued environmental exposures, or environmental concentrations of a particular substance, could affect the functioning of habitats, or the services provided them. A recent report for the European Environment Agency "A Common International Classification for Ecosystem Services[8]" defines 10 different groups of potential 'services' that relate to: provisioning services, regulating services and cultural services. It then describes the linking of these groups to different service classes which can be more directly linked to outputs and products.

Table 4.4 sets out the ecosystem Service Groups proposed in the European Environment Agency report. This system combines a range of different thinking with regard to how ecosystem services should be defined, building on the UN Millenium Assessment and other more recent work.

Table 4.4: Common International Classification for Ecosystem Services

CICES Service Groups	Classes	Examples
Food & Beverages	Crop based production	Cereals, Honey bees
	Animal based production	Wild and farmed animal products
	Marine fishing	Crustaceans, fisheries, shellfisheries
	Freshwater fishing	Wild salmon, trout and other species as food fish
	Aquaculture	Salmon Farming
	Potable water	Spring, well water
Materials	Biotic materials	Timber, straw, wild genetic resources, ornamental resources, medicinal resources
Regulation of waste assimilation processes	Remediation	Natural bioremediation mechanisms on brownfield sites
	Waste assimilation	Decomposition of organic materials in soils
Regulation against hazards	Air flow regulation	Windbreaks
	Water flow regulation	Wetlands reducing peak discharges when in good condition
	Mass flow regulation	Stabilisation of mudflows, erosion protection
Regulation of biophysical conditions	Air quality regulation	Dust removal and filtering odours
	Water quality regulation	Water purification through pollution assimilation
	Soil quality regulation	Maintaining soil structure
	Global climate regulation (incl. C-sequestration)	Atmospheric composition, hydrological cycle
	Local climate regulation	Modifying temperature, humidity, providing shade etc.

[8] Haines-Young et al (2009): Towards a Common International Classification of Ecosystem Services (CICES) for Integrated Environmental and Economic Accounting, Report to the EEA, Contract No EEA/BSS/07/007.

Table 4.4: Common International Classification for Ecosystem Services		
CICES Service Groups	**Classes**	**Examples**
Regulation of biotic environment	Lifecycle maintenance & habitat protection	Pollination, nursery functions for fisheries, maintaining the health of foodchains
	Pest and disease control	Biological control mechanisms
	Gene pool protection	Maintaining wild populations
Information	Scientific research	
	Education	
Symbolic	Aesthetic, Cultural	Sense of place
	Religious	Sacred places or species
Experiential	Recreation	Bird or whale watching
	Volunteering	Conservation volunteers
Source: Haines-Young et al, 2009 Note that abiotic Classes and examples have been removed as they would not be relevant to chemicals regulation		

Because of its importance, Box 4.3 sets out the Millenium Ecosystem Services Framework in more detail. It has acted as the basis for application of an ecosystem services type of approach in a wide range of countries, at either regional or site specific scales. For example, the study discussed in Part 1 of this report by Lancaster University (Giacomello *et al* 2006) started from an ecosystem services based approach and examined several case studies, for example, by examining the goods and services provided by the species affected by Tributyl tins (TBT), and by looking at the services provided by honeybees in terms of crop pollination and through production of beeswax and honey. Although not all of the groups and classes given in Table 4.4 may be directly relevant to the types of chemicals that will go through restrictions or may be subject to authorisation, they may be indirectly relevant and should therefore be considered; (they may also be relevant to the assessment of alternatives).

Box 4.3: Millennium Ecosystem Assessment Framework

The Millennium Ecosystem Assessment was developed under the auspices of the United Nations in order to assess the consequences of ecosystem change to human well-being. Its framework identified 4 broad categories of ecosystem service which lead to different types of benefits:

- **Provisioning services:** e.g. obtaining products from ecosystems such as food, fuel, textiles and medicines;
- **Regulating services:** the benefits arising from the results of ecosystem processes such as water purification, air quality maintenance and climate regulation;
- **Cultural services:** gain of non-material benefits from interactions with the natural environment (such as education and well-being); and
- **Supporting services:** functions necessary for the production of other ecosystem services from which benefits arise (such as soil formation, nutrient cycling and pollination).

From: Millennium Ecosystem Assessment (2005)

Information to be Provided from Qualitative Assessment

A summary of the types of information and the approaches that the analysts may need to draw upon when preparing a descriptive qualitative assessment, are illustrated in Table 4.5. It is important to note that these should be considered for their relevance to any risks/concerns to be considered. The intention is, for each concern, to provide an indication of the significance of the exposure scenario(s) being considered in terms of understanding the potential environmental impact that might result to each relevant environmental compartment.

Table 4.5: Checklist of Information Needs, Approaches and Reporting Outputs in Step 2

Reporting Headlines	Data / Discussion Areas
Environmental Compartment of Concern	E.g. freshwater, marine waters, soil, sludge
Geographic Scope of concern	Regional, local, specific point sources
Variation over time	Increase in geographic spread over time due to P properties, potential for increase in levels found in sensitive species due to bioaccumulation
Medium or taxa at potential risk	Description of type of organism (e.g. invertebrate, fish, algae) and any subgroup or vulnerable stage (e.g. larval stage) or abiotic medium (e.g. for substances with high absorption and persistence in particular sediment types)
***Nature of Potential Impacts*:**	
Direct effect (endpoint and species)	E.g. reprotoxic effects in freshwater fish, acute toxicity to invertebrate species
Indirect effect	e.g. possibility of food chain effects caused by drop in population numbers at one trophic level or potential for bioaccumulation leading to high loads in top predators
Nature of Exposures:	
Frequency and duration of exposure	continuous, twice yearly event, etc.
Persistence of substance in the environment	Half-life, indication of expected time to reach concentrations that are below assumed/expected risk level if emissions were stopped/reduced (i.e. to get a RCR < 1 once the effects have been identified)
Potential for bioaccumulation	Evidence for, or predictions of, bioaccumulation reaching toxic levels in predator species via envisaged exposure route
Ecosystem Services Links to Environmental Impact:	
Food, Materials or Energy (Provisioning services)	E.g. loss of fisheries, impacts on crop production, impacts on drinking water supplies, impacts on biotic materials (genetic resources, medicinal resources), impacts on renewable fuel sources
Regulation of waste assimilation, regulation against hazards, regulation of biophysical conditions, regulation of biotic environment	E.g. soil fertility and soil structure, water purification, biological control mechanisms, nursery population and gene pool protection, atmospheric composition
Information, Symbolic and Experiential Services (Cultural and amenity services)	E.g. loss of important species from a symbolic perspective, impacts on species that are important for ecotourism

4.2.5 Step 2d: PBT/vPvB-based Benchmarking

Potential Benchmarking Tools

There is a range of potential tools available which could be used for benchmarking chemicals according to their physico-chemical properties; these tools are discussed in detail in Section 7 of Part 1 of this report. A key issue for this logic framework is the ability of the tool that is selected to rank chemicals in relation to their PBT or vPvB properties.

As previously discussed , the SCRAM spreadsheet tool represents a convenient model to illustrate the benchmarking process. It is described in some detail below to illustrate the underlying nature of this type of tool and the likely strengths and limitations.

SCRAM was designed to evaluate and score the persistence, bioaccumulation and toxicity of chemicals based on limited information in relation to a particular environmental scenario, the American Great Lakes. It seeks to analyse both environmental and human health concerns separately or as a combined (overall) indicator of the risk that might be posed by a chemical.

For the human health (not considered in detail here) and environmental effect aspects, information is entered into a spreadsheet that calculates a 'chemical score' of a substance (essentially an indicator of its relative hazard based on the toxicity and potential exposure and environment behaviour of the chemical). The model places an emphasis on environmental fate and, particularly, on environmental persistence, because a chemical that is not known to cause toxic effects may later be found to cause toxicity through a mechanism not currently investigated. In addition to generating a 'chemical score', SCRAM also incorporates an 'uncertainty' score that attempts to reflect the degree of uncertainty surrounding the dataset used as the basis for establishing a 'chemical' score. It is important that the degree of uncertainty is considered since there may be marked differences in the extent and quality of data for some endpoints for the substances undergoing comparison.

The data needed by SCRAM are:

1. Bioaccumulation data: Bioaccumulation factor (BAF), bioconcentration factor (BCF) or octanol/water partition coefficients. According to the type of data used, different uncertainties are attributed
2. Persistence data: Half-lives in five environmental compartments (biota, air, soil, sediment and water). Only one half-life for one compartment is needed at this stage but this will lead to high uncertainty
3. Acute toxicity data (only if the persistence score is 1 or 2):
   - Acute terrestrial toxicity data: ED_{50} or LD_{50} in five subcategories (plants, mammals, birds, invertebrates, and amphibians and reptiles); and
   - Acute aquatic toxicity data: EC_{50} or LC_{50} for five subcategories (plants, amphibians, warm water fish, cold water fish, and invertebrates)

4. Subchronic/chronic toxicity data (only if the persistence score is 3 or more):
   - Subchronic/chronic terrestrial toxicity data: NO(A)EL or LO(A)EL in five subcategories (plants, mammals, birds, invertebrates, and amphibians and reptiles);
   - Subchronic/chronic aquatic toxicity data: NO(A)EC or LO(A)EC in five subcategories (plants, amphibians, warm water fish, cold water fish, and invertebrates); and
   - Subchronic/chronic human toxicity data: NO(A)EL or LO(A)EL for four categories (general toxicity, reproductive toxicity, developmental toxicity, and other toxicity) and ED_{10} for carcinogenicity.

Only one value for each of the above toxicity categories (Bullets 3 and 4, above) is needed, although where an assessment is based on just a single data point for a given parameter, the score applied for uncertainty of the dataset will be high.

The spreadsheet tool and associated guidance for SCRAM are available online from the US EPA website at http://www.epa.gov/greatlakes/toxteam/pbtrept/index.html. Using the information-types defined above, a final 'chemical' score is determined together with a final 'uncertainty' score. The 'chemical' and 'uncertainty' scores are combined to give a 'composite score' (with separate composite scores developed for the environment and health and which can then be further combined to give an overall score for the substance). This allows benchmarking of the substance against others in terms of relative concern regarding risk to human health, the environment or both aspects combined, depending on the particular purpose of the exercise being undertaken (see example in Box 4.4).

Note there is there is a list of scores for some 146 chemicals available from the SCRAM website and data may also be entered by the user for additional substances for specific scoring exercises.

Box 4.4: Comparison of SCRAM Scores for a Number of Substances used as Flame Retardants

SCRAM is designed as a flow chart that guide's the assessor through steps of gathering information and assessing the certainty of that information. Depending on the assessed chemical, scores can be produced for both acute and chronic environmental/health effects, and due to the nature of SCRAM results can be gained from relatively limited sources of information (Snyder et al, 2000). A shortened example of the SCRAM for anonymous chemicals can be seen in the table below.

Overview of data used in SCRAM with anonymous chemical examples

	Chemical A		**Chemical B**		**Chemical C**	
	Chemical Score	**Uncertainty Score**	**Chemical Score**	**Uncertainty Score**	**Chemical Score**	**Uncertainty Score**
Bioaccumulation (B)	3	1	1	1	5	2
Environmental Persistence (P)*	5	3	4	1	5	6
Subchronic/ Chronic Terrestrial Toxicity (CT)	3	4	1	3	2	4
Subchronic/ Chronic Aquatic Toxicity	5	2	1	4	5	1

(CA)						
Subchronic/ Chronic Human Toxicity(CH)	4	2	4	2	3	2
Final Score (F)	35	13	12	11	48	25
Composite Score	48		23		73	
* hemicals with P ≤ 2 are analysed via acute terrestrial and aquatic toxicity instead of CT, CA and CH. B, P, F and the composite score re all calculated using the same methodology.						

Each factor in SCRAM is calculated from one or numerous sub-factors, for example; chemical bioaccumulation score can be determined from data on bioaccumulation factor, bioconcentration factor or octanol/water partition coefficient. The uncertainty score will then correspond to the sub-factor used. For persistence and toxicity the method is similar although the uncertainty factor will depend on the amount of information available within sub-factors. Final chemical and uncertainty scores are then calculated as follows:

$$*F_{chem/unc} = (B_{chem/unc} \times P_{chem/unc})\ (1.5) + CT_{chem/unc} + CA_{chem/unc} + CH_{chem/unc}$$

The final chemical and uncertainty scores are then compiled to create the composite score, which is used in the final chemical ranking. In the case of table X, Chemical C has the highest composite score and is therefore the chemical considered to have the greatest potential to cause harm to human health and/or the environment (followed by Chemical A and Chemical B). By placing such an emphasis on uncertainty SCRAM allows the analysis of chemicals which could previously not be assessed due to a lack of information and by doing so promotes research to reduce the uncertainty associated with chemicals, for which little information is known.

SCRAM has been applied to a range of substances that are used as flame retardants to provide a more realistic example. Initial consideration of the table below shows that, for the substances considered, the main determinants of the composite scores related to environmental concerns. It is apparent that, in the cases of antimony trioxide and LCCPs, their overall ranking is significantly influenced by the high degree of uncertainty surrounding their datasets. The markedly low overall score obtained for DecaDBE is largely attributable to a relatively low measured value for BCF; if modelled estimates for this parameter or the k_{ow} value are used instead, the resultant composite score for the environment is much larger. This illustrates the inherent sensitivity of the SCRAM model to the data selected for use in estimating the B and P potential of a substance.

SCRAM Scores for a series of flame retardant substances

Substance	**Environment**			**Overall**[1]		
	Chemical score	**Uncertainty score**	**Composite score**	**Chemical score**	**Uncertainty score**	**Composite score**
DecaBDE	8	9	17	12	11	23
SCCPs	31	11	42	35	13	48
MCCPs	33	10	43	38	13	51
LCCPs	15	32	47	18	34	52
HBCDD	39	13	52	43	13	56
ATO	45	23	68	48	25	73

Notes:
[1] Combined environmental and human health scores.
SCCP - Short chain chlorinated paraffins.
MCCP - Medium chain chlorinated paraffins
LCCP - Long chain chlorinated paraffins
DecaBDE - Deca-bromodiphenyl ether.
ATO - Antimony trioxide.

Application of the Output from Benchmarking

Composite environment scores (such as those developed by SCRAM) could be used as a comparator for providing a wider context for the environmental impacts that may arise from the continued use of a chemical with PBT properties or with other properties of equivalent concern, e.g. endocrine disrupting activity. This type of approach enables a systematised and readily understandable output that can be used to compare the hazard potential of substances.

Benchmarking using the outputs of such models would involve:

i) Identifying substances with an environmental impact score above and below that calculated for the chemical of concern, i.e. appropriate benchmarks;

ii) Determining whether exposure routes and environmental media of concern for these other chemicals are likely to be similar to those for the chemical of concern; and

iii) Deciding whether the types of environmental impact are also likely to be similar – in particular, whether they relate to effects of the same severity and with the same implications with regard to sustainability of populations or ecosystems, etc.

If the above analysis suggest that there is sufficient similarity between two chemicals, then as part of any Step 4 assessment, it may be possible to highlight data on the economic costs for the benchmark chemicals as an indicator of the types of benefits of reducing exposures for the chemical of concern.

However, there may be significant limitations to use of the available models (including SCRAM) in the comparative assessment of chemicals. For example, SCRAM focuses mainly on particular aspects relating to hazard but does not, for example, allow for the implications of other potentially important factors, such as where there are differences in the extent or rate that each substance may enter the environment. Such differences could arise for example where significant differences exist in the quantities of the substance needed in a given application to deliver the same performance.

A further limitation is that these models are intended to inform on the relative risks posed by substances based on quite generic indicators of the toxicity of substances and the use default assumptions for 'weighting' the importance of different properties to the end ranking. These will reflect the particular application to which the model was intended to be put or the opinions of the model developers as to what priority should be given to what particular properties. For example, although independent scores are produced for human health and the environment by SCRAM, no further breakdown is possible within the model. Hence, it is unsuited to indicating the relative impacts of different chemicals on particular environmental compartments.

4.2.6 Step 2e: Assessment of the Potential for Quantification of Impacts

The final stage in Step 2 is a decision point that should be applied to each of the risk/exposure combinations under consideration. It is thus necessary at this stage to decide whether it may or may not be possible to develop further quantitative information on the potential environmental impacts or whether the data required to do so are either unavailable or not sufficiently robust to make it a worthwhile exercise.

To address this will require consideration of information relating to:

- the substance's physiochemical properties, the extent of persistence or bioaccumulation, and likely environmental fate and behaviour;

- environmental sources and exposures, e.g. data on the number of sites using the chemical, the emissions associated with each, the geographic distribution of these, the robustness of environmental exposure estimates, and the potential to develop estimates of environmental concentrations to establish a baseline and estimates for the proposed restriction or no use scenarios being assessed within the SEA (for instance this might be undertaken using catchment specific models, etc.);

- toxicity[9], particularly the nature of the effect, the species or taxa affected and the robustness of the dose-response characterisation available based on either individual species data or multispecies approaches such as SSD models (i.e. the hazard information underlying estimates of PNEC or other suitable 'effect' metric); and

- the availability of statistically representative monitoring or modelled data to enable quantification or prediction of the environmental stock at risk (i.e. proportion of 'at risk' media (e.g. rivers) affected, characterisation of impact in terms of local or regional significance, etc.).

Some of the above information should be quantifiable, for example, the number of sites using the substance of concern, the tonnages associated with each, the level of emissions to different environmental compartments, the rate of degradation of the chemical in the environment, etc. In such cases, the assessment should progress to Step 3, where relevant to the SEA. However, given the limitations listed below, it is clear that within the context of SEAs for restriction or authorisation, many impact assessments will not be able to progress further; the limitations include:

- the limited nature of current scientific understanding of cross-species extrapolation of effects and the significance of changes in particular endpoints for various species and their populations;

[9] A similar approach may also be possible for substances possessing adequate information on effects considered of equivalent concern, such as endocrine disrupting potential

- a lack of exposure data and limitations in the predictive ability of exposure models, particularly to address geographical variability, interactions across local, regional and global areas and/or temporal change (which may be of particular importance for substances of marked persistent or bioaccumulative potential); and

- limitations in the extent, suitability and reliability of existing datasets (which may markedly influence the degree of uncertainty surrounding any estimates developed).

While in many cases, a lack of data may restrict the hazard characterisation to the use of single-species based estimates, in some cases, it may be possible to go further and to combine data from a number of species and taxa to derive more robust dose-response functions through the development of Species Sensitivity Distribution (SSD) estimates or in some case by use of data from other, more complex toxicity models (e.g. system level studies). In this way, more robust quantitative assessments of potential impact may be developed or, where not possible, then at least the data may inform the development of estimates that can act as surrogate indicators of the potential scale of environmental impact.

For vPvB substances, a particular aim of Step 3 would be to provide information on the rate at which the substance would build up in the environment over time, and the likely geographic spread of environmental concentrations.

4.3 Step 3 – Quantitative Description of Environmental Impacts

4.3.1 Overview

The aim of this step is to provide an indication of the significance of the proposed restriction, or the change in impacts under an authorisation 'no use' scenario, compared to the current levels of risk posed to the environment. Quantification may be important to justify restrictions as the best risk management option or to demonstrating whether or not the socio-economic benefits of continued use outweigh the risks to the environment.

There are three different levels at which quantification may be possible:

- use of simple physical indicators as proxies for impact, for example:
  - tonnage used,
  - number of sites emitting a substance into the environment,
  - quantity of the substance emitted to the environment,
  - or data on monitored levels in the environment;

- use of dose-response or SSDs data to provide information on the potential impacts on sensitive species; or

- fuller quantification of environmental impacts by combining dose-response, SSDs or systems level data with measured or modelled environmental concentration data to predict the impacts on different ecosystems or food chains. This might also include quantification of impacts related to different types of ecosystem services, following on from the assessment carried out under Step 2b.

Some data in relation to the simple physical indicators listed above should have been developed through the work undertaken as part of Steps 1 and 2. However, further suggestions are provided here.

Fuller quantification may be achieved through a number of different approaches depending upon the types of effect, exposure and dose-response data available. Where data sets permit, both single species and SSD approaches may allow quantitative estimates of the scale of effect to be generated although there are a number of concerns, particularly regarding the extent to which the test species used are representative, the extent to which endpoints may be combined, the arbitrary nature of the choice of a particular percentile of response as the basis for judging the extent of the effect, and the obvious uncertainty that exists in extrapolating from effects estimates based on particular endpoint responses seen in experimental studies to the consequences to ecosystem sustainability.

All of the available approaches that seek to derive quantitative estimates of impact need to draw on the outputs of some form of exposure modelling and data on environmental concentrations in order to provide predictions of the extent of environmental exposures under the scenarios being considered within the SEA.

As data availability will determine the path that any quantitative assessment of environmental impacts might take, Step 3 has been broken down into four different (non-sequential) possible stages.

i) Step 3a: Detailed description of the baseline and the restriction scenario or the no-use scenario for authorisation;
ii) Step 3b: Expanded use of physical indicators;
iii) Step 3c: Dose-response based quantification; and
iv) Step 3d: Assessment of potential for valuation.

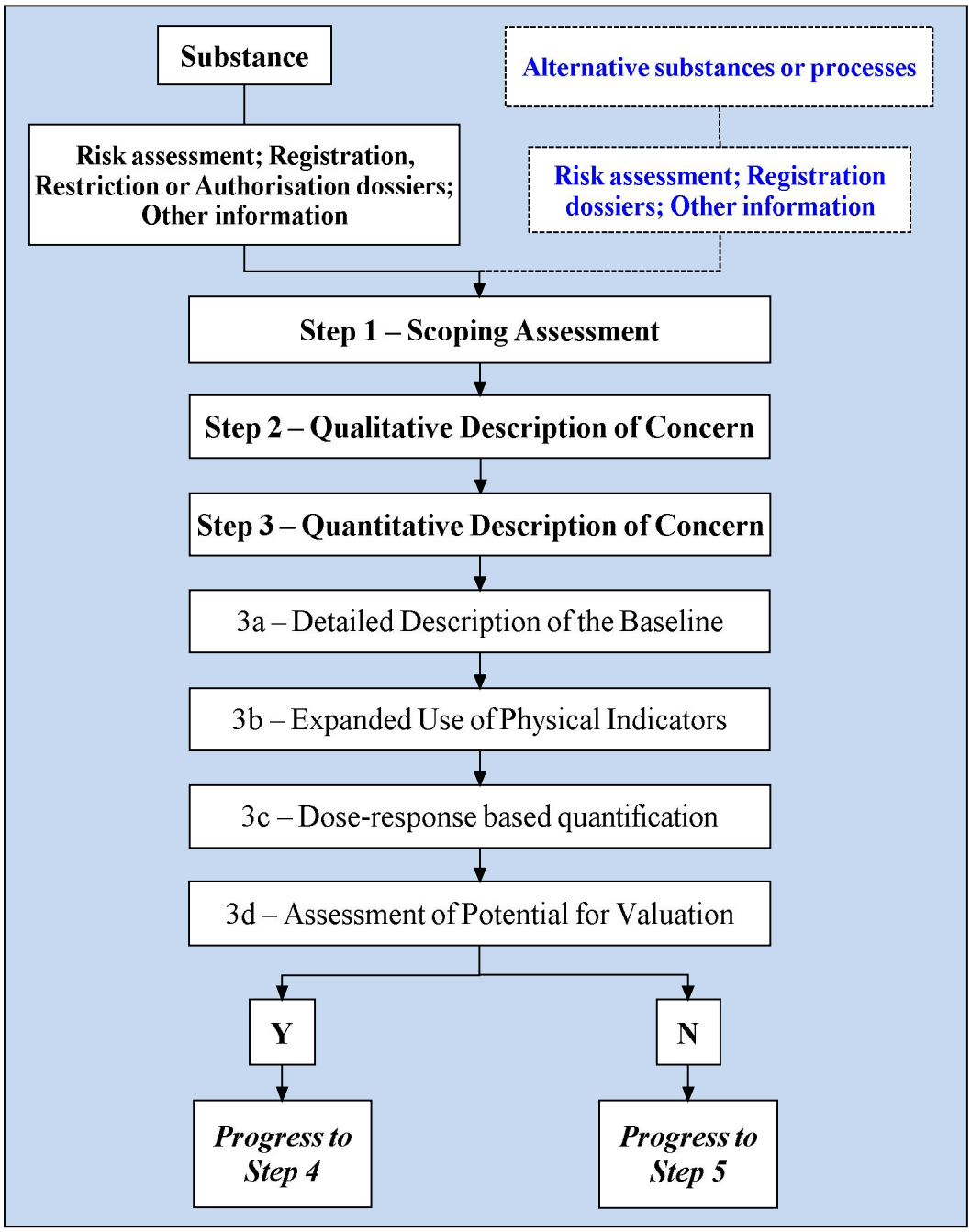


Figure 4.2: Assessment Process for Step 3

Table 4.6 provides a checklist for the types of information that are needed for this step (drawing on the data identified in the previous Steps), and the possible methods of estimation that might be applied, together with the likely nature of the resultant outputs.

Table 4.6: Checklist of Information Needs, Approaches and Reporting Outputs in Step 3	
Reporting Headlines	**Data / Discussion Areas and Outputs**
Definition of Risk Management Scenarios	Baseline plus restriction options (e.g. banning from consumer use, establishing an OEL to protect workers)
Definition of species / ecosystem services at risk	Species at risk in different environmental compartments, or ecosystem services at risk (e.g. soil fertility, drinking water supply, fisheries as a food source, etc.)
Nature of environmental impact	Data on type, distribution and duration of effects, including impact on populations/survivability of specific species, food chain effects, crop / fishery production, impact on drinking water quality, etc.
Method of impact estimation	Data sources, modelling approach, use of Benchmarking, Risk Ranking or single-species SSDs, or other dose-response data, etc.
Outputs	Number of sites at risk, area at risk, geographic extent of elevated environmental concentrations, predicted changes in population numbers, predicted impacts on productivity of ecosystem services, predicted impacts on food chain or at community level
Sensitivity analysis	Derivation of estimates based on worst-case, realistic and mean/average value assumptions

4.3.2 Step 3a – Baseline and Scenarios

As part of the work carried out more generally during Step 2 of preparing a SEA in line with the ECHA guidance, analysts will have defined both the baseline for the assessment and will have defined the restriction and authorisation scenarios.

The detail underlying the definitions of both baseline and the scenario in relation to changes in the direct environmental risks should be carried forward to this Step of the impact assessment and guide any quantification. It is important that the baseline for both the cost and environmental impact assessment are consistent and based on the same assumptions. This includes assumptions on, for example, current uses and quantities used, future use, trends in how the substance is used, including the number of sites using the substance of concern, the emission controls that are or will be in place, the number of units of a product placed on the market, etc.

4.3.3 Step 3b: Expanded Use of Physical Indicators

Simple Indicators

The simplest physical indicators of potential environmental impacts include:

1. Point source related risks:
   - data on total tonnages used across all relevant users/applicants;
   - data on the average quantity used at each site and the associated variation (low and high usage levels);

- GIS or other map based presentation illustrating the location of using facilities to provide information on the degree to which activities are concentrated in particular regions or more spread out across the EU; and
- GIS or other map data on the location of sensitive ecosystems in relation to the location of using facilities (e.g. SACs, SPAs, RAMSAR sites, Marine Protection Areas and potentially nationally important ecosystems).

2. Diffuse sources related risks:
   - data on total tonnages used and fraction emitted to the relevant environmental compartment;
   - details of the extent to which professional activities or products containing chemical of concern are undertaken at an EU-wide level;
   - GIS or other map based presentation on any identified 'hot spots' in terms of environmental concentrations; and, possibly, if relevant;
   - GIS or other map data on the location of sensitive ecosystems in relation to the location of using facilities (e.g. SACs, SPAs, RAMSAR sites, Marine Protection Areas*)*, and potentially nationally important ecosystems).

In the absence of robust data on usage patterns, environmental emissions and exposures (which will severely limit one's ability to estimate the potential scale of impacts), this type of approach might be particularly important. It provides an indication of the potential levels of exposures and, consequently, the degree of risk that might be posed by various contributors to environmental load, using simple metrics. For example, it may provide useful information to regulators where there is concern that the on-going use of a substance could lead to impacts on, for example, groundwater resources, the quality of marine waters in relation to provision of a fish nursery function or the impacts of a chemical on shellfisheries.

These aspects may already have been reported on extensively as part of Steps 1 and 2 (e.g. tonnage, numbers of sites using the substance, emissions levels). If this is the case, then only additional data should be collected as part of Step 3b.

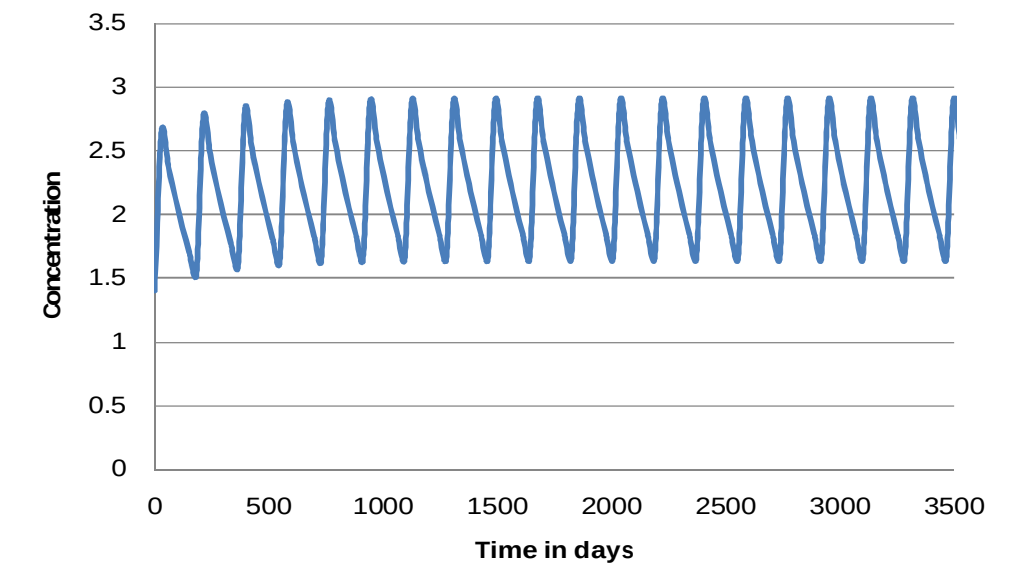
Change in Environmental Concentrations over Time

For persistent or bioaccumulative substances with little or no known direct impact, the time it would take for concentrations in environmental media or biota to degrade to 'acceptable' levels (e.g. from current to a very low concentration at which no risk of any toxic effect was anticipated) could be calculated. This time to degrade to an 'acceptable' level could be estimated for the different environmental compartments to indicate the potential speed of environmental recovery and/or the rate at which environmental burdens would be expected to increase over time for various continuing emission scenarios. For some substances this could be important, for example, where a substance's presence in sewage sludge raised concern over the use of spreading contaminated sludge to agricultural or other land (e.g. as might be the case where the sludge was being used as a soil conditioner, see example in Box 4.5).

Box 4.5: Changes in Substance Levels following Spreading of STW on Agricultural Land

In this example, changes in the levels of the substance, "XXXX" in agricultural land were modelled based on an assumed annual spreading of STW-sludge contaminated with the substance. In developing estimates it is important to note that the degradation rate and the substance's potential speed of removal, or its potential for build-up in the environment, are difficult to determine accurately.

The pattern illustrated assumes an initial concentration of 1400 µg/kg (or 1.4 mg/kg) dwt and addition of a further 1400 µg/kg (or 1.4 mg/kg) dwt once every year for a substance with an estimated half-life in soil of around 190 days.



These results suggest that – for the assumed half-life and a once-per year frequency of application – concentrations in soil would be expected to stabilise at a maximum of just under 3 mg/kg dwt shortly after application of contaminated sludge but would then return to the base level before the time of next application. This further suggests that repeated annual application of contaminated sludge even at a relatively high concentration would be unlikely to represent a particular cause for concern.

This information should assist in identifying the consequences of a delay in action during which further release would occur and lead to the potential further build-up of the substance within the environment. This might be of particular importance for substances for which there is only limited evidence of toxicity currently available and for which the main justification for a restriction or SVHC identification (authorisation) is the prevention of unforeseeable impacts in the future from a highly persistent and/or bioaccumulative, but not toxic, substance.

Use of Environmental Monitoring Data

Environmental monitoring data can provide a useful context for understanding the extent of the potential environmental risks and associated environmental impacts from the continued use of a chemical. Figure 4.2 provides an illustration of how monitoring data could be collated for these purposes, showing a distribution of the number of surface water bodies found to have concentrations of Substance X at different levels. This type of distribution could be created from a large data set of actual monitoring data or could be generated using Monte Carlo analysis, for example.

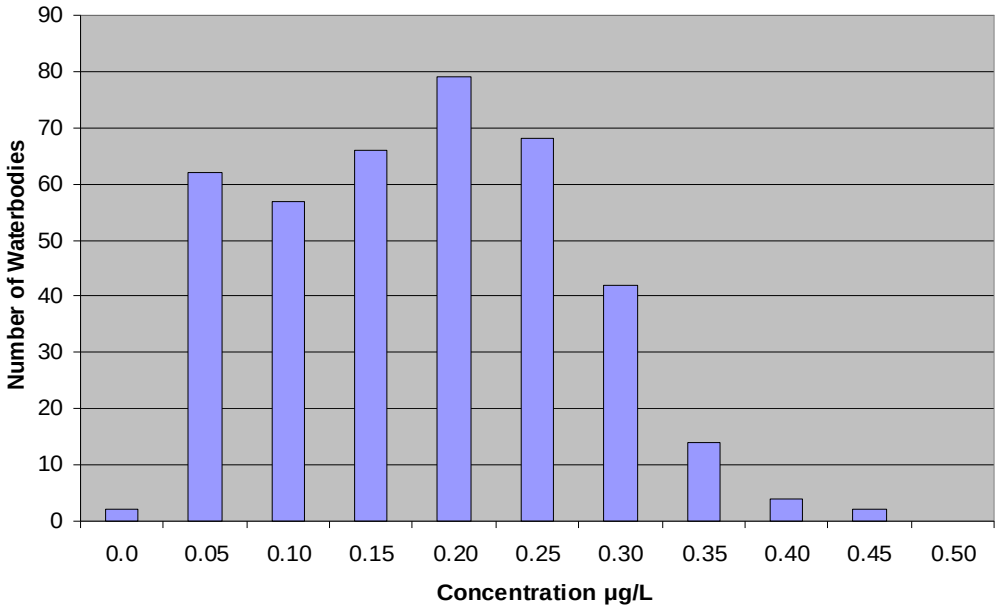


Figure 4.2: Illustrative Distribution of Data on Number of Water Bodies at Varying Concentrations of Substance X

These data could also be presented as a cumulative distribution to allow easy identification of the percentage of water bodies that would exceed a certain concentration limit. This is illustrated in Figure 4.3, which also indicates an illustrative cut-off point for a NOAEC (no observable adverse effect concentration) and a PNEC (which incorporates additional assessment factors).

As Figure 4.3 shows, 33% of all water bodies in this example are estimated to exceed the NOAEC. If the PNEC of 0.10 µg/l was used as the indicator of the point of concern, then about 70% of all water bodies would exceed this value. By preparing such estimates for each of the scenarios being undertaking, an understanding of the extent of change in impact that might be achieved for each scenario considered can be developed, thus providing useful information to decision makers even if subsequent valuation of impacts is not possible.

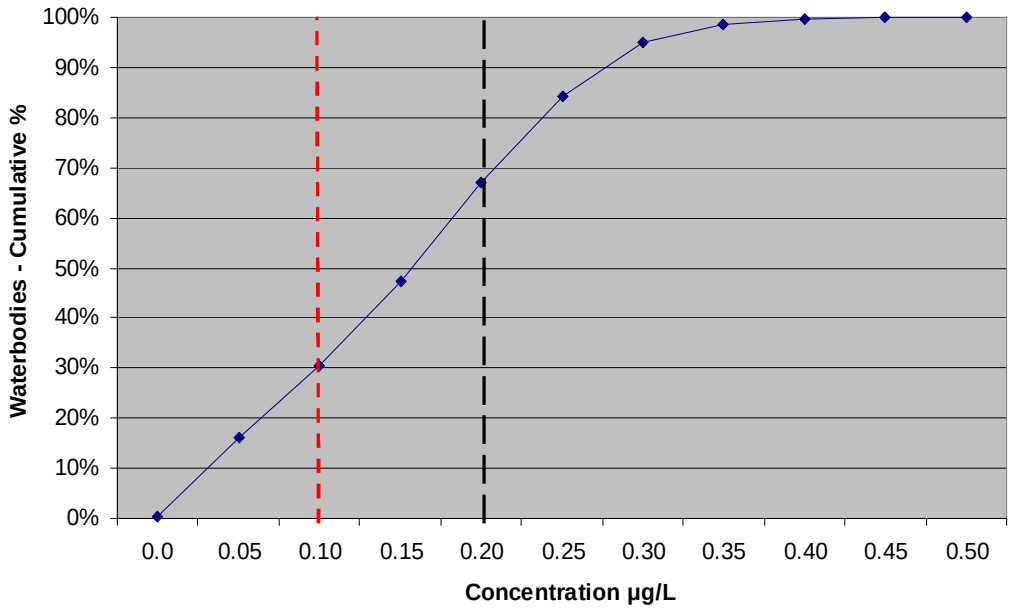


Figure 4.3: Cumulative Percentage of Water bodies with Different Concentrations Levels

Key:

Blue curve:	Distribution of water bodies bearing various concentrations of substance
Black Line:	NOAEC - No Observed Adverse Effects Concentration
Red Line:	PNEC – based on NOAEC divided by appropriate Assessment Factors

4.3.4 Step 3c: Dose-Response Based Quantification

Alternatively, for some substances it may be possible to utilise data generated as part of the risk assessment to provide more information on the dose-response relationships underlying the PNEC values. Importantly, the size of the RCR should not be used to infer, even in a comparative sense, the extent of resultant ecosystem damage.

There are three different approaches to dose-response modelling which may be relevant.

1) **Single species assessment**: It may be possible to quantify impacts for a particular species of concern, e.g. if there is a known risk to survival rates for certain fish species (e.g. x% mortality) then impacts on stocks over time could be predicted. Alternatively, an assessment might be made of the time it would take for stocks to naturally return to original levels (following reductions in emissions). It may also be possible to make qualitative links from such information to food chain level impacts or to impacts on particular types of ecosystems which are highly dependent on the particular species.

2) **Species Sensitivity Distribution (SSD) and resulting fractions of species affected at different concentrations:** If it is possible to generate robust SSDs,

then these should be repeated for each relevant environmental compartment. The results could then be compared to modelled exposure or monitoring data for the current situation (status quo) and modelled exposure data depicting the predicted environmental concentrations after emissions have been reduced (i.e. the various scenarios under consideration), to quantify how impact might change.

3) **Other Dose-Response Data**: Other data demonstrating a correlation between environmental exposures and impacts on reproduction, growth, survivability, etc. may be available and which can be used to develop a quantitative indication of potential future impacts.

SSD and Single Species Dose Responses

Figure 4.4 provides an example SSD for freshwater species based on mean NOEC values for a number of species based on the HBCCD case study (see Annex 2).

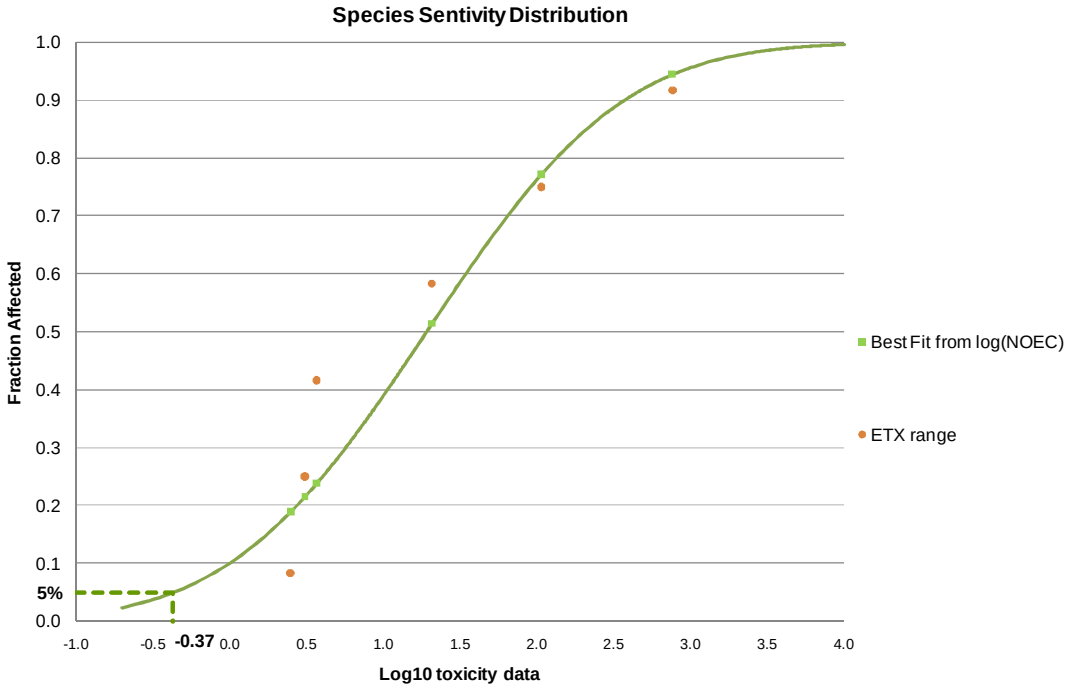


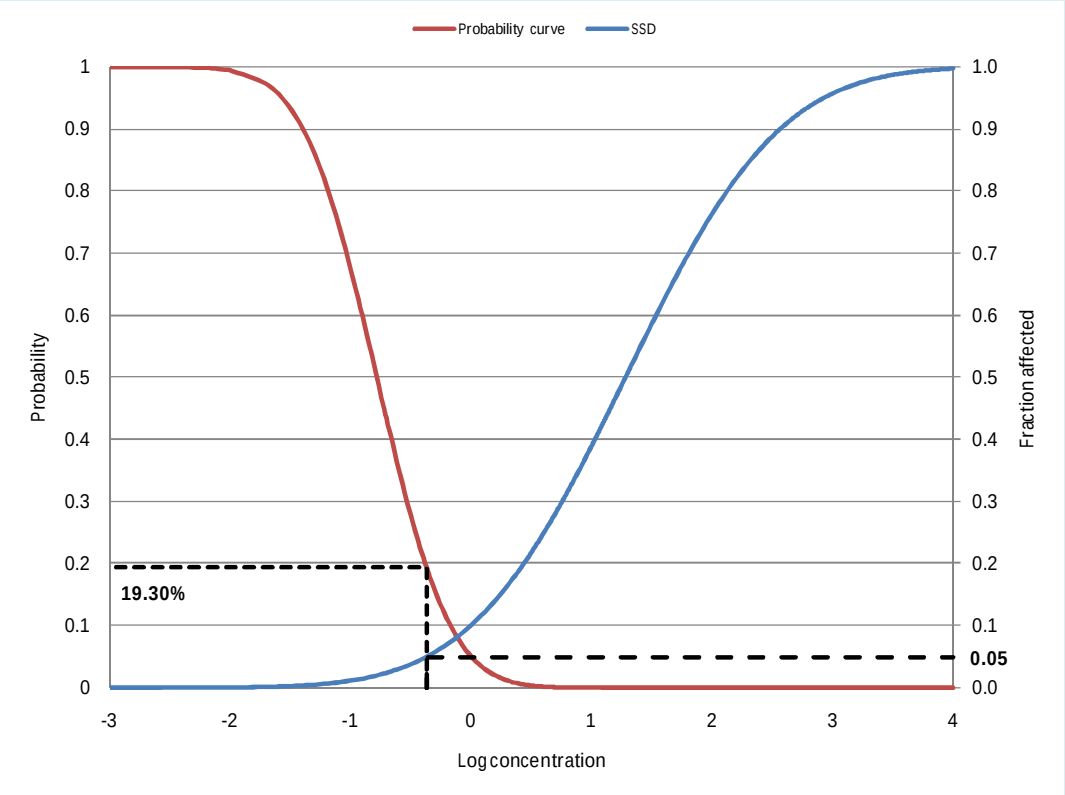
Figure 4.4: Species Sensitivity Distribution and 5% Fraction Affected (HC_5)

Figure 4.4 highlights the concentration at which 5% of species would be affected (i.e. the HC_5[10]); other metrics of effect such as $HC_{0,}$, HC_1 or HC_{10} may also be used depending on the nature of the endpoint under consideration and the appropriate level of concern. As noted above, this type of information could be directly compared with monitoring data or estimates to provide an indication of how frequent environmental concentrations might exceed the HC_5. This is illustrated in Box 4.6 based on the HBCCD case study and the SSD curve presented in Figure 4.4.

10 HC_5 - the concentration hazardous to 5% of species in an ecosystem (discussed further in Part 1 of the report

Box 4.6: Combining a SSD with Monitoring Data

Monitoring data on environmental concentrations of HBCDD across a sub-set of EU rivers were combined to derive the probability (using a lognormal distribution) that environmental concentrations would exceed certain values across all EU rivers. This cumulative distribution was then combined with the SSD to derive estimates of worst case exposure levels in European rivers and prediction of the probability for the proportion of rivers that may exceed the NOEC for 5% of species (i.e. >0.43 µg/l or a log concentration of -0.37) for HBCDD. The resulting estimate is 19.30% of rivers. Note that the case study also concluded that this percentage of rivers would probably decrease if data were available for a more representative sample of water bodies, relating to pristine, non-industrial and other industrial water bodies.



It should be noted that when used in risk assessments, HC_5-type estimates are generally subject to further application of assessment factors to adjust for uncertainties surrounding the potential ecological consequences. The extent to which such assessment factors are relevant within the context of an SEA has however not yet been defined and until such time as a scientific consensus emerges on the correct interpretation of the '%-loss' of species that can be tolerated by particular types of ecosystem, the choice of 'cut off' criteria to denote an 'adverse consequence' must be regarded as essentially a policy-based (nominal) decision rather than being based on sound scientific understanding. Despite such reservations, within the context of

applying this technique to SEAs, consideration might be given to the use of a range of estimate values within a sensitivity analysis.

WCA (2010) also suggest the use of probabilistic estimates of the dose-response across species and their comparison to estimates of the distributions of environmental exposures, such as might be generated from EUSES-type exposure models that incorporate probabilistic functionality. It is suggested that this type of approach could be used in the short term, while more complex computational approaches for chemical risk assessment and SEAs, such as might be provided by more flexible LCIA models.

While the data requirements to generate a SSD analysis for a formal risk assessment are detailed in the ECHA guidance document, the WCA report (2010) has suggested that these requirements may be overly stringent within the context of a SEA. In particular, it has been suggested that useful information can still be generated using a dataset drawing on a much smaller range of species than is specified in the guidance document for risk assessment, provided that the issue of degree of uncertainty is clearly reported.

Other Dose-Response Types of Study

For chemicals which have been the subject of concern for a number of years, there may be a range of other studies which have tried to develop links between environmental exposures and impacts on particular species. These studies may not include any formal development of a dose-response function or a species sensitivity distribution but instead rely on examining correlations between changes in the stock of particular sensitive species (or species of commercial value) and changes in environmental concentrations of a given substances species populations.

Where such studies are identified, their implications should be reported even if they do not enable quantification of impacts beyond a particular region or for varying environmental exposures.

4.3.5 Step 3d: Assessment of Potential for Valuation

At this point, following completion of the quantification exercise (Step 3c), a decision should be made as to whether it is appropriate or feasible to progress to an economic valuation of the predicted environmental impacts.

Step 3d involves the comparison of the nature of the available quantification data with the level, quality and types of information that would be needed to support the various approaches to the valuation of impacts (described in Step 4, see especially Table 4.7).

4.4 Step 4: Valuation of Impacts

4.4.1 Introduction

If it has been possible to develop dose-response data as part of Step 3, then it may be possible to carry out the monetary valuation of those impacts. Note that unlike the case for human health effects, there is no single currently accepted non-monetary unit of value such as a DALY (or QALY). Multi-criteria analysis techniques could be used to derive a unitless measure of value across different types of environmental impact, but at this point in time these will be assessment specific rather than based on a more widely accepted methodology. LCA/LCIA techniques use agreed methods for converting information on impacts into common sets of indicators, but these are generally not aggregated into a single unit of measure similar to a DALY.

The monetary valuation of environmental impact may be achieved using either:

- market based approaches;
- revealed preference based approaches; or
- stated preference based approaches (e.g. willingness to pay for an environmental gain or to prevent an environmental loss, or willingness to accept compensation for an environmental loss).

Market based approaches will be most applicable to those cases where environmental exposures are predicted as having an impact on commercial activities, such as commercial fisheries, forestry or agriculture. They will also be relevant where the current use of a chemical is associated with contamination of drinking water supplies, the need for soil remediation, increases in the costs of other treatment process (for example, to increases in the costs of sewage effluent treatment), or an inability to use an environmental resource for another purpose (e.g. sewage sludge containing the substance could not be spread to agricultural land).

Revealed preferences methods are the least likely set of methods to be relevant. In a few rare cases, studies may exist which link demand for end-products to particular chemical characteristics, but this will be unusual. It is also unlikely that it will be possible to link changes in environmental quality, such as the quality of a recreational fishery, to most of the chemicals likely to undergo restrictions or authorisation to enable use of methods such as the travel cost technique.

The use of stated preferences based WTP values may be relevant although it is likely that further research in this area will be required. In particular, these approaches can capture the values people' hold towards environmental improvements in terms of their own use of the environment, other people's use of the environment (now and in the future) and more generally for conservation and preservation reasons.

As for health, it is not proposed here that MS Authorities and authorisation applicants would undertake original WTP or revealed preferences valuation studies. Instead it is assumed that the most appropriate level for such work to be carried out would be at the EU level with the aim of developing transferable estimates for the types of environmental impacts likely to arise from the types of chemicals subject to restriction and authorisation. This may be particularly important in relation to certain types of environmental effects which reflect people's desire to protect and conserve the environment of reasons other than their own direct use of it (e.g. those linked to ecosystem services classed in Table 4.4 as being symbolic, experiential, and regulation of the biotic environment and of biophysical conditions).

However, look-up tables are provided below setting out examples of the types of valuations that have been derived in the past through such studies. As for health, it may be possible to use these through application of benefits transfer based approaches. There will also be a role though for the generation of estimates of the economic costs associated with impacts on certain types of ecosystem services – particularly those related to market products – and those related to some of the regulating services or functions provided by the environment.

Based on the above, there are four possible steps:

i) Step 4a: Development of market based estimates;
ii) Step 4b: Application of transferable willingness to pay estimates;
iii) Step 4c: Review of revealed preferences literature; and
iv) Step 4d: Aggregation of valuations and check for double-counting.

Figure 4.5 sets out the different stages to Step 4. Table 4.7 summarises the types of information that would have to be considered and reported on in Step 4, drawing on data derived during Steps 3b or c.

Table 4.7: Checklist of Information Needs, Approaches and Reporting Outputs for Step 4

Reporting Headlines	**Data / Discussion Areas and Outputs**
Environmental impact	Extent of impact on key populations, extent of ecosystem damage, time to remove from environment if withdrawn from use, etc
Basis for estimation	E.g. eco-services effects, proportion of environmental compartment affected; extent of reduction in population of key species; data on the human population assumed to hold a WTP or other value; data on market prices and yields under different chemical exposures
Method of quantification	Assignment of economic values to overall change in economic metric: use of benefits transfer techniques; estimates of the change in productivity due to change in environmental quality and the economic value of this
Output	Annual environmental damage costs avoided
Sensitivity analysis	Derivation of estimates based on worst-case, realistic and mean/average value assumptions

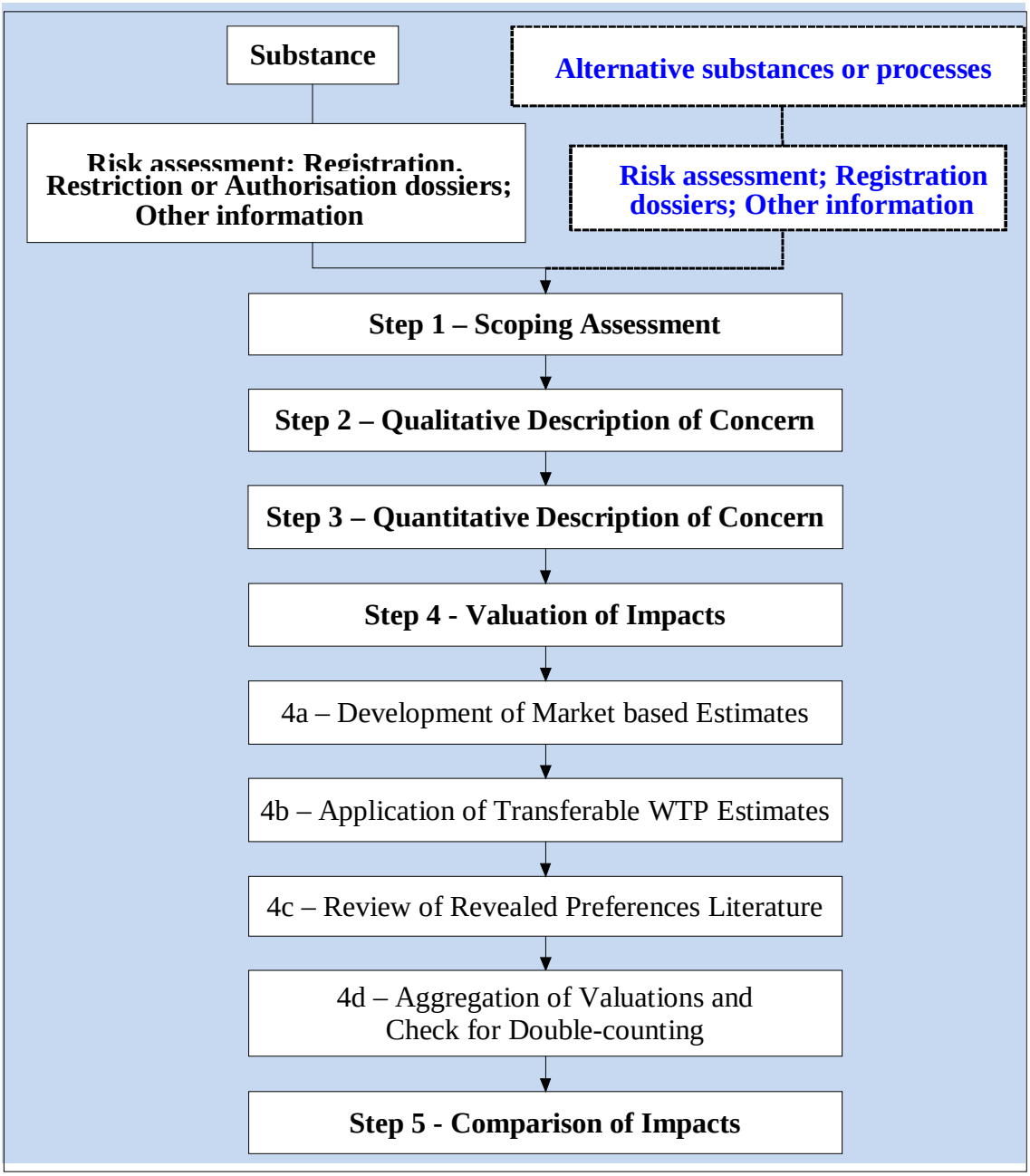


Figure 4.5: Assessment Process for Step 4

In the absence of suitable estimates of the scale of impact on which to draw on, it may be helpful to seek expert ecotoxicological/ecological advice as to the potential implications of the effects identified on ecosystem sustainability. Although this may not provide robust quantitative estimates of impact per se, it could add to the weight-of-evidence supporting any conclusions drawn on the significance of impacts and may enable identification of proxy indicators of impacts or analogous situations for which some measure of valuation had been possible.

4.4.2 Step 4a: Development of Market Based Estimates

Direct Estimates

Where it has been possible through the use of dose-response data to link changes in environmental concentrations to changes in ecosystem services related to production or regulation, then the first step would be to try and place an economic value on the predicted change in productivity or the level of regulating services provided (see Table 4.7 above).

This would most likely be relevant for fishery production, soil fertility and drinking water quality although it may also be relevant to other regulating services such as pollination and bioremediation. Box 4.7 illustrates how this type of approach has been used in other studies to place an economic value on damages to farmers associated with the loss of honey bee pollination and honey production. Note that this study's starting point was the Millenium Ecosystem Assessment approach set out in Box 4.3.

Box 4.7: Valuation of Changes in Environmental Productivity – Honey Bees

An example of the application of this type of framework is a study on the impact that a (generic) insecticide might have on Honey Bee populations. In this, UK data from previous studies on number of honey bee colonies and calculations of their approximate indirect and direct value (via pollination and honey production, respectively) were utilised. The analysis suggested an average annual decline of 4320 colonies (1943-96) had occurred in the UK and the economic loss associated with each colony was £940 (at 2004 prices). A sensitivity analysis was also undertaken to illustrate how various degrees of causality between low of colonies and use of the insecticide might influence the resultant estimates of impact.

Annual loss in honey production and pollination attributable to insecticide exposure		
Level of loss attributable to insecticide	**Number of colonies lost each year**	**Total annual loss via pollination and honey production (£/yr)***
5%	216	203,000
10%	432	407,000
50%	2160	2,034,000
70%	3025	2,950,000

From: Giacomello et al (2006)

Identification of the environmental stock at risk may be aided by any mapping work undertaken as part of Step 2. Otherwise, some concrete justification for the number of sites identified as being at risk would need to be provided. This might, for example, be generated through comparing exposure estimates against SSD model estimates of 'effect' level based on worst case and less conservative assumptions. Interpretation of such estimates is however extremely challenging in most situations due to the limited state of current scientific understanding of ecosystem behaviour. Of particular note is the ongoing ecotoxicological debate over the proportion of species in any given ecosystem that can be adversely impacted without there being a significant challenge in the ecosystems sustainability.

Thus, it is quite difficult at this point to ascertain the nature of any specific services that might be affected. One approach might be to assume that a species of economic value might be adversely impacted leading to a need to restock the water body, i.e. use a market-based approach. However, this would be a very uncertain estimate because of the reasons explained above.

Comparison to Other Market-based Data

There may also be value in considering the types of costs that have arisen in the past in cleaning-up or remediating contamination problems caused by particular chemicals. It is important to note that such estimates do not reflect individuals' willingness to pay for an environmental improvement. They only provide an indication of how much it would cost to undertake clean-up or remediation activities. At best, such estimates should be considered to provide a lower range proxy for the value of the damages that may be caused by chemical contamination.

4.4.3 Step 4b: Application of Transferable Willingness to Pay Estimates

Numerous willingness to pay (WTP) studies have been undertaken in the past to address particular environmental pollution issues. As discussed in Part 1 of this report, few of these are chemicals specific, and those that are may not be relevant to the types of effect that REACH is trying to address or are readily applicable to valuing damages caused by a single pollutant rather than multiple pollutants.

In addition, existing valuations will relate to change in environmental damage levels; as part of this study we have identified no studies that reflect WTP values held solely towards removing persistent or bioaccumulative substances from the environment. This indicates that there is a need for such valuations to be established, without any reference to toxicity effects. In addition, it may also be important to establish valuations for other properties considered of 'equivalent concern' under REACH (e.g. for substances with endocrine disruptive potential, even where it may not be possible to establish direct toxic impacts at this time).

Although research may help fill these gaps in the longer term, in the short term there are two potential options.

Single Species Benefits Transfer

The first would be to focus on the potential for valuing adverse impacts on individual species. For example, particularly highly valued species such as 'signature', 'charismatic' or endangered species may be shown to be 'at risk'. The economics literature could be checked for existing valuations of this or similar species based on the use of stated preferences techniques (e.g. willingness to pay/accept). Table 4.8 summarises 31 studies of 67 WTP observations in a meta-analysis carried out by Richardson & Loomis (2009).

Table 4.8: Summary of economic value of threatened, endangered and rare species

	Low value (€)	High Value (€)	Average of all studies (€)
Studies reporting annual WTP			
Bald eagle	15	32	28
Bighorn sheep	-	-	12
Dolphin	-	-	26
Gray whale	17	33	25
Owl	28	94	47
Salmon/Steelhead	7	100	58
Sea lion	-	-	51
Sea otter	-	-	29
Sea turtle	-	-	14
Seal	-	-	25
Silvery minnow	-	-	27
Squawfish	-	-	9
Striped shiner	-	-	6
Turkey	8	9	9
Whooping crane	32	45	40
Woodpecker	9	14	12
Studies reporting lump sum WTP			
Arctic grayling	14	19	17
Bald eagle	176	252	214
Falcon	-	-	23
Humpback whale	-	-	173
Monk seal	-	-	120
Wolf	16	117	44

Source: Adapted from Richardson & Loomis (2009), Original values given in US $ and converted to € (Conversion rate 1 USD =0.72 EUR).
NB: Values rounded to nearest €.

The basis on which these were derived would have to be checked and the potential for (and validity of) linking such values to the impact of chemical exposures would need to be established. Where it is believed that a previous study could act as an indicator of the economic value people may assign to the protection of a given species/habitat, then the mean and median WTP values from the study could be adopted as benefit transfer values. Note however that many of the valuation set out in Table 4.8 are

based on the extinction of the species rather than abnormalities/population declines, and this will have to be taken into consideration before any values are transferred.

Ecosystem or Habitat Based Benefits Transfer

There may also be the potential to value wider environmental impacts on ecosystems (e.g. on biodiversity, wildlife generally or on the quality of environmental resources such as fresh or marine water bodies). This would again require the availability of WTP values that are relevant to the types of impacts associated with the chemical of concern. It would also require the impact of single chemicals to be separated out (or proportioned) from the combined impact of other environmental pressures.

The latter is a problem that would arise, for example, in trying to use valuations from the AquaMoney project, for example, which derived estimates of people's willingness to pay for improvements in river water quality and hence in the ecological status of rivers.

Aggregation of WTP values

Determining the appropriate population for aggregation of such WTP values is a key difficulty, particularly where such values may be held by people living long distances from the affected sites. As a result, it is proposed here that instead of making assumptions as to what the relevant population is, a backward calculation is carried out.

This would involve calculating how many people would have to hold the median and mean WTP for the benefits of environmental protection to outweigh the compliance costs to industry.

4.4.4 Step 4c: Review of Revealed Preferences Literature

For a chemical that is incorporated into consumer products, there may be studies aimed at establishing consumers' revealed preferences for different end-product characteristics, such as chemical content. Although it is unlikely that such studies will exist for most chemical and product combinations, there may still be merit in checking the economics literature to identify if estimates may be possible through use of analogy, etc.

4.4.5 Step 4d: Aggregation of Valuations and Check for Double-counting

If more than one valuation approach has been used, for example, the estimate of productivity losses under Step 4a and the development of WTP estimates under Step 4b, then it will be necessary to develop aggregate estimates of the environmental benefits of reduced chemical exposures. However, care should always be taken to ensure that individual estimates are reported separately in the SEA prior to aggregation; in other words, the estimate value of damages associated with each environmental impact carried forward to Step 4 should be reported on its own, prior to

be combined with other damage estimates to develop an indication of total environmental impacts.

It will also be important to check that there is no double counting between WTP estimates and either market based valuations or revealed preferences valuations. For example does the WTP value reflect not only an individual's valuation for conservation and preservation of the environment, but also towards harvesting of wild species for food purposes (e.g. protection of wild salmon fisheries).

The approach to developing estimates of total environmental benefits will depend on the approach being adopted more generally for the SEA. See also Step 5.

5. COMPARISON OF IMPACTS - STEP 5

5.1 Introduction

The final step within the logic framework is the comparative analysis of the changes in human health and environmental impacts arising from the proposed restriction or the proposed authorisation decision. This includes bringing together information on:

- **The effects related to the chemical of concern**, with this including both primary and secondary impacts:
  - ***primary impacts*** are those stemming from the risks of concern, while
  - ***secondary impacts*** are those stemming from other relevant risk endpoints (e.g. respiratory sensitisation as an impact on workers in addition to potential carcinogenic effects) or from impacts that may arise from the primary impact (e.g. impacts on particular species may lead to food chain effects or wider effects on ecosystem services).

- **The effects arising from substitution** (in its broadest sense): these are the health or environmental impacts that may arise from a shift to the use of alternative substances, processes or technologies. They may arise across the lifecycle of a chemical or product's use and arise from changes in inputs, changes in process emissions or changes in usage requirements or changes in end waste products (composition or volume).

Although this logic framework has focused on assessing effects related to the chemical of concern, as this was the aim of the study, consideration will also need to be given to the effects arising from substitution (and in this regard reference should also be made to the ECHA Guidance on SEA for further discussion on assessing alternatives). For this reason some discussion is provided on this below.

However, before moving to the issue of alternatives it is important to identify some key principles that should be adopted in providing the comparative analysis of the impacts of restriction or authorisation decisions:

1) Information should be provided for each of the individual impacts. Where it has not been possible to quantify a particular impact, its importance should be summary as the nature of the impact described.

2) Where it has been possible to quantify some impacts but not others, then an indication of the likely importance of the quantified effects compared to the non-quantified effects should be given.

3) Where impacts are quantified in monetary terms, then it will be important that the monetary value of each is set out prior to any aggregation; analysts should also check for the consistency of prices and of any discounting applied to the values prior to developing aggregate estimates of benefits.

4) In particular, if the restriction or authorisation scenario would give rise to both positive and negative health or environmental impacts, then this should be made clear to decision makers. Each set of impacts should be set out clearly so that the trade-offs between health and the environment are made clear. The importance and or value of each set should be identified prior to any aggregation to determine net effects.

More generally, the approach to the comparative assessment should follow the overall approach being taken to the SEA, and in line with the overarching ECHA Guidelines. However, it is clear that there is also a linkage between how far it has been possible to progress through the logic framework proposed here and the type of assessment that forms the basis for the SEA. For example, a cost-effectiveness analysis will require some of the data that would be produced as part of Step 3 to this framework, while a quantitative cost-benefit analysis would call upon the types of data that would be produced under Step 4. More qualitative SEAs could draw upon the types of information and conclusions from Step 2, perhaps supplemented by further quantitative data based on Steps 3 or 4 where available.

5.2 A Note on Assessing the Health and Environmental Effects from Alternatives

The effects arising from alternatives (in their broadest sense) are those health or environmental impacts that may arise from a shift to the use of alternative substances, processes or technologies. They may arise across the lifecycle of a chemical or product's use and arise from changes in inputs, changes in process emissions or changes in usage requirements or changes in end waste products (composition or volume).

To the degree possible the same types of information used to assessing the health and environmental effects of the substance of concern are also required to assess the extent to which a move to alternatives would result in an increase in health or environmental risks.

This applies to both restriction and authorisation cases:

- as part of a restriction dossier, the assessment of alternative risk management options must consider their effectiveness, with this including the degree to which they reduce risks to health and the environment; while

- under authorisation, alternatives must be 'suitable' with this defined in part in terms of no resulting increase in health or environmental risks.

Thus, information from the wider assessment of the potential alternatives will need to be collated to provide an indication of their health and environmental impacts. This may include impacts associated with the hazardous properties of chemical alternatives similar to those being considered for the substance of concern, or a wider set impacts

associated with changes in processes or products and the use and disposal of these (again see the ECHA Guidance on SEAs and Restriction, including Appendix B).

For example, in relation to substitute chemicals, the work involved may include:

- collecting data on the properties of alternative chemicals from manufacturers and importers or other sources (e.g. CSRs on substitutes when these have been registered, or from other sources when registration has not yet taken place);
- examining the hazard profiles of the alternatives to determine whether they would result in a lower level of risk;
- examining information on environmental concentrations of the substitutes and data on current levels of exposure from publicly available sources or impacts associated with alternative options; and
- if appropriate, quantifying and valuing the change in risk following the approach set out above for the substance of concern.

For other alternatives, whether technologies or products, the corollary of the above information will be required. In other words, descriptions of the systems that would be put in place are required together with the inputs associated with these systems to allow an assessment of the changes in environmental impacts to be prepared.

It would obviously not be appropriate to require that the risks associated with alternative chemicals, process or products to be assessed in the same detail as the risks associated with the substance of concern. Instead, the assessment should be proportional to the potential for new risks or significant impacts to arise, and depend on the properties and/or hazards/risks/effects posed by alternative substances and/or processes.

To the degree possible and appropriate, the same type of analysis for the alternatives as has been carried out for the substance of concern, as a parallel stream of assessment should also be undertaken. For example:

- if benchmarking methods are used as part of Step 2, then the alternatives should also be scored in relation to their properties and compared against the chemical of concern. This may require considering properties in relation to both health and the environment to check against any shifts in risk from one to the other;

- if health effects have been valued in terms of changes in DALYs or have been valued in monetary terms, then any expected health impacts from shifting to an alternative should also be assessed in the same units where feasible; and

- similarly, there may be merit in examining the potential for developing SSDs and in modelling environmental concentrations for any alternative that has toxic properties for the environment.

The overall aim here would be to try and identify those effects that may be important enough to change a decision (together with data on the other impacts) as to whether or

not a restriction would be appropriate or the socio-economic benefits of an authorisation would outweigh the net change in risks to health or the environment.

The key difficulties are likely to arise in relation to the move to alternative processes or products, where this may require consideration of a wider set of impacts. For example, if the loss of the use of a given substance would result in a shift to a higher energy demanding technology, then one might estimate the change in energy demand and the implications of this for atmospheric emissions; this change in emissions could in turn be assessed in monetary terms, using the types of benefits transfer estimates that are given in Appendix B to the ECHA Guidance for emissions of SOx, NOx, and CO_2.

ANNEX 1:

TRIS (2-CHLOROETHYL) PHOSPHATE

CASE STUDY TRIAL OF HEALTH LOGIC FRAMEWORK

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1. INTRODUCTION

Tris(2-chloroethyl) phosphate (TCEP) is a chlorinated phosphate flame retardant used in a wide range of industrial applications because of its flame retardant properties. It also has some applications in the chemical industry as an intermediate. Although considered of low risk to the environment, it is classified according to the Dangerous Substances Directive 67/548/EEC (DSD) as being a reproductive toxin Category 2 (R60) and has therefore been identified as a substance of very high concern (SVHC) according to the criteria set out in Article 57(c) of REACH. Under Directive 67/548/EEC, TCEP was also classified as a Carcinogen (Cat 3, R40), harmful (Xn, R22) and dangerous to the aquatic environment (N, R51/53). At a meeting in November 2005, the EU classification and labelling working group (Human Health) established the following final classification for TCEP: Toxic (T), Carcinogen (Cat 3); Reproductive toxicity (Cat 2); Dangerous for the environment (N); Harmful if swallowed (R22); Limited evidence of a carcinogenic effect (R40); Toxic to aquatic organisms (R51); May cause long term effect in the aquatic environment (R53|); and, May impair fertility (R60) (RAR; EC, 2009).

TCEP meets the persistent and very persistent (**P/vP)** and toxic (**T)** criteria set out in Annex I (4) to REACH for the identification of persistent, bioaccumulative and toxic (PBT) substances. However, TCEP does not meet the criteria for bioaccumulation and so is not considered to be a PBT substance.

It has been pre-registered by a number of companies and the first anticipated registrations are expected by the first phase-in date (30 November 2010); TCEP will be subject to authorisation because of its status as a SVHC. The benefits derived from its continued use in any authorised applications will therefore have to be carefully balanced against the potential for adverse impacts on human health.

This case study has been prepared specifically to exemplify the application of the proposed logic framework for the assessment of Human Health Impacts. Although some potential environmental concerns were identified for this substance in the risk assessment carried out under the Existing Substances Regulation (in particular in relation to the substance's persistence), these aspects are not discussed here. The aim is to identify, describe qualitatively, and – to the extent that it proves possible – to quantify the scope and scale of the various potential adverse human health impacts that may be attributable to TCEP exposures.

The overall objective has been to derive information on the various human health impacts in a form that would be appropriate for inclusion in an SEA conducted to support an Authorisation. However, it is anticipated that the case study will also be representative of substances subject to restriction proposals.

This has meant that we have:

1) gone back to the information presented in the ESR risk assessment and to the original source articles;

2) made a number of assumptions as to the likely populations affected;

3) tested the use of alternative sets of assumptions, for example, the use of 'worst-case' assumptions based on the risk assessment conclusions and less precautionary assumptions to provide an idea of what might be the lowest level of effect;

4) we have tested the use of software such as the US EPA's benchmark dose model and used the outputs of this as part of the case study; and

5) we have explored the availability of monetary valuations for and their use to derive estimates of the economic benefits of avoiding disease cases associated with TCEP exposures.

The case study draws heavily on the European Risk Assessment Report (RAR), the Annex XV dossier (EAA, 2009), the Member State report on SHVC status (ECHA, 2009) and the draft background consultation document published by ECHA in July 2010 (ECHA, 2010), supplemented by other sources as necessary. The approaches adopted and the data used in this case study were not discussed with industry. In some cases, we have made assumptions on data relating to the production and uses of HBCDD and on numbers of workers potentially exposed, which industry may be able to provide valuable updates on.

2. LOGIC FRAMEWORK - STEP 1: CHARACTERISATION AND SCOPING

The first step in the logic framework is to collate basic information on usage of the chemical and the risks identified as being of particular concern.

2.1 Characterisation of Production and Use of TCEP

As of 2001/02, TCEP was not produced in the EU-15 but 1,150 tonnes per year (t/y) were imported by three companies (two in Russia and one in Poland). The tonnage exported from the EU was 143 t/y, suggesting an overall EU balance of about 1,007 t/y (RAR). While data based on REACH pre-registration submissions suggested that the volumes used might be higher (7,200-72,000 t/y), these have been judged to be of questionable reliability (EAA, 2009).

On balance, it is currently believed that the overall 2001/02 production estimate represents the best available estimate. Following the European Union expansion to the EU-27, the production at a single site in Poland of 300-500 t/y is now considered to represent EU manufacturing (ECHA, 2010).

Historically, the largest use was in production of celled, rigid or semi-rigid foams (accounting for 80-90%). However, the use pattern for TCEP has changed over the last 15 years. A definitive pattern of use is available for about 44% of the total TCEP consumed which suggests it is generally used in plastics, textiles, adhesives, paints and varnishes. Currently, the main application is believed to be production of unsaturated polyester resins (>80%) with other applications, such as acrylic resins, adhesives and coatings, accounting for most of the remaining consumption. The main end-use sectors that use TCEP are textiles, furniture and construction, as well as cars, railways and aircraft.

Approximately 1 t/y is believed to be used in the production of flame resistant paints; this is considered to be a specialist market with the use of such products limited to professionals. TCEP is understood not to be included in consumer paints on the basis of the absence of any regulatory requirements governing the flammability of domestic paints and the high cost of TCEP compared to other plasticisers; this was confirmed by the largest coatings manufacturer in the world (RAR).

ECHA (2010) also estimates that about 50 t/y is used as a chemical intermediate in the manufacture of wax additives, an application falling outside of the immediate consideration of Authorisation under REACH.

In the light of the somewhat conflicting information available on the volumes and use patterns for TCEP in the available reports, for this case study we have assumed the following production and use patterns:

EU imports	= 750 t/y
EU production	= 400 t/y
EU exports	= 140 t/y
Overall EU balance	**= 1,010 t/y**

Use as chemical intermediate	= 50 t/y
Use in polymer industry (flame retardant/fire prevention agent)	= 950 t/y
Use in paint/varnish industry(flame retardant/fire prevention agent)	= 10 t/y

No direct information on the structure of the supply chain is known (ECHA, 2010).

2.2 Risks and Hazards of TCEP

2.2.1 Risks Identified for TCEP in the RAR

The EU RAR identified unacceptable risks in relation to workers involved in the production of TCEP, its use in the preparation of formulations and in the uses to which these formulations are put.

One consumer application (toys intended for sucking/mouthing in very young children) was also considered of concern.

For convenience (and to avoid repetition), fuller descriptions of the nature of these risks are presented in Section 3 in relation to Step 2 of the logic framework.

2.2.2 Identification of Additional Hazards for SEA

As required by the Logic Framework, the available data on any other potential hazards for TCEP were reviewed, drawing on the findings in the EU Risk Assessment Report (RAR) and other sources, where available (a detailed assessment was prepared but is not reported here). The focus was to establish if any additional consequences of human exposure to TCEP had been identified that might be considered of potential socioeconomic importance or that might act as a surrogate indicator of impact. The findings of this review are summarised below.

Toxicokinetics

While limited, comparative toxicity data on acute oral, dermal and inhalation toxicity (see below) suggested possible route-specific differences.

In the light of the physicochemical properties of the substance, the absence of toxicokinetic data and lack of suitable confirmatory data from repeat dose toxicity studies, the EU Risk Assessment concluded that as a precautionary assumption, complete absorption should be assumed via all routes. However, as many organic

substances tend to show lower dermal absorption compared with that shown via the inhalation or oral routes, it was decided, for the purposes of this case study, to also consider what might have been the implications for risk (and consequent estimation of impact) had the RAR adopted a somewhat less precautionary estimate of the extent of dermal uptake. On this basis, it was decided to also develop alternative estimates of impact based on the assumption that absorption via inhalation and ingestion is complete (100%) but that assumption via dermal absorption is either 100% (the high scenario consistent with the RAR) or 20% (an alternative low scenario).

Acute

No human data are available but, experimentally, TCEP shows moderate oral toxicity but only low dermal and inhalation toxicity.

LD_{50} oral rat = 430-1230 mg/kg
LD_{50} dermal rabbit = >2150 mg/kg
Non-lethal inhalation exposure rat = 25.7 mg/L.

Given the high values reported for acute toxicity compared to the identified PODs from studies involving repeat exposure to TCEP and the exposure estimates identified in the RAR, **acute toxicity is not considered to warrant further consideration.**

Irritation and Sensitisation

TCEP is not considered to be an irritant or human sensitiser. **Hence, these types of toxicity are not considered to warrant further consideration.**

Repeat Dose

In addition to the renal non-neoplastic effects used in the risk characterisation, there is a considerable body of experimental evidence (see RAR) that also identifies the central nervous system (CNA, specifically brain) and liver as other important non-neoplastic target organs following repeat exposure.

Liver

Effects on the liver were observed following oral treatment at relative high doses of F344/N rats (350 mg/kg/day in males and females and 44 mg/kg/day in females only for 16 days; both sexes given 88 mg/kg/day after 66 weeks), CD rats (>192 mg/kg/day for 3 months), and B6C3F1 mice (700 mg/kg/day both sexes and 175 mg/kg/day in females). Effects were limited to increased organ weights without associated treatment-related biochemical or morphological changes.

Given the lack of toxicologically important pathological changes and that the POD identified for repeat dose toxicity in the kidneys showed a LOAEL of 12 mg/kg/day,

it is considered unlikely that significant impacts would be identified for this endpoint under the anticipated exposure scenarios, **therefore hepatic effects are not considered to warrant further consideration.**

Brain

Following the RAR, ECHA (2009) reviewed available data on the CNS (brain) effects of TCEP the findings of which are summarised below. One case study was identified in which a 5-year old girl developed neurogenic defects after sleeping in a room with wood panelling treated with 3% TCEP; shortly after renovation work to remove the wood panelling in this room, the child's clinical status started to improve.

In a recent epidemiology study on children's development, conducted by the Austrian Umweltbundesamt (UBA 2008), the influence of indoor air pollution on children's health was investigated in nine schools. TCEP was measured in house dust and particulate matter PM_{10} and $PM_{2.5}$ and was recovered from nearly all analysed house dust and particulate matter samples. The TCEP concentration in household dust was in the range of 0.59 and 35 mg/kg. Cognitive skills were tested using Standard Progressive Matrices (SPM); this is an indicator for cognitive skills, independent from education or socio-cultural environment. A strong correlation was found between the TCEP concentrations in particulate matter (indoor: PM_{10}, $PM_{2.5}$) and house dust and a decline in cognitive skills of children, although not all potential confounding factors were adjusted for in the statistical analyses.

Experimentally, an acute delayed neurotoxicity study in White Leghorn hens found no neurotoxicity after two oral doses (day 1, and 3 weeks later) at 14.2 g/kg bw but a single oral dose of 275 mg/kg bw to adult female Fisher-344 rats was reported to cause a severe and specific pattern of hippocampal damage, particularly to CA1 pyramidal cells (with lesser damage to CA4, CA3, and CA2 cells). Signs included seizure and abnormal muscle movement. Impairment of repeat water maze performance was noted with a single dose resulting in learning deficits for up to 3 weeks after exposure.

Repeated oral dosing of rodents (22-700 mg/kg bw/day in rats; <1500 mg/kg bw/day in mice) caused dose- and sex-dependent neuronal necrosis in hippocampal and thalamic regions of the brain; this was more severe in female than male rats. In mice, the NOAEL for brain was 175-350 mg/kg bw/day. However, the RAR concluded that the critical study for establishing a NOAEL was a 103-week oral gavage study in F344-rats at 0, 44 or 88 mg/kg bw/day in which a dose- and sex-dependent increase in severity was noted. From this, a repeat dose NOAEL for brain of 44 mg/kg bw/day was defined.

ECHA (2009) also noted an additional experimental study in female Fisher-344 rats exposed to 275 mg/kg of TCEP by gavage (Tilson et al, 1990) which suggested that a single exposure to TCEP might result in a severe and specific pattern of damage to

hippocampal neurons associated with deficits in learning up to 3 weeks after exposure.

Given the emergent toxicity and epidemiological evidence and the potentially serious nature of the potential effects**, it is considered appropriate to study further the potential for neurotoxic impacts in both workers and babies.**

Mutagenicity

There are no human data available but TCEP is reported in the RAR to be negative for mutagenicity in vitro and also in some in vivo studies. Very weak responses noted in SCE and micronucleus tests were considered inadequate to establish a mutagenic potential.

Given this, other than that arising during consideration of the potential carcinogenic impacts of TCEP, **the mutagenic potential of TCEP is not considered to warrant further consideration.**

Reproductive Toxicity

The RAR identified concerns with regard to the risk posed to the fertility of both workers and consumers (see above). However, TCEP does not appear to be embryo/fetotoxic or teratogenic in rodents even at maternal toxic doses using standard test models. Thus, the NOAEL for developmental toxicity established by the RAR was 200 mg/kg bw/day; the corresponding NOAEL for maternal toxicity was found to be more sensitive at only 100 mg/kg/day.

Given that the NOAEL for developmental toxicity of TCEP lies above that for maternal toxicity, **developmental effects are not considered to warrant further consideration**[1].

2.3 Scoping the Impact Assessment

As a result of our review, the toxic endpoints summarised in Table A1-2.1 have been considered with regard to their relevance to human health impact assessment and a number have been selected as requiring consideration in Step 2 to develop qualitative (or semi-quantitative) descriptions of the potential consequences with regard to human health impact.

[1] Excluding the potential for neurodevelopmental impairment, which will be considered in relation to overall neurotoxic profile.

Table A1-2.1: Summary of Health Effects Identified in Step 1 and Relevance to Step 2				
Hazard (Toxic Property)	**Nature of Effect Identified**	**Detailed Study Required (Y/N)**	**Scenarios to be Considered in Step 2**	**Routes of Potential Relevance**
Toxicokinetic behaviour	*Possible lower than anticipated dermal absorption*	*Y*	*1,2,3a,3b*	*Implications for dermal & combined intake estimate*
Acute toxicity	Moderate oral; low dermal; low inhalation	N	-	-
Irritation/ Sensitization	No evidence of hazard	N	-	-
Repeat dose • Brain	Evidence of neurotoxic/neuro-development effects in animals and humans	Y	1,2,3a,3b,4	Inhalation, Oral, Dermal, Combined
• Kidney	Experimental evidence of pathological change; no threshold	Y	1,2,3a,3b,4	Inhalation, Oral, Dermal, Combined
• Liver	Minor non-neoplastic changes of lower sensitive than kidney toxicity	N	-	-
Mutagenicity	Not established	N	-	-
Carcinogenicity • Kidney •	Experimental evidence; no threshold established	Y	1,2,3a,3b,4	Inhalation, Oral, Dermal, Combined
• Liver	Experimental evidence; appears less sensitive than kidney effect	Y	Uncertain	Uncertian
• Other tissues	Some experimental evidence of effects in thyroid gland, Hardarian gland, Monocytic leukaemia, and Forestomach	Y	Uncertain	Uncertian
Reproductive toxicity	Experimental evidence of impaired fertility in both sexes	Y	1,2,3a,3b,4	Inhalation, Oral, Dermal, Combined
Developmental toxicity (excluding neuro-development)	Experimental evidence suggests effects only at maternal toxic doses	N	-	-

2.4 Overview of Outcome of Step 1 - Scoping the Impact Assessment

In this case study, using information in the RAR on the uses of TCEP and the worker and general population groups at particular risk, together with consideration of the risks of concerns as identified by the RAR and in the light of the outcome of the review of the other hazardous properties of TCEP, the output of Step 1 were summarised in Table A1-2.1 (see above).

In particular, concerns relating to the potential carcinogenicity and repeat dose toxicity of the substance and its neuro- and repro-toxic properties were considered to warrant particular attention in Step 2 of the SEA.

3. LOGIC FRAMEWORK - STEP 2: QUALITATIVE AND SEMI-QUANTITATIVE ASSESSMENT OF HUMAN HEALTH IMPACTS

The aim of Step 2 is to ensure that decision makers have a good understanding of the nature of any potential health impacts that may be associated with the continued use of the substance. This will help provide a context for understanding the potential scale of the benefits that would be realised by either restrictions or a refused authorisation.

For each of the effects identified in Step 1 as warranting further consideration, there are essentially 4 possible stages:

i) Step 2a: Hazard characterisation;
ii) Step 2b: Exposure characterisation;
iii) Step 2c: Qualitative description of potential human health impacts;
iv) Step 2d: Benchmarking for human health; and
v) Step 2e: Assessment of the potential for quantification of impacts.

3.1 Step 2a: Hazard Characterisation

The initial phase is to describe – at least in qualitative terms - the nature of each of the hazards. It is then necessary to determine if, for each of the toxic effects considered, there is sufficient information available to enable the development of a qualitative description of potential human health impacts that might be expected from exposure to the substance.

3.1.1 Repeat Dose Renal Toxicity and Carcinogenicity

Renal Toxicity

There are no studies of the effect of TCEP on the human kidney. However, the RAR reported that several experimental studies of various duration conducted in rats and mice suggested that the kidney is a major target organ following repeated exposure. The studies were conducted to guidelines or were comparable to guidelines with acceptable restrictions. The renal effects (organ weight and histopathology) seen in males and females of several strains of each species tested showed dose- and time-related responses for incidence and severity.

Of the available studies, one in F344/N rats reported significant changes in the kidney at 44 mg/kg bw/day or above (NTP 1991, Matthews 1990) while, in rats of the CD strain, changes in body weight-relative kidney weight were noted in males after 3 months exposure at approx. 65 mg/kg bw/day and in females at approx. 215 mg/kg bw/day or above; evidence of regenerative hyperplasia was also noted in males at approx. 506 mg/kg bw/day (Stauffer Chemical Company 1980a). Long-term exposure to 175 mg/kg bw/day or above led to renal tubular karyomegaly, and

the overall LOAEL for renal toxicity in the rat was established as 175 mg/kg bw/day (NTP 1991, Matthews 1993).

A long-term study on SCL:ddy mice (Takada et al, 1989) found hyperplasia and hypertrophy of the urinary epithelium, together with associated cell nuclei enlargement, at approximately12 mg/kg bw/day while cysts, necrosis and interstitial fibrosis were seen at about 1500 mg/kg bw/day; the high dose associated with reduced survival and impaired bodyweight gain demonstrating that the maximum tolerated dose (MTD) had been exceeded.

Thus, the LOAEL for renal non-neoplastic toxicity (particularly hyperplasia and hypertrophy of the tubular epithelium) in SCL:ddY mice was established as 12 mg/kg bw/day and the RAR therefore concluded that renal toxicity was the most sensitive endpoint available for repeat dose toxicity and that **12 mg/kg bw/day should be used for risk characterisation of repeat dose toxicity.**

Suitability for Progression to Step 2c

The study by Takada et al (1989) provides the most sensitive indicator of susceptibility to non-neoplastic toxicity and hence was key for the risk assessment process to establish RCRs or, as was done in the case of this substance, facilitate derivation of MOS values. However, the value of the data available on this endpoint to inform a SEA is limited. In particular, while the critical study on which a LOAEL was established incorporated several treatment levels, a NOAEL dose was not established and no quantitative information is available on the incidence of non-neoplastic change with which to construct a dose-response function to support a dose-response based approach for impact assessment. Furthermore, the clinical significance of the non-neoplastic changes described in rodents to humans is uncertain, making any attempt to extrapolate to a human health impact of questionable validity.

Given these limitations, it is considered impractical to attempt to move from beyond a qualitative description of the nature of the rodent renal non-neoplastic effects as a result of repeated exposure to any extrapolation to humans. However, had such an extrapolation been considered appropriate, consideration could have been given, for example, to applying physiological-based modelling approaches to extrapolate from the rodent dose-response as a means of estimating the scale of potential human impacts under various exposure scenarios. **Overall, it is concluded that there is insufficient information available to permit estimation of human impacts based on the finding of renal non-neoplastic toxicity in rodents, suggesting that this endpoint is unsuitable for further progression.**

Carcinogenicity

As identified in Step 1, there is no evidence to suggest that TCEP is mutagenic. Also, there are no human data on carcinogenicity that would allow direct assessment of health impact. TCEP has, however, been the subject of a number of experimental

rodent studies using various routes of exposure that have demonstrated that it is carcinogenic and capable of causing tumours at multiple sites.

Evidence of a carcinogenic response was reported in a robust study in F344/N rats (NTP 1991; Matthews 1993) at 44, or 88 mg/kg bw/day, where apparently treatment-related increases in renal neoplastic lesions (mainly tubular proliferative lesions and adenomas) and in thyroid gland follicular cell adenoma and carcinoma and mononuclear cell leukaemia, were found. However, the significance of the thyroid and mononuclear cell leukaemia changes was judged uncertain in the RAR.

A study in B6C3F1 mice at 175 or 350 mg/kg bw/day (NTP 1991, Matthews 1993) again found an increase in incidence of renal tumours, as well as intergroup differences in incidence of Harderian gland tumours. In the previously discussed study by Takada et al (1989) on SCL:ddY mice a spectrum of non-neoplastic and neoplastic kidney changes was noted. This study also found an increase in liver tumours in treated males compared with their concurrent controls while, in females, a significant increase in tumours of the forestomach and leukaemias were noted.

Overall, the RAR concluded that TCEP was clearly carcinogenic in the ddY strain of mouse. The principal focus of attention in the RAR was the increased tumour incidences in the kidney and liver of males of this strain, for which a dose-related increase in renal tumours was apparent from 300 mg/kg bw/day and an increase in hepatic tumours from 60 mg/kg bw/day. Furthermore, it was noted that the available database suggested that this strain was not more susceptible to renal cell and liver carcinogens than other mice. Importantly, although 60 mg/kg bw/day could be considered a NOAEL for liver tumour formation, because an increase in the number of possibly associated proliferative lesions and atypical cells was apparent in the renal tubule epithelium of mice at 12 mg/kg bw/day, it was concluded that it was not possible to establish a clear NOAEL from this study for kidney tumours.

In considering the mechanisms by which TCEP might exert its carcinogenic action in rodents and the relevance to humans, the RAR noted that cancers had been detected at multiple sites in rodent species including kidney, liver, Harderian gland, forestomach and haemopoeitic system.

The kidney appears particularly sensitive in rats compared to mice. Thus, while both sexes of F344 rat developed renal tumours in a 2 year study, only males developed tumours at this site in mice of the B6C3F1 and Scl:ddY strains. In the absence of any apparent genotoxic potential for TCEP, consideration was given to the possibility that it might cause the induction in male rats of a specific protein, α2μ-globulin, since this protein is known to be induced by a number of chemicals (e.g. light hydrocarbons and d-limonene), an occurrence that is known to associate with development of a syndrome termed hyaline droplet nephropathy; this nephropathy can lead to a sex-specific carcinogenic response in this species. Chronic progressive nephropathy (CPN), a degenerative condition that affects male rats to a greater extent than females, was also considered since this disease involves a sustained regenerative response by the kidney leading, in later stages, to atypical tubular

hyperplasia (a preneoplastic lesion). However, the histopathological appearance of both mechanisms are well known to rodent pathologists and there is no evidence from the available studies to suggest that either mechanism could account for the renal effects seen with TCEP.

The renal cortex is particularly vulnerable to non-genotoxic injury because of its high blood flow, the presence of active and passive transport systems in the proximal tubule cells and the high metabolic capacity of renal tissue (including metabolic pathways capable of activation as well as detoxification). Also, the kidneys of animals treated with TCEP showed clear evidence of cell damage and an associated proliferative response; this type of regenerative response is a well known predisposing factor for cancer development in rodent species. While there are some inter-species differences in levels of specific enzymes in the kidneys that might influence sensitivity across species, in general predisposing factors of this type can be considered to be potentially relevant across all mammalian species.

Similarly, the mechanism underlying the liver carcinogenesis in male Scl:ddY mice was suggested as possibly arising as a result of a cycle of cell damage followed by reparative responses. This is supported by the observation of local necrosis and vacuolation in the livers of treatment mice of this strain but not seen in the controls of this strain or in studies on other mouse strains. Unlike the situation with the kidney, a NOAEL of 60 mg/kg bw/day was clearly definable for the liver neoplasia. This could be conjectured to possibly reflect the greater metabolic capacity possessed by the liver compared with the kidney, if the balance between metabolic activation and deactivation was an important part of the cancer induction process.

The Harderian gland is not present in primates including humans (e.g. see Albert et al, 1986) and the significance of a marginal (but outside historic control range) increase in tumours of this organ in female B6C3F1 mice (NTP, 1991; Matthews, 1993) was discounted as not of relevance to humans in the RAR. It should however be noted that the neoplastic response of this organ forms a model for study of radiation cancer induction (e.g. Cucinotta and Wilson, 1994) and the trans-generational carcinogenicity of diethylstilbestrol (Walker and Haven, 1997), and was included in evidence considered by SCCNFP (2004). Harderian gland neoplasia is certainly rare in mice and it was noted in the RAR that the design of the NTP study was such as to raise the possibility that the scale of effect might have been under-reported. While the scale of the effect of TCEP on Harderian gland tumours and potential implications for humans could be questioned, it is clear that a response was only elicited at exposures well above those at which the liver and kidney showed a clear neoplastic response.

No detailed consideration was given to the possible mechanisms by which TCEP might elicit tumours of the forestomach, thyroid gland or haemopoietic system, since the RAR concluded that a clear association with TCEP treatment had not been established. However, even if it were supposed that these could be potential markers of neoplastic response, the doses at which any intergroup difference in incidence

occurred were not such as to have influenced the selection of a point of departure (POD) for risk characterisation.

While the carcinogenicity of TCEP can be assumed to operate via a non-genotoxic (epigenetic) mechanism and, in the key study in ddY mice, no clear increase in the incidence of renal tumours was seen at the low dose (12 mg/kg bw/day), this dose was not considered suitable to define the NOAEL for renal neoplastic response because pre-neoplastic changes (arising from cytotoxicity and cell proliferation, and hence closely related to the development of neoplasia) were observed. Thus, **12 mg/kg bw/day was defined as the LOAEL for renal tumour formation.**

Suitability for Progression to Step 2c

TCEP was associated with an increase in incidence of tumours at multiple sites (most clearly the kidney and liver) in rodents. The available information does not establish an underlying mechanism(s) but suggests a genotoxic mechanism is unlikely. Even assuming a non-genotoxic mechanism, the available rodent data on renal neoplasia does not allow a threshold to be established. The RAR noted though that the change is of potential human relevance.

Although non-genotoxic mechanisms of carcinogenicity are generally assumed to exhibit a threshold, changes were still apparent in SCL:ddY mice at the lowest dose tested (12 mg/kg bw/day) so a NOAEL was not available. The tumourogenic effect on the livers of male Scl:ddY mice is also assumed to arise from a non-genotoxic process such as a repeated cycle of cell damage and reparative response.

Given that the endpoint, cancer, is of potential significance to humans, **it is considered that an attempt to describe the potential human health impact for this endpoint should be progressed (Step 2c),** although the limitations of the available dataset are acknowledged to be such as to potentially limit the extent to which quantification may be practicable.

3.1.2 Fertility

The RAR identified no information on reproductive or developmental effects of TCEP on humans. However, it included details of a number of experimental studies that suggest a range of adverse effects on reproductive organs and fertility. These include studies to investigate repeat dose systemic toxicity that suggest TCEP may affect the weight of the primary and secondary sex organs in rats and mice.

Several other studies were designed to specifically investigate reproductive function and developmental toxicity. In a continuous breeding study in CD-1 mice given TCEP by oral gavage at 175, 350 or 700 mg/kg bw/day, that included a cross-over phase and investigation of the F1 reproductive performance, a progressive reduction in reproductive capacity occurred in the F1 high dose; this was mainly attributable to effects in males. Other effects included impaired reproductive capacity in the F1 generation at 175 mg/kg bw/day or above (Gulati et al, 1991). Studies of sperm and

vaginal cytology showed a significant impairment of sperm numbers and quality but no effect on oestrus cyclicity or cycle length in females. Other studies in rats and B6C3F1 mice (Gulati and Russel, 1985; Morrissey et al, 1988; Shepelskaja and Dyschinewitsch, 1981) also report effects on sperm of treated animals and, in B6C3F1 mice, changes in oestrous cyclicity in females.

The RAR concluded that TCEP is a rodent reproductive toxicant and significantly affects fertility. TCEP was classified and labelled as a reproductive toxicant Cat. 2, R60. **A NOAEL for fertility of 175 mg/kg bw/day was established** based on the study in CD-1 mice by Gulati et al (1991).

Suitability for Progression to Step 2c

A NOAEL is available for reproductive fertility based on commonly used endpoints considered sensitive markers of reproductive toxicity. However, our current ability to interpret the significance of changes in many such endpoints in terms of a definable potential impact on a specific parameter of human reproductive function is rather limited.

Given the severity of the effects seen in the rodent and the clear potential importance of reproductive impairment for human health and well-being, **consideration will be given to seeking ways to infer possible implications for humans from these findings in Step 2c.** To this end, it is noted that the NOAEL established by the RAR is based on reproductive performance (from the continuous breeding study). Some other findings were excluded, including those of Shepelskaja and Dyschinewitsch (1981) which were omitted because of very poor reporting. In addition, the intergroup differences in weight of male sex organs seen in a number of repeat dose studies were also excluded on the grounds that lack of associated pathology data. However, Step 2c will consider all available dataset solely in the context of datas usefulness to a SEA.

3.1.3 Neurotoxicity

There is limited human evidence suggesting that TCEP may be neurotoxic.

One case study (Ingerowski and Ingerowski, 1997) considered in the RAR related to a 5 year old girl who slept in a room equipped with wood panelling treated with a wood preserver shown to contain 3% TCEP. The girl developed a progredient paresis; EMG and nerve conduction velocity tests identified neurogenic defects later clinically diagnosed as "spinal muscle dystrophy of Kugelberg-Welander type" with tetraparesis. Following removal of all timber panels from the house, the clinical status was noted to improve and no functional deficit was identifiable after 2 years. No quantification of exposure was possible although the symptoms were shown to increase with increasing time of exposure and to diminish and eventually cease after removal of the source.

Another study, not included in the RAR, was reported by the Austrian Umweltbundesamt (UBA, 2008). This study considered the influence of indoor air pollution on child health using a cohort drawn from 9 schools. A total of 445 children, aged 5 to 9 years, drawn mainly (86%) from urban environments were investigated. A range of chemicals in air, house dust and particulate matter were measured; from the samples taken, TCEP was measured in house dust (n = 19) and PM_{10} and $PM_{2.5}$[2] (n = 86,) samples and was found to be present in nearly all cases. Levels in household dust ranged from 0.59-35 mg TCEP/kg. Cognitive skill of the children was assessed using Standard Progressive Matrices (SPM) (Spearman 1938; Raven 1938); in this method, the score achieved is indicative of cognitive skill independently of education and socio-cultural environment. The study found that there was a high correlation between TCEP level in PM_{10}, $PM_{2.5}$ and house dust and a decline in cognitive skill of -0.69, -0.68, -0.73, respectively (n = 436, boys: girls = 50%:50%, study participation = 73.1%). However, it was reported that no adjustment was made for potential confounding factors such as time spent watching television or level of encouragement.

Most of the available experimental evidence on the neurotoxicity of TCEP was reviewed in the RAR. Available short-term studies in standard models (e.g. hen and rat) provide conflicting evidence on the potential neurotoxicity of TCEP; the reason for the differences is unknown.

However, clear neurotoxicity was noted in a number of longer term studies in rodents. In F344/N rats dosed for 16 weeks, changes in behaviour, organ weight and in the pathology of the brain, were detected following oral doses of 175 mg/kg bw/day or above; the severity was dose–related in females. Associated changes in serum cholinesterase were also reported. This study identified a NOAEL of 88 mg/kg bw/day (NTP 1991, Matthews 1990). A 103 week study in this strain again found a range of histopathological changes in several regions of the brain at 88 mg/kg bw/day or above (NTP 1991, Matthews 1993).

The RAR concluded that the NOAEL for CNS toxicity was 44 mg/kg bw/day in both sexes in F344/N rats based on NTP (1991) and Matthews (1993). As no pathological changes in studies on B6C3F1 mice at up to 350 mg/kg bw/day, this was considered the NOAEL for mice.

Suitability for Progression to Step 2c

TCEP is a organophosphate, a structurally diverse group of chemicals, the properties of which vary depending on detailed chemical structure; the electrophilicity of the phosphorous atom is generally considered the crucial determinant of biological activity. Many organophosphorous chemicals inhibit a serine esterase, acetylcholine (AChE), that occurs widely throughout the central and peripheral nervous system of vertebrates including humans, leading to acute neurotoxicity. This inhibition is

[2] PM 10 and 2.5 refers to atmospheric particles having mean aerodynamic diameters of 10 and 2.5 μm respectively

achieved through phosphorylation of the enzyme by loss of a 'leaving group' on the organophosphate, followed by covalent bonding to AChE at the serine residue. The phosphorylated enzyme thus formed can in some cases be very stable, only showing slow reactivation through spontaneous hydrolysis. For some chemicals, the enzyme deactivation may become permanent as a result of a process termed 'aging' where there is dealkylation of the bound inhibitor. AChE's normal physiological function is to deactivate, through hydrolyse, a neurotransmitter acetylcholine (ACh) which results in the activation of cholinergic receptors being terminated. Inhibition of AChE will thus cause an accumulation of ACh at the nerve junction and potentially signs of cholinergic neurotoxicity. The degree of effect seen depends on level and distribution of the organophosphate in the body and which receptor junctions are affected (Mileson et al, 1998).

In addition to the acute toxic effect, there is also evidence from human and experimental studies that at least some organophosphorus chemicals cause other forms of neurotoxicity as a result of, for example, chronic low level exposure. These effects are thought to arise through mechanisms independent of cholinesterase inhibition (IEH, 2002).

There are thus good grounds to believe that the neurotoxicity identified by the RAR is of direct relevance to humans. The experimental data available provides evidence of both acute and long-term effects of TCEP on the nervous system, including structural changes in the brain, and also defines an experiment NOAEL. Importantly, there is limited epidemiological data also available which offers offer possible approaches to inferring human health impact estimates. **The possible human health impacts of TCEP in terms of neurotoxicity will therefore be explored further in Step 2c.**

3.2 Step 2b: Exposure Characterisation

The total number of workers exposed to TCEP in Europe is unknown. However, some insight into the potential scale of exposure is given by estimates for the US population (NIOSH, undated) that the total numbers of workers exposed to TCEP in the USA between 1981-83 at about 5,000 (of which 11% were female) from a relevant labour force of approximately 1,800,000 workers.

In Step 2b, a fuller characterisation is given of the numbers potentially exposed in Europe and the level of exposure under each use scenario; this will inform Step 2c consideration of the health effects (hazards) identified in Step 2a.

3.2.1 Scenario 1: Production of TCEP

Consideration of Size of Exposed Population

It has been established (in Step 1) that there is one producer of TCEP in the EU, located in Poland; this company is believed to produce approximately 400 tonnes per year (RAR; ECHA, 2010).

For the current exercise, based on publically available information on large chemical production companies in Poland, it has been assumed that the company involved in producing TCEP is a major chemical manufacturer employing approximately 1,000 workers; of these it has been assumed that no more than **200 workers would be engaged in TCEP production activities**. The gender distribution of these workers is uncertain so a generic estimate for the proportion of female scientists and engineers in Poland of 33.7% (Wilén, 2006) is applied leading to an estimate of **133 male workers and 63 female workers.**

Estimated Worker Exposure Levels

As reported in the RAR, TCEP is produced by addition of ethylene oxide and phosphoryl chloride in a closed catalytic system with pure product produced after cleaning steps, removal of catalyst and drying in a vacuum in an advanced, highly contained, continuous or batch production system. Hence, inhalation exposure would only be anticipated to be a possibility during activities associated with the coupling or uncoupling of transfer lines, drumming, cleaning, maintenance and repairs, or sampling during the reaction process. The RAR assumed that such activities would be performed under conditions of local exhaust ventilation (LEV), and information from producers indicated that they had requirements for the wearing of personal protective equipment (gloves, eye protection and protective clothes).

The RAR derived 'reasonable worst-case' exposure estimates for production workers using the EASE model; these were stated to be representative for the Polish company although supporting data were not presented. In the absence of contradictory information, it was assumed that production occurred daily and, hence, exposure frequency was assumed to occur daily, potentially lasting throughout the work shift. On this basis the estimated **inhalation exposure was modelled at up to 1.2 mg/m^3** (based on estimated air levels of up to 0.1 ml/m^3, irrespective of the use or not of LEV). While accepting that gloves would be worn as a routine in such an operation, the RAR assumed that the gloves may be unsuitable and therefore developed estimates for dermal exposure based on immediate dermal contact without gloves. This gave a precautionary model estimate, assuming 100% absorption, of **42–420 mg/person/day for dermal exposure.**

For this SEA, as part of a sensitivity analysis, an alternative 'lower exposure' scenario has also been developed that assumes that gloves providing a high degree of protection (reducing external exposure by 90%) are worn resulting in a low rate of dermal absorption of only 20%, thus reducing the quantity absorbed by a

corresponding amount[3]. On this basis, a 'low' **dermal exposure estimate of 0.84-8.4 mg/person/day is derived**.

3.2.2 Scenario 2: Production of Formulations Containing TCEP

This scenario considers the risk to workers involved in the production of a range of different formulations that contain TCEP and includes the incorporation of TCEP as a plasticizer in formulations such as paints and lacquers, in resins (for glue and adhesive production) and in polymers (e.g. polyurethane and cellulose acetate).

Consideration of Size of Exposed Population

i) Workers in the plastics and polymer industry

In Europe, the general plastics/polymer industry is estimated to produce about 60 million tonnes, i.e. about a quarter of world production. Amongst Member States, the largest producer is Germany, followed by Benelux, France, Italy, UK and Spain (EUPC, 2009). Based on the membership of an industry association, PlasticsEurope, it appears that there are more than 100 companies across the 27 EU Member States (plus Norway, Switzerland, Croatia and Turkey) involved in the production of over 90% of all polymers in Europe[4].

In the United Kingdom alone, numbers employed in this industry amount to approximately 276,000 (Cogent, 2008) and data from Eurostat (2009) show the number employed in direct plastics production in the EU-27 was 1.38 million in 2006. This estimate is similar to data from PlasticsEurope (2009) which suggests the number of workers in polymer production, conversion and manufacturing is around 1.6 million. However, the global organophosphorus/chlorinated flame retardant sector (as of 2007) accounted for about 18% of the total plastics market by volume of which the European share was 363 million metric tonnes (Reilly and Beard, 2009). Another source indicates the market share for chlorinated phosphate esters at only 10% (i.e. 46,400 tonnes) out of an estimated 464,000 tonne European flame retardant market[5].

Assuming that 10% of the market is held by chlorinated phosphate esters and given an estimate use of TCEP in the polymer industry of 950 tonnes per annum (according to the RAR), it can be assumed that the share of the overall market specific to TCEP must be minor. On this basis, it may be estimated as no more than 2% of total chlorinated/phosphate ester market (i.e. 0.2% of the total European flame retardant market). Even allowing for the large uncertainty surrounding such an

3 Note – toxicities of concern are systemic not local in nature

4 Information from Plastics Europe, available at Internet site http://www.plasticseurope.org/plastics-industry/plasticseurope.aspx.

5 Estimate by European Flame Retardant Association (part of Cefic) available at Internet site http://www.cefic-efra.com/Content/Default.asp?PageName=openfile&DocRef=2006-02-13-00008.

estimate, it is not unreasonable to suppose that the proportion of European companies that are involved in polymer production using TCEP is small.

The European Flame Retardants Association (EFRA) - which represent the major flame retardant industry in Europe - identifies member companies involved in the production of flame retardant polymers in the EU (Table A1-3.1 below) and also provides an indication of the number employed. The total number of employees at EFRA members producing polymers is estimated as being over 21,200; this constitutes around only about 1.5% of the entire EU polymer workforce (based on the low estimate of 1.38 million). The majority of EFRA's members are, however, multinational companies (or subsidiaries thereof) while the employee statistics are quoted on a 'whole company' basis. Hence, it could be supposed that the numbers employed in the EU would be only a fraction of this and, of course, not all the workforce will be at risk of TCEP exposure.

Table A1-3.1: EFRA Members and Employee Numbers

Company	Number of Employees (Approximately)	Data Source
Albemarle Europe Sprl	4100 worldwide	Albemarle, 2010
Chemtura	4400 worldwide	Articles Base, 2010
(ICL)ICL-IP Europe	9300 worldwide	Supresta, 2007
PCC Rokita	2800 worldwide	PCC, 2005
Schill & Seilacher	Over 600, worldwide[2]	Schill & Seilacher, 2010
Tegewa	Not available	-
Total	**>21,200**	

Extrapolation from the available market data suggests:

- perhaps 18% of the >21,200 workers may be employed in Europe of which 10% might be anticipated to be involved in processes using TCEP; and
- this could equate to more than **382** workers.

More conservatively, it could be assumed that all production of flame retardant polymers by these companies occurred in the EU. In this case, the assumption that only 10% of production involves use of TCEP could still be applied. This would give an estimate of the order of 2,120 workers potentially exposed to TCEP. In practise, it is unlikely that this number of workers would be undertaking production activities involving TCEP exposure. Given this, we assume that no more than **2,000** workers would constitute a sufficiently precautionary estimate.

In the EU, manufacturing tends to be male dominated. 2006 data suggests females constitute only 30.8% of the overall workforce (<50% in all Member States; Eurostat, 2008). The rubber and plastics sectors follow the same trend; 28.5% of workforce were female as of 2007 (Eurostat, undated). Therefore a male:female ratio of 70:30 will be adopted. For simplicity, **it is therefore assumed that the**

number of workers exposed in this sector is 2,000 (of which 1,400 are male and 600 female).

ii) Workers in the paint and lacquer manufacturing

The paint and lacquers manufacturing industry is also an important business area in Europe, valued at around €17 billion. It is estimated to directly employ about 120,000 people[6]. In 2005, the estimated production of paint by the top 50 European paint manufacturers[7] alone amounted to 6,565 million litres of paint. In contrast, the total usage of TCEP in the formulation of such products is estimated by the RAR at no more than 10 tonnes per annum (see Step 1).

According to the European Council of producers and importers of paints, printing inks and artists' colours (CEPE)[8], this organisation has a membership of approximately 1,000 covering the European Union, Norway and Switzerland which constitute approximately 85% of the industry. This suggests that no more than 1200 companies would be involved in the production or import of paints, printing inks and artists' colours in Europe. Of these only a small subset are likely to be involved in production of specialist paints, say no more than 200 companies. Information on the proportion of specialist paint manufacturers that use TCEP in their paint production and related products is limited. However, the RAR identified that a survey of members conducted by CEPE indicated that it was still used by only 3 out of 10 responding companies operating in the EU.

Given that the evidence in the RAR suggests that paints containing TCEP are products with a very limited market (since their use is economically viable only for highly specialised applications), it seems likely that assuming that only 30% of the estimated 200 specialist producers, i.e. 60 companies, would be likely to still use TCEP would represent an upper estimate of the numbers involved. CEPE reports that 120,000 people are directly employed by their membership of 1,000 companies, suggesting that the average number of employees per company is about 120. It can be assumed that no more than half of this number would be directly involved in the production process. **Thus, the number of workers likely to be at risk of exposure to TCEP from paint production is considered to be highly unlikely to be in excess of 3,600 and will probably be considerably less.** Based on a generic estimate of the proportion of female scientists and engineers in Europe of 29% (Wilén, 2006), it will be assumed that **2,556 of these are male and 1,044 female**.

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6 Estimate by the European Council of producers and importers of paints, printing inks and artists' colours (CEPE) available at Internet site http://www.cepe.org/ePub/easnet.dll/ExecReq/Page?eas:template_im=100087&eas:dat_im=1002FD.

7 Estimate obtained from Internet site http://www.allbusiness.com/manufacturing/chemical-manufacturing-paint/618255-1.html.

8 Information on CEPE available at Internet site http://www.cepe.org/EPUB/easnet.dll/execreq/page?eas:dat_im=100088&eas:template_im=100087.

Estimated Worker Exposure Levels

The content of TCEP in formulations was estimated to range from up to 40% at the start of processing to 5-16% by the later stages. It was assumed that the production process involves multiple steps so there may be several times when filling, mixing, emptying and transport activities are required during production of a batch. Some, but probably not all, of these may be undertaken within closed systems. It is also known that the production processes do not involve handling of TCEP in powder form nor the use of high temperature reaction stages (RAR). Furthermore, it can be assumed that LEV is in place at process steps when exposure of operatives is considered possible.

There are, however, insufficient data to characterise the extent of operator exposure during the working day since this would depend on the nature and duration of the production process and the frequency of producing batches. The duration and frequency of exposure were assumed in the RAR to be daily and that there was a risk of exposure throughout the entire shift, although it was acknowledged that in some cases production was likely to be discontinuous which would result in lower overall exposure.

In the absence of measurement data, EASE was used to generate exposure estimates for use in the RAR. This gave an **estimated inhalation exposure of 0-1.2 mg/m^3**; this was assumed to apply throughout a work shift.

In estimating the dermal exposure for production of polymers and formulations, the RAR again assumed that suitable gloves and eye protection were not worn, giving **a dermal exposure of 42-420 mg/person/day.** As for Scenario 1, however, a low exposure assumption was also adopted as part of a sensitivity analysis, for which it was assumed that gloves of a type providing a high degree of protection were worn and that dermal absorption was no more than 20%. This results in a **dermal exposure of only 0.84-8.4 mg/person/day.**

3.2.3 Scenario 3: Use of Formulations Containing TCEP

Scenario 3 of the RAR considers the downstream uses to which formulation containing TCEP may be put and identifies the following uses as warranting consideration: glues; adhesives; flame-retardant coatings; and paints or lacquers.

Consideration of Size of Exposed Population

The types of product that may contain TCEP are such as to suggest its use in a very wide range of industries. Those applications defined as being of importance by the RAR comprise:

- in flame-retardant plasticiser used in furniture manufacture, textiles and in the building industry (roof insulation);

- paint applications - assumed to relate to specialist applications in the building industry (i.e. not TCEP is not included in paints available to consumers); and

- manufacture of vehicles (cars, railways, aircraft and other transport equipment).

Other than establishing that the use of TCEP in paints accounts for no more than 1% (10 t/y) of total, the RAR did not define unequivocally the proportion of the remaining 950 t/y that may be used within each of these diverse applications.

The total size of the European labour force in 2008 for 23 Member States was estimated by the International Labour Organisation, Department of Statistics[9] as:

- furniture manufacturing 1,623,377 (of which 69.85% are male in States for which sex specific data are available);

- textile manufacturing 53,704 (of which 23.28% are male in States for which sex specific data available); and

- vehicle and other transport manufacturing 4,355,187 (of which 81.37% are male in States for which sex specific data available).

i) Workers in furniture manufacturing and textiles

In the case of furniture manufacture, it is considered unlikely that there will be significant use of spray applications and, therefore, for simplicity exposure of workers is considered to most likely to fall under Scenario 3b; this may not be the case for textile workers where both methods might occur. Also, particularly in the case of the furniture industry, not all workers will be employed in the production of furniture that requires use of flame retardants; in any case, for those that do and for the textile sector, TCEP is only one of several alternatives available for these applications[10].

Given these consideration, the following assumptions have been made regarding to numbers of workers that may be exposed to TCEP in these industries:

- **furniture manufacturing: 5% subject to Scenario 3b – 81,169 (of which 56,696 male); and**

- **textile manufacture:**
  - **5% subject to Scenario 3a - 2685 (of which 625 are male and 2060 female)**

[9] Available at Internet site http://laborsta.ilo.org/STP/guest.

[10] See ECHA (2010) and SFT (2009) which is available at Internet site http://chm.pops.int/Portals/0/docs/POPRC4/intersession/Substitution/pentaBDE_revised_Stefan_Posner_final%20version.pdf.

- **5% subject to Scenario 3b - 2685 (of which 625 are male and 2060 female).**

ii) Workers in vehicle/other transport vehicles manufacturing

Among those involved in vehicle and other transport manufacturing (and potentially repair), few will actually be involved in activities such as paint application and, of these, those employed by large scale car manufacturers would be considered at very low risk of exposure since use of either automated spray equipment (excluding the need for any worker exposure) or high efficiency PPE (with appropriate operational controls on its use) can be assumed to be in place. However, such a situation cannot be assumed to apply at smaller companies (frequently SMEs) that may be involved in vehicle repair/re-spray activities.

Therefore, for convenience, it has been assumed – on a purely nominal basis for this case study - that perhaps 1% of workers in the sector may be at risk of exposure and that this would be most likely equate to **Scenario 3a** (in practice, this is likely to be a considerable over-estimate given the relatively low usage reported of TCEP in paints and lacquers and more definitive estimates could be anticipated in a formal SEA). **This would equate for workers in the vehicle/transport sector to 43,551 (of which 35,438 would be male and 8,113 female).**

iii) Workers in the building industry

EC (1997) estimates the scale of the construction industry in 1990 at 8.8 million workers directly involved in construction, out of a total industry labour force of 12.1 million. This source was also cited in a recent publication by the European Construction Industry Federation (FIEC, 2010). A 2008 estimate of the size of the construction sector by Eurostat[11] indicates an EU-27 workforce of 18,346,600 (of which 90.9% are male); this value is considered to be comparable to the earlier 1990 estimate of the total labour force at 12.1 million rather than the value for those directly involved.

An approach to deriving an estimate of the potentially exposed workforce would be to consider the size of the current EU-27 workforce directly involved in construction activities. This may be of the order of 13.3 million (of which 91% are assumed to be male) giving a total worker population in this sector that could be potentially exposed to TCEP of about 19.3 million. However, there is a very diverse range of occupations within this sector and the RAR recognises the highly specialised nature of uses for TCEP (i.e. economically constrained to only those applications where fire resistance is an important/essential property). Thus, it is apparent that only a very limited proportion of these will be at risk of exposure.

[11] Available from Eurostat at Internet site http://epp.eurostat.ec.europa.eu/portal/page/portal/employment_unemployment_lfs/data/database.

Perhaps the employment sector within the construction industry with the greatest risk of exposure is those working as specialist (non-electrical) insulators. Detailed data for workers in England from the Construction Statistics Branch of the Office for National Statistics suggests that this sector accounts for approximately 0.9 % of all construction employment. Applying this to the estimated 19.3 million employed in construction in EU-27, suggests that about 173,700 (158,067 male) might be at risk of exposure. This estimate appears reasonable given that the total number of building installation (F453) workers – which comprises insulation workers, plumbers and electrical trades – in the EU has been estimated at 2,892,00 for 2002[12]. If it is assumed, as a nominal estimate, that most of the workers would be at risk (say 75%) from non-spray related activities, the **nominal numbers exposed in construction would be 43,425 (39,517 males and 3,908 females) under Scenario 3a and 130,275 (118,550 males and 11,725 females) under Scenario 3b.**

Although purely nominal estimates, these assumption for numbers of workers that may be exposed to TCEP for these scenarios do not seem unreasonable in the light of knowledge as to the market volumes of TCEP used in these sectors.

Estimated Worker Exposure Levels

i) Scenario 3a – Spray application of formulations containing TCEP

Scenario 3a addresses the occupational exposure resulting from the use of TCEP products (e.g. paints, flame-retardant formulations and glues) that require spray application. The RAR assumed that a typical TCEP content for such formulations is 25%, and derived estimates of inhalation exposure based on extrapolation by analogy from polyisocyanates in line with the Technical Guidance Document (TGD)[13] requirements.

This suggests an **inhalation exposure level of 8.3 mg/m^3**, with exposure assumed to occur throughout the shift on a daily basis. **Dermal** exposure was estimated on the basis of there being no use of PPE, and gave an **anticipated exposure value of <2,500 mg/person/day**.

The above estimates assume that no PPE were worn. While this is a reasonable supposition in many instances (e.g. construction where 95% of companies are SMEs), this is unlikely to be the case for larger companies for which systems to

12 Taken from 'The construction industry in the European Union, 2002' by Tolkki V. (2005), available at Internet site http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-NP-05-026/EN/KS-NP-05-026-EN.PDF.

13 TGD (2003): Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances, and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, **Institute for Health and Consumer Protection of the European Chemicals Bureau**, European Commission – Joint Research Centre, Office for Official Publications of the European Communities, L – 2985 Luxembourg.

ensure robust health and safety provisions can be anticipated to be in place. Hence, if it is assumed that in some instances either automated spray equipment (excluding the need for worker exposure) or high efficiency PPE is used, workers in such instances might reasonably be expected to have a significantly lower exposure (of the order of 90% less). Hence for the workers using adequate PPR, we have assumed here for the purposes of illustrating the use of sensitivity analysis that a more realistic estimate of exposure would be **0.83 mg/m^3 for inhalation**. If the low dermal absorption assumption is applied to this figure (i.e. a **nominal 20% dermal absorption rate), exposure would equate to 50 mg/person/day via the dermal route**.

ii) Scenario 3b– Non-spray application of formulations containing TCEP

Scenario 3b considers formulation application methods that do not involve the generation of droplet aerosols. To estimate exposure under this scenario, the EASE model was used which suggested that **inhalation exposure would be of the order of 0-1.2 mg/m^3. Dermal exposures under this exposure scenario were anticipated at 21-210 mg/person/day**.

Again these estimates assume no appropriate PPE is worn; this may not be the case for larger companies where appropriate health and safety measures may be enforced. Thus, for the low exposure scenario it is also assumed that, **with adequate PPE, exposure would be no more than 0.12 mg/m^3 for inhalation and (assuming only 20% dermal adsorption) 0.42-4.2 mg/person/day for the dermal route.**

It should however be noted that the above figures may represent an over-estimation of the extent to which some workers may be exposed to TCEP since the Annex XV dossier (EEA, 2009) identifies a study measuring worker exposure at a number of locations including a furniture workshop. Although TCEP was present in more than 75% of the air samples taken in offices and in more than 50% of samples from a circuit factory and furniture workshop, the highest levels measured were in a Finnish dismantling and sorting facility where the personal air sample level was 450 ng/m^3 and stationary air sample reported a workplace level of only 50 ng/m^3.

3.2.4 Scenario 4: Consumers - Infant Exposure from Sucking Toys

Consideration of Size of Exposed Population

Scenario 4 is the only one that relates to non-worker exposure and considers the sucking of toys containing TCEP by infants, in particular those under 3 months of age. However, given that there is evidence that the amount of time spent mouthing peaks at 6-9 months of age (DTI, 2002), it may be appropriate to also consider the population under >1 years of age.

The Eurostat database (data extracted 2 September 2010) indicated that, as of 2008, there were 10,440,387 children aged less than 2 years of age in the EU-27. Of these, 5,256,561 children are under the age of 1 year of which approximately 51% are

males. Assuming an equal age distribution within under 1 year olds, it can therefore be estimated that the number of babies aged under 3 months of age is about 1,314,140. However, while data on the EU population in these age ranges are readily available, estimating the proportion at risk of exposure to TCEP through the sucking of toys containing this substance in a migratable form is much less certain.

A study by RPA (2000) previously reported that, while the overall market for toys in the EU was worth €13.5 billion and the market share of toys intended for use by infant and pre-school children at that time was estimated at 14% of the total, the value for articles intended to be placed in the mouth of children under 3 years of age was estimated at only €140,000,000 (i.e. less than 1% of the total market). However, this report also notes that the size of the market for 'soft PVC' toys for children under 3 years of age is about 5% of the total.

Although likely to be somewhat precautionary, it will therefore be assumed that about 5% of total market (i.e. about one-third of the under-3 year old toy segment) could be of a type that might potentially contain TCEP in a migratable form. Obviously not all such toys would be anticipated to actually contain TCEP – and, as a nominal assumption, it will be assumed that only 1% might contain TCEP.

Recent estimates suggest that expenditure on toys in general has increased over time with the retail market (excluding video games) for toys in the EU-27 estimated to be €14.234 billion in 2008, of which approximately 20% (€2.8468 billion) related to toys for infant and pre-school children (TIE, 2008 and 2009).

Given the current awareness across Europe of the potential hazard posed by TCEP as a result of its current status as a candidate for Authorisation and the rigorous safety requirements established by EU toy legislation, it is considered unlikely that TCEP would be included in a migratable form within toys produced by EU Member States to any appreciable extent. Nonetheless, there exists a significant importation of toys from non-EU countries - amounting to €11.6 billion during 2007 - of which 97.6% originates from Asia/Oceania and, hence, for which the non-use of hazardous substances can not necessarily be confidently assumed.

Applying the estimate of 20% of the total toy market relating to toys for under 3 year olds, suggests that the size of this sector of the import market may be of the order of €2.26 billion. Applying the assumptions established above that possibly one-third might relate to toys intended for mouthing, of which 1% are assumed to be 'at risk' of containing TCEP, the nominal market for toys (that may contain TCEP) for mouthing by young children is about €7.5 million. It is likely that the retail cost of such toys would be relatively low. Assuming a nominal cost of about €10 per item, this gives an estimate of about 750,000 items each year 'at risk' of containing TCEP.

Given this estimate of numbers of toys on the market each year and that the estimated number of children in the **EU-27** (see above) falling within the age ranges of interest equates to **2,680,846 males under 1 year of age,** of which **670,212 are aged 3 months or less**, this could be taken as indicating that all males under 3

month of age might potentially be at some risk of being given one such toy; this equates to approximately 28% of those under 1 year of age.

However, it is known that in monetary terms the market for such toys is not uniform across the EU-27 with 7 Member States (Belgium, France, Germany, Italy, Netherlands, Spain and UK) accounting for over 90% of toy imports by value (TIE, 2008). Data extracted from Eurostat suggests that, as of 2008, the numbers of children in these 7 countries aged <1 year is 3,621,462 (of which 1,827,653 are male and 1,793,809 female) so particular concerns might be focused on this subsector of the European population.

Regrettably, no information on unit market pricing for the types of toy considered to represent a potential source of exposure is available for use in this Case Study. As a result, it is not possible to derive more refined estimates of the numbers of toys of concern sold in individual Member States or to develop estimates of the probability that toys of this type may contain TCEP. As a result, it is not possible to develop robust estimates of the potential scale of the exposed population. However, it is considered that given the assumptions made, the above estimates of numbers 'at risk of exposure' probably represent a significant over-estimation.

Estimated Infant Exposure Levels

The exposure scenario considered in the RAR is based on a Danish EPA study on a toy cube for babies (recommended for 0 months and above) that was intended to stimulate their senses and exploring behaviour. Thus, the pathway of exposure considered is of particular importance for young children (infants), particularly babies under 3 months of age since sucking plays an important part of their sensing and exploring behaviour.

The estimate of the exposure arising from this toy assumed it was sucked intensively for 90 days by an infant of 6 kg and that this resulted in 50% of the total TCEP content of 260 mg being dissolved and swallowed. Extensive sucking of toys is certainly a realistic scenario since children aged up to 3 months may mouth/suck toys for up to 1 hour while those in the 6 to 9 month age range may mouth/suck toys for nearly 4 hours a day (DTI, 2002). The estimate of exposure was derived as follows:

> Intake = (Total release factor x Amount in toy)/(Duration x Weight of infant);
>
> i.e. = 0.5 x 260 mg/90 d x 6 kg = **0.24 mg/kg bw/day for 90 days.**

Since, as noted above, there is evidence that extensive sucking of objects continues throughout the period of early childhood, consideration could also be given to the possibility that children may continue to be exposed to TCEP at this dose until the age of at least 1 year.

It should, however, be stressed that the concern identified by the RAR was not the presence (content) per se of TCEP in the foam core (since this aspect might in reality be most appropriately regulated for a CMR through use of the Toy Directive[14]) but the degree of risk posed if the TCEP in the foam was present in an easily migratable form under conditions such as sucking. It should also be noted that the RAR scenario specifically related to 'sucking toys' (i.e. one intended for a baby or infant to use for sucking/mouthing). However, it is recognised that, particularly in children up to the age of 3-5 years, any object they come into contact with – including toys even if not specifically intended to be used for sucking – are highly likely to be subject to mouthing behaviour/sucking if they are shaped in a manner that allows parts to be placed in the mouth.

3.2.5 Summary of Estimates of Exposed Populations and Exposure Ranges

Based on the above discussion, the assumptions as to the numbers and extent of human exposure to TCEP that will be considered in any quantification of impact for the scenarios under consideration, are summarised in Table A1-3.2.

It should be noted that in this case study we have focussed on deriving estimates of the numbers of workers and children within the EU that may be exposed to TCEP from sources identified as relating to industrial and commercial activities within Europe. Of course, for an actual SEA it may also be important to consider the potential for impacts arising outside of Europe as a result of EU commercial activities.

3.3 Step 2c: Qualitative Description of Potential Human Health Impact

In this step a qualitative description of the potential human health impacts is prepared for each hazard identified in Step 2a as important and requiring further assessment. Of the toxicological properties identified for TCEP, only 3 endpoints can be directly equated with human health impacts; these are:

1. Cancer - particularly in relation to development of renal tumours;

2. Fertility impairment - in relation to infertility of males; and

3. Neurotoxicity - in relation to potential intellectual impairment of workers and neurodevelopmental impairment in children.

[14] See http://ec.europa.eu/enterprise/sectors/toys/index_en.htm

Table A1-3.2: Summary of Assumptions Regarding Exposed Populations and Levels, for use in Impact Assessment									
Scenario		**Estimated Number of Exposed Worker**		**Exposure Based on RAR Estimates**			**Exposure Based on 'Low' Exposure Assumptions**		
		Industry	**Estimate[A]**	**Inhalation**	**Dermal**	**Combined**	**Inhalation**	**Dermal**	**Combined**
1	Production of TCEP	Production	200 (133 male)	1.2 mg/m^3 (0.17 mg/kg/day)	420 mg/p/day (6.00 mg/kg/day)	432 mg/p/day (6.17 mg/kg/day)	1.2 mg/m^3 (0.17 mg/kg/day)	8.4 mg/p/day (0.12 mg/kg/day)	20.4 mg/p/day (0.29 mg/kg/day)
2	Production of formulations	Plastics/polymers	2000 (1400)						
		Paints/lacquers	3600 (2556 male)						
3a	Spray application of formulations	Furniture	-	8.3 mg/m^3 (1.19 mg/kg/day)	2500 mg/p/day (35.71 mg/kg/day)	2583 mg/p/day (36.9 mg/kg/day)	0.83 mg/m^3 (0.19 mg/kg/day)	50 mg/p/day (0.71 mg/kg/day)	58.3 mg/p/day (0.83 mg/kg/day)
		Textiles	2685 (265 male)						
		Vehicles	43,551 (35,438 male)						
		Construction workers	43,425 (39,517 male)						
3b	Non-spray application of formulations	Furniture	81,169 (56,696 male)	1.2 mg/m^3 (0.17 mg/kg/day)	210 mg/p/day (3.00 mg/kg/day)	222 mg/p/day (3.17 mg/kg/day)	0.12 mg/m^3 (0.02 mg/kg/day)	4.2 mg/p/day (0.06 mg/kg/day)	5.4 mg/p/day (0.08 mg/kg/day)
		Textiles	2685 (265 male)						
		Vehicle & related	-						
		Construction	130,275 (118,550 male)						
4	Sucking of toys by children[B]	0 to 3 month	<670,212 males	-	-	0.24 mg/kg/day for 90 days	-	-	-
		>1 years	<2,680,846 males	-	-	0.24 mg/kg/day for 1 year	-	-	-

Notes:
[A] Overall scale of workforce assumed to be at risk of exposure to TCEP is about 483,798 (of which 396,573 are male); non-EU workers excluded from consideration
[B] Assuming that the population at risk include all the EU-27, although imports of such toys are noted to not be uniform across the EU at least in monetary terms

It must be emphasised that the intention here is not to infer that the other toxic effects (such as repeat dose toxicity, female reproductive effects, etc) of TCEP seen in experimental studies do not pose a risk to human health or are, necessarily, of lesser importance. Rather, it is the case that the experimental endpoints from which these hazard determinations were made cannot be directly associated with a specific human health effect given current scientific understanding in the field.

3.3.1 Cancer

Rodent studies have shown that TCEP can cause tumours in several tissues. However, the kidney was identified as the most sensitive target. The RAR also established that the tumour-inducing effect was probably due to mechanisms such as cytotoxicity and cell proliferation, rather than to a non-threshold mechanism such as mutagenicity.

A **LOAEL** of **12 mg/kg/day** for renal tumour formation was identified in the RAR; this was based on the same 18 month study in mice as had been used to establish an identical LOAEL for repeat dose toxicity based on renal non-neoplastic pathology. This dosage was selected since there was clear evidence of non-neoplastic (probably pre-neoplastic) change in the kidneys at this dose although no mice given this dose were diagnosed with renal tumours.

Although TCEP is not considered mutagenic, the RAR concluded that there was insufficient information available to determine the mechanism(s) of tumour formation but, importantly, stated there was no indication that the effects were due to a species- (or rodent-) specific mechanism. Hence, it is not possible to discount the experimental carcinogenicity finding in terms of significance to humans. However, it was suggested that tumours would not be anticipated to develop at exposures below the yet-to-be defined 'critical level' above which repeat dose (non-neoplastic) renal toxicity occurred.

Various forms of kidney cancer occur in humans. However, the term 'cancer of the kidney' (ICD-10 C64-C66, C68; ICD-9 189[15]) is often limited to cancer of renal cells, excluding the renal pelvis and other associated tissues[16]. Other forms include cancer of the renal pelvis[17], cancer of the ureter[18] and cancers of other/unspecified urinary organs including the urethra[19]. Cancers of the urethra[20] are sometimes included in

[15] Codes relate to the WHO's International Classification of Diseases (ICD) which provides a standard diagnostic classification for human diseases and health conditions, the latest version of which is ICD-10. Individual disease types are assigned an alphanumeric code, e.g. C64 relates to malignant neoplasms of the kidney (excluding the renal pelvis; for further details see http://www.who.int/classifications/icd/en/).

[1616] ICD-10 C64/ ICD-9 189.0.

[17] ICD-10 C65/ICD-9 189.1.

[18] ICD-10 C66/ ICD-9 189.2.

[19] ICD-10 C68/ICD-9 189.3 - 189.9.

[20] Those classified as ICD-10 C68.0/ ICD-9 189.3.

estimates for kidney cancers (Cancer Research UK, 2007) since they are thought to have similar aetiologies despite showing differing strength of association with causal agents such as chemicals.

Data for adults in England and Wales show that almost 90% of malignant kidney cancers are renal cell carcinoma (RCCs), mainly adenocarcinoma. These arise from cells of the proximal convoluted renal tubule (Stewart and Kleihues 2003; Quinn et al, 2001). Rates of kidney cancer incidence and mortality across Europe vary, particularly in men (Cancer Research UK 2007). It is high in Eastern Europe, especially the Czech Republic and Estonia, and low in southern Europe (Zatonski et al, 1996); rates in males are also high in the Bas Rhin area of France and Trieste in Italy. Overall the European Cancer Observatory[21] reports the age-standardized incidence rate for EU-27 in 2008 to be 11.0 per 100,000 (15.8 per 100,000 in men and 7.1 per 100,000 in women); most cases occur between 50-70 years of age (Quinn et al, 2001).

Cigarette smoking is the most well established causal risk factor for RCC, and a dose-response has been observed for men and women (Wynder et al, 1974; McLaughlin et al, 2006). Individuals exposed to high levels of arsenic in drinking water have also elevated risk of cancer of the renal pelvis or ureter (Guo et al, 1997; Hopenhayn-Rich et al, 1998) and an association between analgesic use, specifically phenacetin-containing pharmaceuticals, and RCC has been reported (Kreiger et al, 1993). Predisposition to RCC may also arise in cases of long-term kidney dialysis and in renal transplant recipients following renal cystic disease (Ishikawa et al, 2003; Stewart et al, 2003). There is thus strong evidence that renal cancer risk in humans is influenced by chemical exposures and the presence of long-term kidney disease. Based on the assumption that TCEP may be capable of eliciting pre-neoplasic damage in humans, it can therefore be assumed that TCEP poses a potential renal cancer risk to humans. The dose-response data on cancer incidence in mice provides an appropriate basis with which to generate indicative estimates of the risk of renal cancer to humans. **This will be discussed further in Step 2c.**

3.3.2 Infertility

The RAR identified a range of endpoints indicating that TCEP causes a number of adverse effects on rodent reproductive fertility. Effects observed include: alterations in weight of primary and some secondary sex organs following repeated exposure; reductions in various markers of fertility (e.g. number of litters produced and of viable offspring) following TCEP exposure of either the male or female parent although – from a cross-over phase[22] included in one study – it appears that the magnitude of effect is much greater where the male rather than the female is treated. Other effects of TCEP included changes in female oestrus cycle length and significant impairment of sperm quality and number in males.

[21] Available at Internet site http://eu-cancer.iarc.fr/cancer-19-kidney.html,en#block-9-33 (Accessed 2 September 2010).

[22] Male treated crossed with untreated female, and treated female crossed with untreated male, as opposed to routine design where both parents treated and compared with data from untreated pairs.

The RAR established a NOAEL for fertility of 175 mg/kg bw/day using data from the CD-1 mouse study by Gulati et al (1991). This was based upon a statistically significant reduction in the number of litters produced in the F0 generation, reduced pregnancy and fertility indices noted in the F1 generation and a statistically significantly reduction in litter size in both F0 and F1 generations (Table A1-3.3).

Table A1-3.3: Summary of Key Fertility Findings Identified by RAR

Effect	Dosage (mg TCEP/kg bw/d)			
	0	175	350	700
F0 generation (continuous breeding phase)				
Number of litters per breeding cycle:				
1	37/38	18/19	18/18	18/18[a]
2	37/38	18/19	18/18	12/18[a]
3	37/38	18/19	16/18	2/18[a]
4	37/38	17/19	16/18	0/18[a]
5	35/38	17/19	13/18[a]	0/18[a]
Average litter size[b]	4.9 ± 0.0	4.9 ± 0.1	4.5 ± 0.2[a]	1.8 ± 0.2[a]
F1 generation				
Pregnancy index	17/20	18/20	14/20	-
Fertility index	17/19	18/20	14/20	-
Litter size	11.4 ± 0.5	11.0 ± 0.5	7.6 ± 1.1[a]	-

Notes:
[a] Chi-squared test $p<0.05$
[b] for number of fertile pairs producing live pups
Source Gulita et al (1991)

The critical endpoints that form the basis for a NOEL in the RAR are commonly employed rodent reproductive endpoints considered sensitive markers of reproductive toxicity. As such, it is appropriate to use them to characterise reproductive risk for humans. However, currently our ability to interpret the significance of changes in some of these specific endpoints with regard to direct human health consequence is very limited. That is to say, while the rodent endpoints indicate a risk to human fertility, the nature of the corresponding change that might occur in humans is unclear.

Of the reproductive endpoints affected in the Gulita et al (1991) study, the F0 dams given 350 or, in particular, 700 mg/kg/day showed progressive reduction in number offspring per litter as the continuous breeding program progressed. For some chemicals, this type of observation may suggest an early loss of reproductive capacity due - for example - to depletion of ovarian follicle reserves[23]. However, no evidence of such a mechanism is suggested by the available findings. Indeed, the cross-over phase indicated that much (although not all) the reproductive impairment seen was attributable to effects on the male. Given the demonstrably greater susceptibility of

[23] Such a change if quantifiable through organ weight or histopathological analysis might conceivably form a suitable metric by which to extrapolate to a potential impact on onset of human female reproductive aging (see Wallace and Kesely (2004) and Zaidi et al (2007)). In this study however no meaningful ovarian weight data were generated because of confounding by the presence of ovarian follicles in several treated females.

male than female rodents. and the reports of impaired semen quality in several studies, together with an apparent preponderance of males in the workforce of most industries using TCEP (with the exception of textiles), it may be concluded that the changes seen in rodent sperm quality may represent the most robust of the available indicators of adverse impact on human fertility.

In Europe, overall fertility has decreased with an EU-25 average of 1.5 births per woman (compared to a rate of 2.1 necessary for population replacement). While it is believed that life-style and economic factors are a major contributor to this change, it is also considered increasingly important to address biological obstacles to reproduction, such as infertility (EC, 2007). A significant number of couples have problems in conceiving. The prevalence of infertility[24] in European couples is around 14%, i.e. one in seven couples. About 20% of observed infertility is directly attributable to low sperm count or quality, and this is a contributory factor for a further 25% of couples (National Collaborating Centre for Women's and Children's Health, 2004). This suggests that male infertility may contribute to about 45% of cases of infertility among couples (i.e. 6.3% of all infertility) in Europe.

Clinically, the lower reference values (i.e. the 2.5th%ile) defined by WHO (Cooper et al, 2009) for semen quality in fertile men is: semen volume of 1.2 (1.0-1.3) ml; sperm concentration of 9 (8-11) x 10^6; total number of 23 (18-29) x10^6 sperm per ejaculate; and total sperm motility of 34 (33-37)%. The corresponding 50th%ile values among fertile men are: semen volume 3.7 ml; sperm concentration 73 x 10^6; total sperm number 255 x 10^6 per ejaculate; and total sperm motility 61%. Hence, males with sperm concentrations below 20 million per ml, with total sperm numbers per ejaculate of less than 40 million and motility levels below 25-50%, and/or less than 30% normal morphology, are likely to be clinically infertile (National Collaborating Centre for Women's and Children's Health, 2004).

A number of causal factors in male infertility have been established but there remains at least 30% for which no specific cause can be established. While some of these idiopathic causes may reflect undefined genetic abnormalities, many instances are thought to arise from endocrine disruption or direct toxicity by chemicals or through secondary mechanisms (e.g. production of reactive oxygen species in seminal fluid) involving chemical exposure. Some contributing factors are non-occupational in nature, such a stress, under-nutrition, socioeconomic issues and emotional deprivation and some pharmaceuticals as well as life-style factors (such as diet, clothing, exercise, alcohol, tobacco, and recreational drugs, e.g., marijuana). Adverse effects may also be due to occupational exposure to chemicals such as: pesticides (e.g. chlorinated nematocide dibromochloropropane (DBCP), chlordecone, carbaryl and ethylenedibromide); glycol ethers; metals and metal fumes; and some solvents. Indeed, it has been suggested that the human seminiferous epithelium is more susceptible to the effects of toxic chemical than other animals (Skakkebæk et al, 1994; Figà-Talamanca et al, 2001; Aziz and Agarwal, 2008). There is therefore good

[24] based on infertility being defined as failure of a couple to conceive after frequent unprotected sexual intercourse for 1-2 years

scientific reason to suppose that occupational exposure to TCEP, if at a sufficiently high level, might result in male infertility via an effect on semen quality.

Sperm quality following TCEP exposure was assessed in several rodent studies (Gulati et al, 1991; Gulati and Russel, 1985; Morrissey et al, 1988; and Shepelskaja and Dyschinewitsch, 1981). However, the RAR does not present detailed data on the scale of these changes. Detailed data are currently only available for the Gulati et al (1991) study (see Table A1-3.4) which provides a very scant dataset. The extent to which determination of dose-response relationship for the various endpoints is limited and any estimates will be subject to considerable uncertainty (particularly given the cross-species differences that exist between rodent and human sperm production processes and parameters). Despite this, the potential use of data on % motility and abnormal sperm parameters **will be considered further for male worker populations,** so as to illustrate potential approaches to the extrapolation of such data**.**

Table A1-3.4: Summary of Available Rodent Dose-response Data on Sperm Quality

Mouse dosage (mg/kg/d)	0[a]	0[b]	175[b]	350[b]	700[a]
Human equivalent dose (mg/kg/d)	0	0	25	50	100
Concentration (10^6 per g)	1223.1±68.7	1429.9±48.8	1562.5±50.5	1456.2±50.4	810.0±76.8
% motile	77.8±1.6	76.8±2.2	78.0±2.2	73.5±3.9	35.0±8.0
% change[c]		101	95		45
% abnormal	9.1±0.59	7.2±0.45	6.8±0.76	7.9±0.92	31.5±3.1
% change in normal sperm		101	100		75

Note:
[a] FO generation; [b] F1 generation; [c] compared to mean of FO and F1 generation controls
Source Gulati et al (1991)

3.3.3 Neurotoxicity

TCEP shares a chemical structure with a group of known human neurotoxicants and there is animal and human studies suggested TCEP is neurotoxic.

The critical study identified by the RAR established a NOAEL for central nervous system (CNS) (brain) toxicity of 44 mg/kg bw/day following long term exposure of F344/N rats (NTP, 1991; Matthews, 1993). Although B6C3F1 mice given 350 or 700 mg/kg bw/day for 16 days suffered ataxia and convulsive movements during the initial first 3 days of dosing (NTP, 1991; Matthews, 1990), mice were considered less sensitive to TCEP since no pathological changes were observed in their brains up to 350 mg/kg bw/day. The neurotoxicity of TCEP was largely characterised in the RAR using chronic pathological change (cell loss) in the brain of rodents but these studies provide only very limited insight into the dose-response, and the extent to which these experimental findings can be used to infer human health impacts is questionable. There is, however, limited experimental rodent evidence suggesting impairment of

higher functions (e.g. learning and memory) following TCEP exposure. Tilson et al (1990) reported that – in addition to eliciting histopathologically-observable neuronal damage - a single dose of TCEP at 275 mg/kg bw/day caused mild impairment of acquisition of spatial memory and significant impairment of memory when retested at intervals using a water maze. Findings of this type might potentially constitute a means of quantifying the potential scale of human impact. However, the acute nature of the study and its design makes it impossible to attempt this for this case study. In contrast, Kawashima et al (1983) dosed pregnant female Wistar rats at 50, 100 or 200 mg/kg bw/day on gestation days 7 to 15, and subsequent examination of offspring using open field, water maze, rota rod, slop test, pain reflex and Peyer´s reflex examinations showed no evidence of neurotoxicity; only a summary was available and hence it is not possible to determine the appropriateness of the design or robustness of findings. Other rodent developmental studies considered in the RAR did not identify concerns for neurodevelopment but endpoints that might be informative do not appear to have been included in the studies.

There is one case study, noted in the RAR, which raised particular concerns about the neurotoxic potential of TCEP in children. In addition, an epidemiological study (UBA, 2008) reported apparently strong associations between the TCEP content of airborne dusts and children's cognitive abilities. The main objective of the UBA (2008) study was to investigate the effects of airborne pollutants (including particulates) in the school environment on the respiratory health of children (5-9 years of age) but the study also included assessment of cognitive abilities (using SPM testing) to infer the children's general intelligence level. Findings on respiratory function and cognitive ability were compared to the analysed levels of a range of pollutants (including TCEP) in various types of dust and particles. The study drew on a cohort of children from nine primary schools in Vienna, Carinthia, Graz and St. Poelten. Of 596 invited to participate, 225 boys and 224 girls provided completed questionnaires (return rate 75.3%). Standard Progressive Matrices (SPM) tests were used to assess cognitive development and general intellectual potential (as defined by Spearman and Raven) by means of a non-verbal examination; Raven, 1938; Spearman, 1938). Testing considered ability to: pay attention/concentrate; perceive/appreciate; recognise, make decisions; ability to learn; memory/retentiveness-ability; as well as faculty of abstraction and rationality. The total number of points achieved by a test subject is believed to be indicative of their cognitive abilities 'relatively' independent of educational attainment or socio-economic background.

Comparison of SPM data with that on exposure to TCEP showed statistically significant correlations between the SPM t-value and TCEP-content in the particulate fraction (t-values = -0.68 for PM_{10}, -0.68 for $PM_{2.5}$ and -0.73 for dust). For the exposure metric showing the strongest correlation – dust - the effect was consistent for exposures up to 25 mg TCEP/kg dust and the graphical representation included in the report suggests a loss of approximately 3 SPM points between exposures of 5 and 20 mg/kg.

The authors note that cognitive ability is strongly linked to a child's domestic experience and a number of important factors that may adversely affect ability (e.g.

spending excessive periods watching TV, extent of intellectual stimulation) were not adjusted for in this study. Also, the study's cross-sectional design precludes inference of causality. Despite these significant limitations, the authors suggest that, since the hippocampus is important for learning and memory in humans[25], there may be a link between the changes observed in children and the findings in rodents of learning/memory impairment and hippocampal damage by Tilson et al (1990).

The UBA study, although not definitive, appear to support an adverse effect on children's cognitive development from TCEP exposure. Hence, the possibility that a young child might experience harm as a result of early life exposure to TCEP (e.g. due to sucking a toy containing TCEP) is a justifiable concern. Furthermore, the experimental findings of specific histopathological change in the brains of rats after a single exposure suggest that any effect might be permanent.

These findings suggest that it is possible that adult workers and young children might suffer adverse impact on their cognitive ability as a result of TCEP exposure; any such impact could have profound consequences, particularly for children with regard to life-time adverse consequence following early-life exposure. However, **the available study data are unsuited to deriving impact estimates.**

3.3.4 Overview of Potential Impacts Identified in Step 2c for TCEP

In Step 2c, three important potential impacts of TCEP on human health and well-being have been identified and assessed in terms of suitability for quantification. These are: cancer of the kidney; male infertility; and neurological impairment.

Renal Cancer

In humans, cancer of the kidney has become an increasingly common tumour over recent decades (Quinn et al, 2001) and most of the tumours diagnosed are found to be malignant in nature (Stewart and Kleihues 2003; Quinn et al, 2001). It occurs most frequently in individuals between 50 and 70 years of age (US EPA, 2010). As kidney cancer commonly causes no obvious symptoms during the early stages of development, tumours are often advanced at diagnosis limiting the possibility of curative medical intervention. It is also quite an aggressive cancer with the result that overall prognosis is poor, as are rates of long-term survival (Stewart and Kleihues, 2003; US EPA, 2010). Although estimated 5-year survival rates have shown apparent improvements in recent years – reaching, for example, 50% in men and 49% in women for England and Wales 2001 (Cancer Research UK, 2007) – this is thought to, at least in part, reflect improvements in early diagnosis (due to ultrasound, computed tomography and other techniques) and hence the earlier certification of the disease (Levi et al, 2004). In cases of advanced disease, survival may be only 37% by 2 years or, if bone metastases are present, the median survival may be only of the order of 12 months (Toyoda et al, 2007). Furthermore, the survival rates show a marked decline

[25] The crucial role of the hypothalamus is supported by de Haan et al (2006) and Nair (2010)

with increasing age at diagnosis; this is particularly marked beyond the age of 40 years (Quinn et al, 2001), the time when most cancers of this type develop.

Currently the main therapy involves radical surgical excision (often involving the adrenal gland and associated tissue and regional lymph nodes) with chemo-, radio- and hormonal-therapies considered of limited additional value. Additional surgical interventions may be required in late stages of the disease (last 6 months of life) to alleviate secondary complication (US EPA, 2010). Recently several new treatments have been introduced but these tend to result in only a limited prolongation of survival time (currently estimated to be of the order of 5-6 months) but are not curative in nature and incur considerable expense (estimated for the UK at £20,000 to £35,000 (approx. €24,500-€43,865) per patient year[26]).

Thus cancer of the kidney can be characterized as a generally malignant tumour associated with a very poor prognosis and a median survival time of 5 years or less. Treatment involves major surgery followed by supportive therapies and, possibly additional surgery to alleviate unacceptable secondary symptoms.

Male Infertility

Infertility of males cannot be considered a disease per se but may result in profound psyco-social and economic consequences for both the male and his partner. Amongst infertile couples, men may suffer decreased mental health, increased physical stress reactions, decreased social support and increased negative social stress over time (Peronace et al, 2007) and, although determining the contributory causes is complex, there appears an increased risk of break-up amongst involuntarily childless couples (Clark and Berrington, undated).

Options for use of assisted reproductive technology (ART) treatments where the male is infertile due to low sperm count, low motility or a high count of abnormal sperm are limited but include use of in vitro fertilization techniques - such as intracytoplasmic sperm injection (ICSI[27]), which may require surgical interventions on both the male and female. Depending on where the couple live, access to such treatments may be limited and, depending on the Health Service arrangements of the Member State, may incur private medical costs. If the female is fertile, an alternative approach may be use of donor sperm although this has itself been suggest to result, in some instances, in negative effects on the couples' relationship and adverse societal ramifications (Eisenberg et al, 2010). There are also concerns that use of in vitro techniques such a ICSI might associate with an increase in risk of birth defects, possibly of the order of 30–40% (Hansen et al, 2005); possible effects include increased chromosomal anomalies, cystic fibrosis (CF) gene mutation and Y-chromosome micro-deletions (Kurinczuk, 2003) which could lead to socio-medical costs associated with treatment or increased support needs of offspring.

[26] See Internet site http://www.timesonline.co.uk/tol/life_and_style/health/article4474425.ece.

[27] See Internet site http://www.advancedfertility.com/icsi.htm (Accessed 13 September 2010)

Neurological Impairment

The consequences of neurological impairment of workers as a result of chemical exposure may be minor or profound, depending on the nature and degree of the effect and the particular area(s) of the brain that suffers damage. Thus, for example, some substances at low levels of exposure may cause only sub-clinical change of fine motor skills leading to limited impacts while others might result in profound impairment of neuromuscular function or increased risk of neurodegenerative conditions such as parkinson's-like conditions or dementias (Landrigan et al, 1994).

In the case of children, perhaps one of the most worrying consequences of a reduction – even slight – in cognitive ability is that lower IQ has been suggested to associate with profound socioeconomic consequences throughout life and a lowering of life expectancy. For example, it was reported that, in the US, median annual earnings in 1992 for individuals with IQs of 125+, 90-109, and 75-89 were $27,000, $20,000 and $12,400 respectively (Murray, 1997) while 1-standard deviation difference in IQ score is reported to associate with a 20% increase in odds-of-dying for any given age before mid-life (Jokela et al, 2009).

3.4 Step 2d: Benchmarking of Human Health

As noted above, it is not possible to infer particular human health consequences for some toxic effects (e.g. repeat dose toxicity and female reproductive effects) of TCEP noted in experimental studies but it is possible that consideration of these aspects could be addressed using benchmark or risk ranking techniques. Indeed, the potential value of benchmarking and risk ranking approaches to enable comparison of the human health risks associated with chemicals is clearly recognised in the logic framework.

Given the nature and importance of the health effects suitable for progression to Step 3 of this case study (described in Step 2e below), it was decided that illustration of these Step 2d methods in this case study was inappropriate; these are discussed in some detail in the case study on HBCDD.

3.5 Step 2e: Potential for Human Health Quantification of Impact

Step 2e considers which of the qualitative impacts identified by Steps 2a-c are suitable for progression to Step 3. The possibility of quantifying human health impacts for the effects considered are therefore summarised below.

3.5.1 Cancer

TCEP has been associated with development of cancer of several tissues in rodent life-span studies, of which cancer of the kidney appears the most sensitive. Importantly, kidney cancer is a tumour that occurs in humans in whom it is noted to

be sensitive to chemical insult. The available rodent studies are relevant to worker scenarios since they addressed chronic exposures lasting throughout most an animals' lifespan and there is no evidence that the neoplastic effect of TCEP is route- or species-specific. The critical oral study identified by the RAR used doses of TCEP of 12 to 1500 mg/kg bw/day. As this was a mouse study use of an inter-species scaling factor of 7 is appropriate, implying a human equivalent dose range of 1.7 – 214 mg/kg bw/day; this would indicate that overall exposure levels experienced by workers in some of the scenarios were of concern.

Because the renal neoplasia caused by TCEP in rodents appears to arise as a consequence of sustained tissue toxicity not compound-induced mutagenicity, the scientific basis on which to extrapolate experimental findings to the impact on children of a short (90 day) exposure during early life is much more questionable. Even if it were assumed that oral exposure from sucking of toys continued throughout the first 1-3 years of life, it is unknown if this could cause sufficient tissue damage to make an appreciable impact on life-time risk of any initiated cells progressing to tumours. There is also uncertainty as to the change in frequency and dose (and consequent toxic insult) over this period since a child's level of sucking activity will diminish/cease with increasing age. While recognising that it is possible that the kidneys may be particularly susceptible to insult during this early life stage, the extent to which this might be the case is unknown. Together with the uncertainty as to the biological consequences of limited duration exposures, this precludes any extrapolation of life-time cancer impact for children.

Given the apparent relevance of experimental findings on renal cancer in mice to humans, and in the light of availability of dose-response information, consideration will be given to the possibility of generating estimates of impact of exposure of workers – but not children - in Step 3.

3.5.2 Infertility

TCEP is associated with a range of adverse rodent reproductive effects. Of these, only the effects on male sperm quality are considered amenable to extrapolation to humans although, even in this case, the degree of uncertainty is very high and not scientifically robust. Consideration will however be given in Step 3 to an estimation of the nature of impacts on fertility in male workers because of the marked severity of the effect in animals at high exposure, and the profound consequence to the individual human male should such an impact be elicited. Therefore, **assessment of the possible scale of impact on fertility of male workers will be considered in Step 3**.

Although it is believed that the early life period of males is particularly susceptible to chemical insult of the gonad and can lead to irreversible changes[28], the mechanism of the TCEP effect in rodents is unknown. In particular, the design of the key study is unsuited establishing what – if any – is the critical window of exposure (i.e. the age

[28] This possibility has been increasing attention, particularly following the paper by Sharpe and Skakkebæk (1993).

when testes are susceptible to TCEP damage) and hence establishing if this correlates with the early life period in human children. The consequences for fertility of withdrawal of TCP exposure is also unknown (i.e. does fertility recover). Given the gaps in knowledge and the very high degree of uncertainty, **it is not considered feasible to infer the nature of the potential impact on male infants of TCEP exposure**.

3.5.3 Neurotoxicity

The available evidence base raises concern as to the scale of potential neurotoxic risk to humans from atmospheric or oral exposure to TCEP. The UBA (2008) study in particular suggests a correlation may exist between TCEP in inhalable particles and cognitive development. Unfortunately, the information as provided in the UBA study does not lend itself to extrapolation to either workers or children.

For example, in the UBA study analysis, raw SPM data scores were converted into t-values, based on age-related norms; the SPM scores themselves are not presented. This conversion is unfortunate for this case study since there is publically available information on how to extrapolate between SPM and IQ scores with a high degree of accuracy ($R^2 = 0.98$) using the equation (Egan, 1994):

$$IQ = 32.4+(1.6 \times \text{SPM raw score}).$$

Had raw data been available, this might have facilitated conversion of estimates of intellectual ability impairment into estimates of loss of IQ. The use of equivalent IQ scores would then have facilitated economic evaluation (i.e. facilitated progression to Framework Step 4) since estimates of the cost associated with loss of IQ are available. Approaches to valuing such effects are discussed in the Main Report.

The available information is considered insufficient to allow determination of the impact on human cognitive performance for the scenarios considered in this case study.

3.6 Overview of Step 2 - Qualitative and Semi-Quantitative Assessment of Human Health Impacts

In Step 2, the hazardous properties of TCEP are described in detail (Step 2a). Also, for each of the exposure scenarios identified as of concern, detailed estimates of the potential numbers of workers exposed (and, because of the nature of some of the hazards considered, the proportions of males and females) were defined. Furthermore, exposure estimates were developed for the assumptions established in the RAR and under a 'low' exposure scenario based on varying levels of dermal absorption due to the use of varying qualities of PPE equipment (see Step 2b).

Drawing on the outputs from Steps 2 a and b, and considering the potential clinical consequences that might equate to the toxic properties described for TCEP, detailed

qualitative descriptions of potential impacts on workers and children were developed where ever possible (Step 2c). Human health impacts could not be inferred for all the toxic properties of TCEP described. If applying the logic framework in a formal SEA, the remaining properties could have been used to further characterise the nature of TCEP's human health impact through use of approaches such as benchmarking or risk ranking (Step 2d). However, for this case study, resource priority was given to illustrating the later stages of the logic framework and, therefore, benchmarking was not progressed.

Step 2e drew on the conclusions in Step 2c to identify the impact-exposure scenario combinations (summarised in Table A1-3.5 below) for which it was considered feasible to progress to quantification in Step 3 of the framework.

Table A1-3.5: Outcome of Step 2 of the Logic Framework for Human Health Impact

Health Impact	Scenarios Considered	Outcome (Progression to Step 3 ?)
Renal Cancer	Workers (Scenarios 1-3)	Y
	Infants (Scenario 4)	N – insufficient information on toxic mechanisms/susceptibility
Male infertility	Workers (Scenarios 1-3)	Y
	Infants (Scenario 4)	N – insufficient information on toxic mechanisms/susceptibility
Neurological impairment	Workers (Scenarios 1-3)	N – insufficient information for dose-response characterisation
	Infants (Scenario 4)	N – insufficient information for dose-response characterisation

4. LOGIC FRAMEWORK - STEP 3: QUANTITATIVE ASSESSMENT OF HUMAN HEALTH IMPACT

Quantitative assessment of the human health impact of TCEP is only attempted for kidney cancer and male fertility (sperm quality).

The dataset available for the other identified toxic effects of TCEP is considered inadequate for progression to this stage of a SEA.

4.1 Step 3a: Baseline and Scenarios to be Considered

Although having a clear understanding of the baseline is important for the previous steps, it is more critical to this step in terms of accounting for future trends in use, etc.

For the purpose of this case study, we have simply assumed that applications for authorisation are made by all current users and that the trend in use would remain constant. Thus, the data and scenarios as presented in the RAR and developed in the steps above, are assumed to hold under the 'continued use' scenario. Importantly, the likely nature and scale of impacts considered here reflect those derived from the RAR assumptions regarding exposures used in the risk assessment and hence essentially constitute the baseline situation.

We also consider the possible scale of impacts under the lower dermal absorption assumptions discussed in Step 2.

The 'no- use' scenario then equates to a total ban in use across all current applications and hence a reduction in exposures to zero.

4.2 Step 3b: Use of Experimental Data (Dose-response based Quantification)

4.2.1 Cancer of the Kidney

Tumours of the kidney are relatively common in humans showing a European age-standardised incidence of 11.0 per 100,000 although there appears to be a sex difference in susceptibility with rates of 15.8 per 100,000 in men and 7.1 per 100,000 in women (Quinn et al, 2001). While several chemicals and occupations are known to influence risk of this cancer, no epidemiological data are available to directly inform on the human health burden from TCEP.

While for most SEAs, it would be appropriate to consider the potential impacts of repeat dose toxicity and cancer endpoints separately, the RAR for TCEP identified that the critical endpoints for both toxicities were changes in the kidney. In particular, the RAR established that there was a spectrum of effects as a result of the same (or

very closely related) threshold mechanism. However, the dataset on the non-neoplastic toxic effects are incomplete. In particular, the critical study used in the RAR to establish a LOAEL for the repeat dose and cancer effects does not provide adequate data to establish a threshold and does not permit derivation of a robust dose-response curve (EC, 2009). Given this limitation, it is impractical to estimate human impact using the dose-response data based on pre-neoplastic lesions. However, the RAR does provide data on the renal tumour incidences from rodent studies (Table A1-4.1).

Table A1-4.1: Incidence of Adenoma or Carcinoma of the Kidney in Rodents given TCEP

Species/Strain							
Rat - F344/N[1]	Dose (mg/kg/dy)		0	44	88	-	-
	Incidence	Male	2/50	5/50	25/50	-	-
		Female	0/50	2/50	5/50	-	-
Mouse – B6C3F1[1]	Dose (mg/kg/day)		0	175	350		
	Incidence	Male	0/50	0/50	1/50		
		Female	0/50	1/49	0/50		
Mouse – Scl:ddY[2]	Dose (mg/kg/day)		0	12	60	300	1500
	Incidence	Male	2/50	0/49	2/49	5/47	41/50

Notes:
[1] From NTP (1991) and Matthews (1993)
[2] From Takeda et al (1989)

While inadequate for use in modelling for a risk assessment, the data from Takeda et al (1989) shows a dose-response that allows generation of at least indicative estimates of the potential scale of human cancer burden, within the context of a SEA[29]. Approaches that might be utilised to derive estimates of this human health impact include use of bench-mark dose or linear extrapolation models. These are discussed below.

Bench Mark Dose Approach

To illustrate the application of Bench Mark Dose (BMD) models to derive estimates of the scale of impact, the US EPA BMD[30] program was applied to data from the study by Takeda et al (1989) using allometric extrapolation to human-equivalent doses.

To achieve this, the doses from the study on mice were first converted to give 'human equivalent' values using a TGD-based assessment factor of 7 (for mouse to human extrapolation). Also, while acknowledging that there would almost certainly be inherent differences in susceptibility to tumours across species, the scale of effect seen in the mouse study (when expressed as 'extra response above control level) was applied to indicate the possible additional 'risk' of renal cancer in humans as a result

[29] Any estimate derived is not intended to be an accurate prediction of health impact but rather is intended to inform an SEA of the likely magnitude of any effects, to facilitate comparison with the projected costs arising from particular regulatory action.

[30] Available at http://www.epa.gov/ncea/bmds/

of a particular TCEP exposure (see Table A1-4.2). As the intention is to derive estimates for a SEA, not a risk assessment, the extrapolation did not include any other adjustment factors as would normally be included (for example to adjust for inter-individual variability or other contributors to uncertainty) in a risk assessment.

Table A1-4.2: Data set from Takeda et al (1989) used in BMD Modelling

Mouse dose (mg/kg/day)	0	12	60	300	1500
Human equivalent dose (mg/kg/day)	0	1.71	8.57	42.86	214.29
No. Animals with tumours	2/50	0/49	2/49	5/47	41/50
Incidence of animals with tumours above control level	0/50	0/49	0/49	3/47	39/50

The US EPA BMD-programme allows cancer data to be modelled using various assumptions on the shape of the dose-response relationship and associated factors. Several model selections were investigated (including Multistage-Cancer 2nd and 3rd degree, quantal linear, logprobit and loglogsistic) to establish which gave the 'best fit' statistically for the dataset; this showed that output values were extremely dependent on the model and the conditions applied and underlines the need for expert input into this process. Although the logprobit modeFl gave a slightly higher p-value, the model chosen here to exemplify the extrapolation of impact was a multistage cancer model of degree 2 since this was thought to be potentially more representative of the nature of the biological processes being modelled (this passed the Chi Square goodness of fit test, significance = 0.05 and gave the lowest AIC value). This model is plotted in Figure A1-4.1 below.

The BMD and BMDL values associated with this model were 56.6 and 40 mg/kg/day respectively. By convention, the lower confidence limit of the bench mark dose (BMDL) is considered to represent a value suitable for use as a point of departure (POD) for risk characterisation and, as such, represents an alternative POD to a NOAEL/LOAEL value derived from a traditional NOAEL/LOAEL toxicity study design. In the case of cancer endpoints, estimates are generally based on the calculated dose that results in a 10% effect (i.e. $BMDL_{10}$; Setzer and Kimmel, 2003; Barlow et al, 2006) for risk assessment. However, as is done below, the model can also be used to derive estimates of the scale of effect at any particular dose within an established response curve.

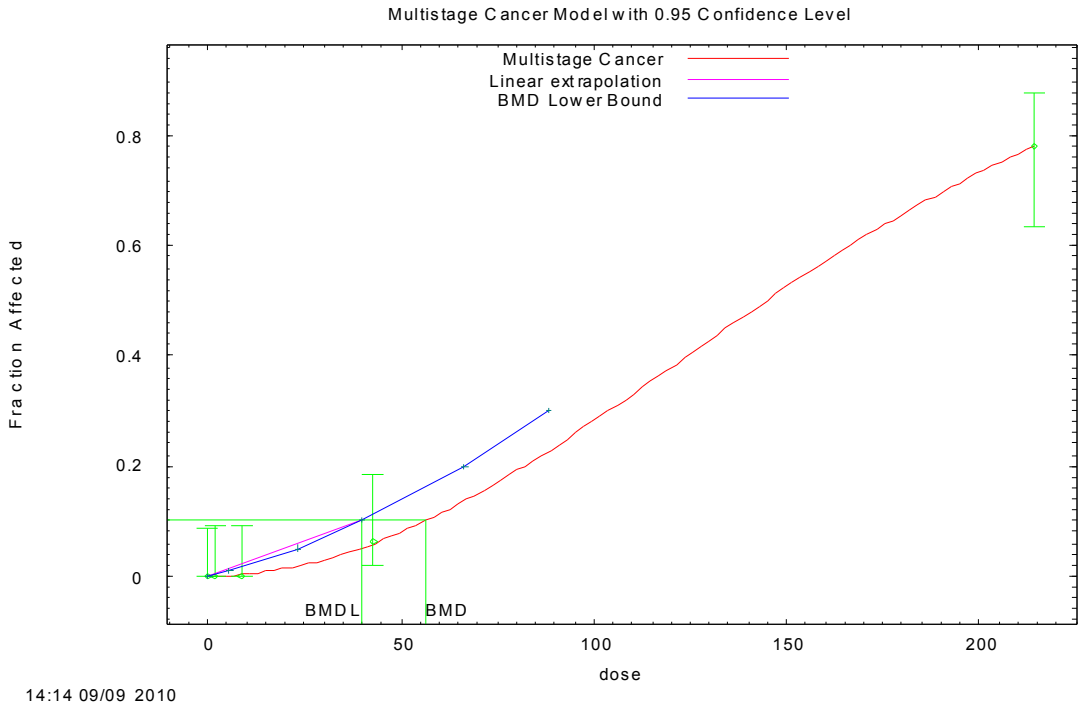

Figure A1-4.1: Benchmark Dose Modelling (Multistage Cancer Model)

Estimates of Impact in Worker Populations

In applying the BMD output to the worker scenarios (see Framework Step 2b), it has been assumed that the additional cases of kidney cancer caused would be reflective of the total systemic dose not route-specific exposures. Hence impacts were estimated using the estimated total daily dose values for each scenario.

The scale of the predicted additional burden that might be borne by the workforce exposed to TCEP under exposure estimates based on: 1) those in the RAR (i.e. based on an assumed dermal exposure of 100% and no or ineffective PPE); and 2) a 'low' exposure estimate developed specifically for this SEA (i.e. assuming dermal absorption of 20% and use of effective PPE), are summarised in Table A1-4.3. It should be noted that only data for male mice were available, with which to develop the dose-response used for extrapolation to humans. Hence, the estimates are of most relevance to the human male population. In the light of evidence that human females are significantly less susceptible to this type of cancer than males[31], to approximate this inter-sex difference in susceptibility, a nominal adjustment was therefore made by halving the predicted number of cancers in females.

Based on these assumptions, our estimate suggests that the additional number of kidney cancers among the exposed worker population based upon the exposure

[31] General population incidence for renal cancer = 15.8 per 100,000 men and 7.1 per 100,000 women

estimates established by the RAR may be of the order of 3,702.4 (3,376.7 male and 325.7 female).

The basis for extrapolation is a dose-response curve from a life-span rodent study and, as such, can be assumed to be indicative of human life-time risk from exposure through working life. On this basis, it might be estimated that the **annual incidence of extra kidney cancers attributable to occupational TCEP exposure** (assuming a 40-year occupational exposure period) **for the RAR-based exposure estimates is unlikely to be in excess of 93 cases for the European worker population.**

The total number of extra cancer cases estimated assuming 'low' exposure scenarios is much lower, at 2.0 (1.7 male and 0.3 female). Again, if annualised across a 40 years period, this would equate to **0.05 extra cancer cases per annum for the European exposed worker population.**

Of course, the above estimates are simplistic and contain a considerable degree of uncertainty (e.g. in extrapolation of rodent findings directly to humans, in assumptions regarding the period over which exposure would need to be maintained to elicit initiation/progression of renal cancer in humans and, of course, no adjust was made for actual numbers of years an individual may be exposed to or for workforce turnover). However, the estimates are considered of value in placing into context the anticipated scale (and – in Step 4 - the associated socioeconomic costs) of this risk posed by TCEP.

Linear Extrapolation

The REACH Guidance Documents state that a linear extrapolation approach can be used in the "absence of sufficient information on modes of action or when mode of action information indicates that the dose-response curve at low dose is, or is expected to be, linear". Furthermore, it is suggested that a T_{25} should be used as the default dose descriptor for linear extrapolation (ECHA, 2008). However, the guidance also indicates that a BMD method – such as is explored above - might be valuable when the data are sufficient to allow such modelling. The TGD also notes that linear extrapolation may result in overestimation of risk at low exposures; while this is acceptable for risk assessment, the resultant precautionary estimate might be less suited for use in estimating health impacts for a SEA.

The RAR for TCEP establishes a T_{25} of 130 mg/kg/day (i.e. 44 mg/kg/day x 25%/ 6% x 5d/7d x 103 wk/ 104 wk), calculated using the combined rates for animals bearing renal adenoma or carcinoma in a carcinogenicity study. The RAR also uses this estimate to establish a critical exposure level of 2 mg/person/day (i.e. 0.029 mg/kg/day or a worker inhalation exposure level of 0.2 mg/m^3) and this dose was also stated to equate to a cancer risk of 5.58×10^{-5} (i.e. 0.25 x 0.029/130). The RAR also stated that inter-species extrapolation and differences in exposure schedule did not substantially modify the risk estimate.

Table A1-4.3: Estimated Scale of Renal Cancer Impact for Workers									
Scenario		**Workforce**		**Impact Based on RAR Exposure Estimate[1]**			**Impact Based on 'Low' Exposure Estimate[2]**		
		Industry	**Estimate**	**Total Exposure (mg/kg/day)**	**BMD Model Additional Cancers (per 100,000)**	**Consequent Additional Cancers (No. in males & females)**	**Total Exposure (mg/kg/d)**	**BMD Model Additional Cancers (per 100,000)**	**Consequent Additional Cancers[1] (No. In males & females)**
1	Production of TCEP	Production	200 (133 male)	6.17	125.9	0.2 males; 0.1 females	0.29	0.3	0 males; 0 females
2	Production of formulations	Plastics/polymers	2000 (1400 male)			1.8 males; 0.4 females			0 males; 0 females
		Paints/lacquers	3,600 (2556 male)			3.2 males; 0.7 females			0 males; 0 females
3a	Spray application of formulations	Textiles	2,685 (265 male)	36.9	4,404.7	11.7 males; 53.3 females	0.83	2.30	0 males; 0.1 females
		Vehicles	43,551 (35,438 male)			1,560.9 males; 178.7 females			0.8 males; 0.1 females
		Construction workers	43,425 (39,517 male)			1,740.6 males; 86.1 females			0.9 males; 0.1 females
3b	Non-spray application of formulations	Furniture	81,169 (56,696 male)	3.17	33.2	18.8 males; 4.1 females	0.08	0	0 males; 0 females
		Textiles	2,685 (265 male)			0.1 males; 0.4 females			0 males; 0 females
		Construction	130,275 (118,550 male)			39.4 males; 1.9 females			0 males; 0 females
Total Estimated Size of Worker Population Exposed to TCEP					**307,190 (254,820 male)**	**3376.7 male; 325.7 female**	**-**	**-**	**1.7 male; 0.3female**

Notes:
[1] RAR exposure estimate assumes that PPE employed is ineffective at controlling exposure and that dermal exposure is 100%
[2] 'Low' exposure scenario assumes that high quality PPE is worn (reducing exposure levels by a factor of 10 compared with RAR estimates) and that only 20% of that reaching the skin is systemically absorbed

While the RAR stated that the linear extrapolation approach was not scientifically valid, it is suggested that the use of the linear extrapolation model might allow alternative indicative cancer risk estimates for an SEA. If generated, such estimates could then be compared to the above BMD-modelled values to inform on the range of values predicted using the differing approaches. This has not been undertaken here, however, due to time and resource constraints.

4.2.2 Male Infertility

Estimates of Impacts in Worker Populations

As described above, available experimental data on the effects of TCEP on semen quality, although very limited, suggest that at least at high doses there is a significant risk to male fertility.

Of the available datasets that from Gulati et al (1991; Table A1-4.4) does at least offer some possibility of dose-response modelling within the context of an SEA. While the sperm concentration data are very variable, the parameters of sperm motility and, to a lesser extent, sperm abnormalities appear to show a more consistent pattern. Ideally one would wish to obtain more informative and robust data on the effects of TCEP on sperm parameters before attempting any extrapolation to humans, however, the available data on sperm abnormalities and motility were used to illustrate one potential approach to such modelling.

Table A1-4.4: Summary of Available Rodent Sperm Data

Mouse dosage (mg/kg/d)	0[a]	0[b]	175[b]	350[b]	700[a]
Human equivalent dose (mg/kg/day)	0	0	25	50	100
Concentration (10^6 per g)	1223.1±68.7	1429.9±48.8	1562.5±50.5	1456.2±50.4	810.0±76.8
% concentration[c]			118	110	61
% motile	77.8±1.6	76.8±2.2	78.0±2.2	73.5±3.9	35.0±8.0
% change[c]			101	95	45
% abnormal	9.1±0.59	7.2±0.45	6.8±0.76	7.9±0.92	31.5±3.1
% change in normal sperm[c]			101	100	75

Note:
[a] FO generation; [b] F1 generation; [c] compared to mean of FO and F1 generation controls
Source Gulati et al (1991)

Given the difference in control values between generations, it was decided to use a composite value (by combining data from the F0 and F1 generation controls). The motility and abnormality values for each treated groups were then transformed into a measure of the difference between the treated groups value and the relevant composite control value. The doses from the mouse study were allometrically converted to their human equivalent values using a standard factor to drive the dataset used for modelling (see Table A1-4.5).

Table A1-4.5: Summary of Available Rodent Sperm Data				
Human equivalent dose (mg/kg/day)	0	25	50	100
% motility[1]	22.7	22	26.5	65
% decrease in normal sperm	8.15	6.8	7.9	31.5

Applying a LogProbit (Added Risk) model from the US EPA BMD software to the data for sperm motility gave a BMD of 61 mg/kg/day and a BMDL[32] of 44 mg/kg bw/day; this model was found to give the best fit, having a p-value of 0.90. A LogProbit (Added Risk) model was also fitted to the sperm abnormality data (p-value=0.72) and give a somewhat higher BMD of 81 mg/kg/day and a BMDL of 60 mg/kg/day. Thus, of the data available, that on sperm motility appears the most sensitive market of TCEP's effect on semen quality.

It is known that human sperm production and semen quality are low in comparison with many other species (Johnson et al, 1980) resulting in, within the human population, a significant proportion of males being at or below the threshold of fertility. In humans, sperm count is an established indicator of fertility although repeated measurements on an individual show considerable variability. Sperm motility and morphology are, however, also useful markers of fertility and show considerably less intra-individual variability and a significant positive correlation has been established between these three parameters (Katz et al, 1982; Mortimer et al, 1982). It was therefore considered appropriate to utilise sperm motility as the basis for the impact estimation.

A study by Pease et al (1991) has previously considered approaches to estimating impacts on the fertility of occupationally-exposed males using of a BMD model of rabbit data for the spermotoxic pesticide, 1, 2-dibromo-3-chloropropane (DBCP). In this study, based on estimates that a 50% fall in sperm count equates to a 4% increase in male infertility on a population basis and a 10% reduction equates to a 0.44% increase, the authors estimated the fertility impact (at a population level) of reductions in sperm count following exposure to various levels of DBCP.

Although in the extrapolation used in the Pease et al study, the association between sperm count and human infertility was used, we applied here the same assumptions to the sperm motility metric. This is considered a reasonable approximation given that a recent prospective study has demonstrated a very close association between fertility outcome and both metrics (total sperm count and numbers of motile sperm; Zinaman et al, 2000). Thus, applying the BMD model for sperm motility, the magnitude of the anticipated reduction in semen quality was estimated for each worker scenarios based on either the RAR assumptions or the 'low' exposure estimates (see Table 4.6). Using the assumed relationship between sperm quality and additional risk of infertility (Pease et al, 1991), estimates of change in population infertility rate were developed and used to estimate the corresponding number of extra cases of infertility that might be anticipated to occur in each worker population considered.

[32] Based upon a 10% reduction

This approach (see Table A1-4.6) suggests that there is a potential additional burden only for Scenario 3a (spray applications of formulations containing TCEP) for the RAR exposure assumptions. For the total male workforce of 75,220 estimated to be potentially subject to this exposure, **the total number of extra cases of infertility is estimated at 92.1** (i.e. about 0.12% of all those exposed). To place this in context, the background level of infertility in a population of this size is likely to be of the order of 5,000 individuals. The simplistic modelling employed here does not, of course, address the question of what may be the duration and frequency of worker exposure that is required to elicit infertility or address the influence of turnover in the workforce, etc.

In order to estimate the likely annual scale, it might be assumed that the effect on fertility may develop reasonably early during an individual's working life. Assuming that infertility might develop (and be of critical concern) to those between the ages of 25 and 55 (i.e. a 30 year window), an **indicative estimate could be made that this overall estimate might equate to an extra 3.07 cases of infertility per year.**

To place this in context, approximately 14% of European couples are infertile, with male infertility being a contributory factor in about 45% of these. Most of the cases of male infertility are attributable to clearly defined medical conditions with only 30% (i.e. 1.9% of total population) considered idiopathic in nature. Of those suffering idiopathic infertility, only a small fraction (significantly less than half, probably near to a quarter) are suspected to be due to the effect of chemicals on semen quality. Therefore, it might be suggested that male infertility due to the effect of all chemicals would not be anticipated to be a contributory factor to more than 0.5% of couples. Given this, the above estimate of 0.12% of those exposed at a sufficiently high level being affected, does not seem unreasonable.

4.3 Step 3c: Epidemiology Based Quantification

In the current case study there is very limited epidemiological data on the possible consequences of exposure to TCEP. Only one study (UBA, 2008) was identified that suggested a possible association with cognitive impairment in children. However, this study may be considered methodologically weak and the study findings were not reported in a manner suitable for establishing the scale of impact that might arise in either children or potentially workers. Hence, this step was not illustrated in the case study.

Table A1-4.6: Estimated Scale of Possible Fertility Impact for Male Workers											
Scenario		**Workforce**		**Impact Based on RAR Exposure Estimate[1]**				**Impact based on 'Low' exposure estimate[2]**			
		Industry	**Estimate**	**Total Exposure (mg/kg/day)**	**BMD Model Estimate of Sperm Motility Reduction Factor**	**% additional Infertile Males in Population**	**Number Additional Cases of Infertility**	**Total Exposure (mg/kg/day)**	**BMD Model Estimate of Change in Sperm Motility**	**% Additional Infertile Males in Population**	**Number Additional Cases of Infertility**
1	Production of TCEP	Production	133	6.17	1	0	0	0.29	1	0	0
2	Production of formulations	Plastics/polymers	1400								
		Paints/lacquers	2556								
3a	Spray application of formulations	Textiles	265	36.9	1.0306	0.12%	0.3	0.83	1	0	0
		Vehicles	35,438				43.4				
		Construction workers	39,517				48.4				
3b	Non-spray application of formulations	Furniture	56,696	3.17	1	0	0	0.08	1	0	0
		Textiles	265								
		Construction	118,550								
Total Estimated Size of Male Worker Population Exposed to TCEP						254,820	92.1				0

Notes:
[1] RAR exposure estimate assumes that PPE employed is ineffective at controlling exposure and that dermal exposure is 100%
[2] 'Low' exposure scenario assumes that high quality PPE is worn (reducing exposure levels by a factor of 10 compared with RAR estimate) and that only 20% of that reaching the skin is systemically absorbed

4.4 Step 3d: Assessment of Potential for Valuation

Estimates of the adverse impact, in terms of additional cases of renal cancer and of male infertility, were successfully developed for the European work force for the various scenarios considered above.

The potential economic implications of this additional human health burden are therefore explored in Step 4 of the framework, below.

4.5 Overview of Step 3 - Quantitative Assessment of Health Impacts

As discussed above, in this case study the additional health burdens attributable to occupational TCEP exposure were defined for various scenarios in relation to the important health endpoints of renal cancer and male fertility. In each case, this was achieved through application of BMD-based extrapolation from rodent experimental data using allometric scaling although the possible use of linear extrapolation approaches on experimental data is also discussed.

No suitable epidemiological studies were identified for this case study that could be used to illustrate the use of this type of data to develop impact estimates (examples of such approaches are, however, included in the description of the logic framework for human health impact assessment).

The impact estimates derived are accepted as incorporating a high degree of uncertainty and do not address all the toxic properties of TCEP. Nonetheless, they represent the best available estimates of human health burden given current scientific understanding and also provide impact measures suitable for economic valuation. Furthermore, in the light of the available experimental dataset, it may be assumed that the effect on renal cancer is a highly sensitive endpoint and hence may be considered as a potential indicator of the overall scale of adverse health impacts that could occur in worker populations exposed to TCEP.

5. LOGIC FRAMEWORK - STEP 4: VALUATION OF IMPACTS

5.1 Summary of Impacts

The RAR identifies a number of concerns regarding the level of risks posed to workers by TCEP when conducting spray application of formulations containing this substance. A second specific concern for the risks to young children (under 3 months of age) from mouthing of toys that contained TCEP was also identified. Together these scenarios formed the basis for this Case Study.

Initial review of the available information on the human health risks associated with TCEP (Step 1) indicated that no substantive concerns exist with regard acute toxicity, irritation and sensitization or developmental effects. However, a number of hazards were identified that were described in detail in Step 2; these relate mainly to risks of repeat dose toxicity and carcinogenicity. A spectrum of non-neoplastic (in some cases, pre-neoplastic) and neoplastic changes were noted in the kidneys and livers of rodents; however, detailed examination of the available pathological evidence suggested that the kidney was the more sensitive tissue and attention was therefore focused on characterising the nature and scale of effects in this organ. Increased tumour incidences in some other tissues has also been noted in rodents exposed to TCEP but the RAR considered them of limited relevance to humans and, since they occurred only at higher doses than the kidney changes, their relevance was considered equivocal.

Although a detailed description of the non-neoplastic kidney changes is given in Step 2, the nature of the changes seen in rodents are of a type that cannot be extrapolated to humans. As a result, it has only been possible in Step 3 to estimate, on the basis of cross-species extrapolation using a bench mark dose (BMD) model, the number of potential cases of kidney cancer that might occur in worker groups exposed to TCEP. Depending on the assumptions made regarding the level of exposures that workers may be subject to, it is estimated that between 93 and 3 extra cases of kidney cancer per annum may occur within this population group.

An impact on the lifetime risk of kidney cancer in children exposed through mouthing of toys can also not be discounted. However, the knowledge base on the underlying pathological processes involved in tumour development is such that it has not been possible to quantify the extent of any adverse impacts. It is important to note though that the potential exposed population could be around 670,000 males aged 3 months or less or up to almost 2.7 million males under 1 year of age depending on assumptions concerning the length of time over which these age groups continue sucking on the types of toys in question.

Another are of concern is that that TCEP may cause acute and chronic effects on the nervous system. This is perhaps not unsurprising given that TCEP is a member of a group of compounds termed ‘organophosphates’, several members of which inhibit an enzyme acetylcholine (AChE) that occurs widely throughout the nervous system of vertebrates leading to acute effects and that can also elicit chronic effects on the

nervous system through other mechanisms. Although there are good grounds to believe that TCEP may be neurotoxicity, neither the available experimental or human data were suitable to allow definition of the precise nature of the effects for workers or children; nor was it possible to develop any detailed dose-response characterisation. However, this aspect remains a significant albeit unquantified concern.

An extensive range of changes in reproductive fertility endpoints were also identified in studies on both sexes of rodents. These include: alterations in weight of primary and some secondary sex organs following repeated exposure; reductions in various markers of fertility (e.g. number of litters produced and of viable offspring) following TCEP exposure of male or, to a lesser extent, females parents; and changes in oestrus cycle length and impaired semen quality. It was not possible, however, in all but one case to directly infer the form in which such toxic damage might become evident in humans. This reflects the limited extent to which we are currently able to interpret the significance of changes in specific endpoints in terms of direct human health consequence. Thus, although it is recognised that female workers are clearly at risk of fertility impairment, only an estimate of the potential scale of impact on male workers could be derived in Step 3 based on changes in semen quality seen in rodents. Cross-species extrapolation using a BMD model suggested that the impact might amount to up to 0.05 extra cases of infertility per year among male workers exposed to TCEP. As for kidney cancer, it was also not possible to estimate the scale of impacts that might occur in exposed children of either sex due to uncertainties regarding the underlying mechanisms of toxicity and the possibility of recovery following a transitory exposure.

Table A1-5.1 summarises the estimates for the quantifiable health impacts per annum for the high and low exposure scenarios. We examine below the different methods for placing an economic value on the quantified impacts. However, it would be important to also carry the above information on the potential effects that could not be quantified through to Step 5.

Table A1-5.1: Number of Cases Per Annum Among Exposed Worker Populations

Scenario	Kidney Cancer Cases	Male Infertility Cases
High scenario based on RAR exposure assumptions	93	3.07
Low exposure scenario	0.05	0

5.2 Step 4a: Development of Market Based Estimates

The market based, cost of illness estimates for the health impacts detailed above will relate to the cost of medical treatment and the costs of lost productivity. These are both discussed further below.

5.2.1 Kidney Cancer Medical Costs (Direct Costs)

Around 63,000 people are diagnosed with kidney cancer in Europe each year, which accounts for three per cent of all cancer cases. Kidney cancer is slow to develop, and may reach relatively advanced stages before detection although recent advances have improved the situation somewhat. Symptoms may include fever, weight loss, generalized weakness, abdominal pain, abnormal increases in red blood cells or blood calcium levels, anaemia, bloody urine, cardiac enlargement or liver dysfunction without evidence of liver cancer.

Surgery remains the main treatment for kidney cancer that has not spread. Chemotherapy, radiotherapy, and hormone therapy have all proven ineffective as a systemic treatment. Although no specific cost estimates have been found for surgery for kidney cancer, more general information on the costs of an operation to retrieve a kidney suggest a figure of around €18,000 (based on a UK estimate of £15,000).

The Table A1-5.2 shows the survival rate for kidney cancer[33]. As can be seen from the table, although showing a degree of dependency on age-at-diagnosis, the average time to death is about 12 to 18 months.

Table A1-5.2: Survival Rate – Kidney Cancer

Age	5 Year Survival Rate	Average Time to Death (Years)
under 55	0.62	1.516
55-64	0.50	1.232
65-74	0.44	1.428
75 and over	0.33	1.019

The treatment of metastatic RCC (advanced kidney cancer) has been improved by the recent introduction of molecularly targeted agents. Sunitinib and bevacizumab, in combination with IFN, are approved for first-time treatment of patients with metastatic RCC and recent clinical studies demonstrate that they provide comparable levels of efficacy (Escudier et al, 2007 and 2009; Motzer et al, 2007; Coppin et al, 2008). One six-week cycle of sunitinib costs £3,140 (28 tablets of 50 mg) in the UK, equivalent to c. €3,500. The average annual cost in the UK for a patient taking sunitinib is around £24,170, **c** €26,700 (this price includes one free treatment cycle). The drug has been shown to increase survival by several months, normally around 6 months but in some cases up to two years; but it does not cure the disease. Around 50% of the people diagnosed in the UK are eligible for this treatment.

Table A1-5.3 shows the costs associated with medical treatment of kidney cancer for the RAR-based scenario presented in Section 5.1. This includes figures for the costs of surgery for 50% of the cases and treatment through drugs for the remaining 50%; the estimates exclude those associated with lost productivity and mortality and therefore underestimate the total social costs.

[33] Based on Australian estimates, available at http://www.health.vic.gov.au/healthstatus/bodvic/daly.htm

The basis for the estimates forming the RAR scenario is quite pessimistic and compare to those for the 'low' exposure scenario at around €1,335 per year assuming treatment of metastatic RCC.

Table A1-5.3: Costs associated with Medical Treatment of Kidney Cancer from RAR-based scenario		
Treatment	**Number of cases**	**Costs (annual)**
Number of surgery cases	46	€830,000
Number of cases receiving treatment	46 (assumes same eligibility to received treatment across the EU of 50%)	€1.34 m

5.2.2 Medical Costs of Treating Male Infertility

Infertility treatment requires the use of one or more expensive procedures. In the context of this case study, given the nature of the anticipated male infertility it can be assumed to require the use of Intra-cytoplasmic Sperm Injection (ICSI) techniques since ICSI is most commonly used to overcome male infertility problems where this is due to poor semen quality associated with low sperm count or motility, or high levels of abnormal sperm (teratozoospermia). ICSI may also be used where eggs cannot easily be penetrated by sperm (i.e. a type of female infertility) and occasionally as a method of in vitro fertilization. It has been found that once the egg is fertilized, the use of genetic material from sperm with abnormal morphology does not appear to influence blastocyst development or morphology. Even with severe teratozoospermia, use of microscopy at selection generally allows detection of a few sperm cells with 'normal' morphology allowing for success in such circumstances.

Costs reported from the UK are in the order of around €3,000 per treatment cycle[34]. Based on the number of cases as given in Table A1-5.1 for the RAR scenario, the costs would be around €9,000 per annum per person (assuming an estimated average success rate of about 30%), giving a maximum estimated cost under the RAR-based assumptions of about €27,000. There would be no costs under the low exposure scenario.

Again, the above estimates for the RAR scenario may be an underestimate of the total economic costs in terms of the pain and distress suffered by the people undergoing the treatment.

5.2.3 Lost Productivity

In addition to the medical costs of treating the cases of kidney cancer, other market based estimates could be developed based on lost productivity. The productivity loss related to RCC cases has been estimated for the US at around €2,500 per patient, annually (Lang et al, 2007), with this reflecting lost productivity from morbidity.

[34] Information from Internet site http://www.womenrepublic.co.uk/family_pregnancy/icsi.htm (Accessed 23 September 20100.

Assuming that this can be applied to those cases receiving surgery, the market-based estimates for lost productivity can be estimated at around €115,000 annually. However, this estimate assumes that all cancer cases resume work after treatment and therefore may underestimate the total productivity loss, particularly given the poor prognosis for this disease.

The number of years lost for an average cancer is around 11 (Huijbregt et al, 2005). Assuming that the average earnings across the EU for the group affected by cancer is €30,000 per person annually, the costs in terms of lost productivity over that 11 year period for the 46 cases assumed in the RAR-based scenario would be around €1.38 million per annum or €15.2 million (undiscounted) over the 11 year period. For the 'low' exposure scenario of 0.05 cases per annum, lost productivity would be around €1,500 per annum.

5.2.4 Total Resource Costs

Based on the above estimates, the total per annum resource costs that could be avoided under the RAR scenario are equal to €3,773,000 covering both types of kidney cancer treatment, infertility treatment and lost productivity.

In contrast, the per annum resource costs for the 'low' exposure scenario would be around €1,835.

5.3 Step 4b: Using Benefit Transfer for the Assessment of Intangibles

Willingness-to-pay estimates (WTP) to reduce the risk of death or to avoid illness provide a means of capturing the benefits to individuals of a reduction in the risk of disease. The most recent estimate used at the EU-level and quoted in the ECHA Guidance on Restrictions is €2,258,000 as an upper bound figure and €1,052,000 as a lower central estimate for the value of a statistical life (in 2003 prices). Assuming an average of 2% growth in incomes, the value in 2010 can be estimated at around €2.55 million as an upper bound and €1.19 million as a central estimate. Multiplying this figure by the 50% of kidney cancer cases associated with metastatic kidney, indicates a total WTP to avoid the loss of 46 statistical lives of around €54.74 million per annum.

As indicated in Table A1-5.2, the number of years' life lost to kidney cancer is 11 on average. Thus, if the above WTP value for the value of a statistical life is based on an average age of 40-45, then it may overestimate the benefits of reducing the risk of death in someone aged 60 or higher. This suggests that it may be preferable to apply instead WTP values for an additional life year. As also indicated in the ECHA Guidance, the current standard value for a life year is €55,800 in 2003 prices. Assuming an average of 2% growth in incomes, the value in 2010 would be around €63,200. If we assume that this figure applies equally to all of those who would not survive kidney cancer beyond one year, then the annual benefits from reducing exposure to TCEP in terms of individuals' WTP for additional life years can be estimated at around €29.07 million (covering all 10 years' of life saved). If we apply

this above approach to the 'low' exposure scenario, then we get benefits of additional future life years of around €31,600 per annum (associated with 0.05 avoided cases of cancer and 10 years additional life).

In the case of non-fatal cancer cases, the WTP to avoid a cancer case has been estimated at €400,000 per case. Thus, if this figure is applied to the 46 cases projected to go through surgery, the benefits from reducing exposure to TCEP to avoid a case of cancer would be around €18.4 million per annum. Again, it is not clear whether this figure of €400,000 per non-fatal case also includes an element of lost productivity within it; as a result, we carry forward only this figure and do not also add the lost productivity estimates for this group.

It is important to note that use of the above WTP figures in addition to the resource cost estimates associated with lost productivity may result in double counting. As a result, in developing total estimates of the potential economic damage costs associated with continued use of TCEP we carry forward these higher WTP estimates only.

With regard to male infertility impact, it is expected that WTP to avoid this condition would also be significant. However, very few studies have reported such values, probably because the preferred method in this context would be to look at revealed preferences as established by the actual price paid by people to undergo treatment.

A US study conducted in 1994 concluded that the average WTP among 150 respondents for a 10% chance of conceiving through IVF in the event of infertility was $17,730 (Neumann and Johanneson, 1994). This study however appears to be out of date given recent improvements in access and success rates of such treatments and it is uncertain whether the possibilities of conceiving in the context used by the study are directly comparable.

5.4 Step 4c: Revealed Preference Studies-based Valuation

Another means of determining the value of reductions in the risk of cancer or infertility would be through the use of revealed preferences which would include the use of personal protective equipment (PPE). Consultation has not been undertaken to determine what is currently spent on PPE but the value of such risk management measures will be captured by the lower estimates of the number of cases of cancer developed under the 'low' exposure scenario.

5.5 Summary of Impact Valuation

As might be expected, the number of cancer cases considered in the RAR-based scenario makes reduction in exposure quite beneficial in terms of human health gains. The greatest benefits arise from consideration of the intangible benefits to individuals as opposed to the cost of illness based aspects. This is because the possibilities of recovery from kidney cancer are low and surgery and treatment of RRC are painful

procedures. Importantly, the marked difference in the numbers of cases estimated for the RAR-based and the 'low' exposure scenarios highlights a significant source of uncertainty in assessing the benefits of restrictions on the use of TCEP by workers.

While the RAR-based scenario could be used as a check against the costs that would be incurred by industry were an authorisation not granted, the inclusion of conditions on uses, including PPE and other measures, could significantly reduce the total economic cost estimates presented in Table A1-5.4 below.

Table A1-5.4: Summary of Economic Costs per Annum of On-going Use of TCEP (€ million)

Scenario	**Number of Cases**	**Measure of Costs**	**Kidney – Surgery Cases**	**Kidney - Drug**	**Infertility**
RAR Scenario	93 cancer 3.07 infertility	Medical care WTP*	0.83 18.4	1.34 29.07	0.027 Not avail.
	Totals	€49.64			
Low exposure Scenario	0.05 cancer; 0 infertility	Medical care WTP*	0.0013 0.0316	Already accounted for	No cases
	Totals	€0.0329			
* WTP to avoid years life lost and WTP to avoid cancer					

It is of note that the figures presented above relate to a single year. These estimates would need to be multiplied up by the time period over which an authorisation is being sought and then discounted at the same rate as the estimated costs to industry to provide a comparison of costs and benefits as part of a cost-benefit analysis.

It should be also underlined, that the benefits presented above include only those which have been quantified. For an appropriately informed costs-benefits analysis, all benefits (including those identified only qualitatively) should be brought to the picture.

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ANNEX 2:

HEXABROMOCYCLODODECANE (HBCDD)

CASE STUDY TRIAL OF ENVIRONMENT LOGIC FRAMEWORK

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1. INTRODUCTION

Hexabromocyclododecane (HBCDD) is a brominated flame retardant which is used mainly in textile coatings (mainly for upholstered furniture) and polystyrene to help protect against fire damage. There are three main chiral diastereomers of HBCDD - termed α- β- and γ-HBCDD - and the distribution of the diastereomers in technical HBCDD varies between about 70-95% γ-HBCDD and 5-30% for α- and β-HBCDD. The occurrence of the three diastereomers (pairs of enantiomers) in technical HBCDD complicates risk assessment as they posses different environmental behaviour and hence fates such that the composition ranges found in technical material do not reflect the relative concentrations found in the environmental abiotic and biotic media.

HBCDD has undergone a formal Risk Assessment (RAR; EC, 2008) for environment and human health published in May 2008. This identified a number of environmental concerns associated with its use and showed that it's Persistent, Bioaccumulative and Toxic (PBT) properties met the requirements of Article 57(d) of REACH (concern related to its aquatic and terrestrial toxicity, bioaccumulation potential and persistence). As a consequence it was identified as a substance of very high concern (SVHC) according to Articles 57 and 59 of REACH, and is therefore included in the candidate list for authorisation and prioritised by ECHA for inclusion in Annex XIV of REACH. It has also been nominated by Norway as a candidate for the Stockholm Convention on Persistent Organic Pollutants (POPS) and for the UNECE POP Protocol (see Stockholm Convention on POPS, 2008-09 and Norden, 2008).

This case study has been prepared to illustrate the application of the proposed logic framework for the assessment of environmental (i.e. non-human) impacts. Throughout, the intention is to use the available information in a manner that illustrates the methods and approaches suggested in the logic framework, in order to identify, describe qualitatively and – where possible – to quantify the potential environmental impacts of HBCDD. The objective was to develop information in a form that would be of value for an actual SEA conducted to support an Authorisation application. However, it is anticipated that the case study will also be representative of substances subject to restriction proposals.

Finally, in this case study, we only examine the direct environmental impacts of HBCDD use. In a 'real world' situation, it would be important to also consider any human health effects associated with the use of HBCDD and any environmental and health effects arising from the use of alternatives. This latter aspect may be particularly important as ECHA, in its technical report on HBCDD (ECHA, 2009b), identified some commercially-available non-halogenated substances that may constitute technical alternatives for most applications of HIPS, textile coatings, EPS and XPS but also raised concerns over their toxic properties.

The case study draws on information in the Risk Assessment Report (RAR), the Annex XV dossier (EAA, 2009), the Member State report on its SHVC status (ECHA, 2008a), the background document and technical report published by ECHA in January and June 2009 (ECHA, 2009a&b), as well as and other published sources where

appropriate. Additional information, particularly with regard to its long-range transport potential comes from the Stockholm Convention on POPS (2008-09) and Norden (2008). The approaches adopted and the data used in this case study were not discussed with industry. In some cases, we have made assumptions on data relating to the production and uses of HBCDD which industry may be able to provide valuable updates on.

2. LOGIC FRAMEWORK - STEP 1: CHARACTERISATION AND SCOPING

The first step in the logic framework is to collate basic information on usage of the chemical and the risks identified as of particular concern in previous risk assessment(s), in this case from the Existing Substances Risk Assessment Report (RAR).

2.1 Characterisation of Production and Use of HBCDD

HBCDD is now produced in only one European plant, located in the Netherlands. Two other production sites were closed in the autumn of 2003 and June 1997, respectively. The reported amount of HBCDD produced at the site varies from one year to another; in the RAR, the total HBCDD production was assumed to be 6,000 tonnes for 2005. HBCDD is also produced in the USA and Japan.

HBCDD is mainly used in Expanded and Extruded Polystyrene (EPS and XPS) insulation foam boards, which are widely used in construction. The substance provides a high degree of flame retardancy when used at very low concentrations and its use therefore helps protect properties and lives from potential harm from fire. HBCDD is also used in textile coatings, mainly for use in upholstered furniture, and in High Impact Polystyrene (HIPS) for use in electrical goods.

The RAR was unable to give exact use tonnages for HBCDD as industry provided information on production and import in ranges and for different years. Different methods were therefore used to estimate the total amount used, and each method provided different results (EC, 2007), as follows:

- based on the maximum of the quoted industry ranges, 6,000 tonnes of HBCDD were produced in the EU per year (between 1995 and 1997) and 5,500 tonnes were imported from the US (i.e. a total use of 11,500 tonnes in the EU); however
- industry reported that the 1999 market for HBCDD in Europe was 8,900 tonnes; and
- adding the reported amounts used in the EU for individual applications suggests a total consumption of over 9,600 t/yr - this was the value used in the RAR.

The RAR concluded that it was not possible to quantify the import of HBCDD in products (such as polystyrene and textiles) although this was considered likely to occur. It also concluded that EU consumption accounted for around 60% of total global consumption.

From the above, it appears that the volume of HBCCD manufactured in the EU has fallen over recent years and is estimated at only 6,000 tonnes per year in 2005. In contrast, however, overall usage of HBCDD in the EU is increasing, reaching about 11,600 tonnes in 2006. Furthermore, a further unknown amount will enter the EU in the form of preparations or articles; although the volume from these sources are

unknown, they are suspected to be considerable. The estimated usage pattern and numbers of industrial sites based on available data (ECHA, 2009) are summarised in Table A2-2.1.

Table A2-2.1: Usage Pattern of HBCDD		
	Total Usage (Tonnes/Year)	**Number of Sites**
Production	6000	1
EPS	5300	21
XPS	5900	28
HIPS	200	3
Textile coatings	200	16
Source: ECHA (2009) EPS - Expanded polystyrene; XPS - Extruded polystyrene; HIPS - High Impact Polystyrene		

2.2 Risks and Hazards Identified in the RAR

This case study considers the following elements from the risk assessment for HBCDD: the environmental hazard assessment; the PBT/vPvB assessment, and any outcomes of the physicochemical hazard assessment that may be important. Data from the human health hazard assessment carried out for HBCDD will only be considered with respect to potential impacts in higher predators or where this information is of value with respect to benchmarking.

In addition, as part of Step 1, assessors should review not only the specific hazard on which the risk characterisations ratios were based for each compartment considered (see Logic Framework, Section 2.4) but also whether there are any other potential hazards that may be relevant to understanding environmental effects from a socio-economic perspective (see Logic Framework, Section 2.6).

2.2.1 Risks Identified for HBCDD

With regard to the environment, the RAR concluded:

> Conclusion (iii) "There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account" – this conclusion was appropriate for the control of risks to the terrestrial, aquatic and marine compartments.

A summary of the basis on which hazards were characterised (Point of Departure and PNEC values) for each compartment is given in Table A2-2.2. It was also concluded that HBCDD is a PBT substance, with concerns regarding its aquatic and terrestrial toxicity, bioaccumulation potential and persistence. The data and conclusions presented below were based on a detailed review and assessment conducted as part of Step 1 of this case study and drew on all available information included the RAR.

Table A2-2.2: Basis of Risk Characterisation Ratios in the RAR			
Compartment	**POD and Species**	**Assessment Factor**	**PNEC**
Aquatic compartment	NOEC: 3.1µg/l *Daphnia magna*	10	0.31µg/l
Intermittent release, aquatic environment	EC_{50}: 52 µg/l *Skeletonema costatum*	100	0.52 µg/l
Marine environment	NOEC: 3.1µg/l *Daphnia magna*	100	0.03 µg/l
Intermittent release, marine environment	EC_{50}: 52 µg/l *Skeletonema costatum*	1000	0.05 µg/l
Sediment	NOEC: 8.6 mg /kg dwt	10	0.86 mg/kg dwt
Sediment, marine environment	NOEC: 8.6 mg/kg dwt	50	0.17 mg/kg dwt
Micro-organisms in STP	EC_{30}: 15 mg/l	100	0.15 mg/l
Atmospheric compartment	-	-	-
Terrestrial compartment	NOEC: 59 mg/kg dwt Earthworms	10	5.9 mg/kg dwt
Non compartment specific effects	NOAEC: 150 ppm Rats	30t	5.0 mg/kg food
dwt = dry weight			

2.2.2 Identification of Additional Hazards for SEA

As required by the Logic Framework, the available data on other potential hazards for HBCDD were reviewed, drawing on the findings in the RAR together with other sources where available. The aim was to determine whether there were any additional consequences of environmental exposure to HBCDD that might be considered of potential socioeconomic importance or that might act as a surrogate indicator of impact. However, other than the potential impacts arising from the concerns identified above (including non compartment specific effects in higher predators due to accumulation in food chains), no further issues of relevance to the current exercise were identified.

2.3 Exposure Characterisation

2.3.1 Release from anthropogenic sources

The estimated EU consumption of HBCDD was about 11,600 tonnes in 2006 (and 11,000 in 2007) while sales of HBCDD by members of the European Brominated Flame Retardant Industry Panel (EBFRIP) were estimated at 8,913 tonnes in 2008 (stated to equate to approx. 95% total market), suggesting a slightly lower total HBCDD usage in 2008 of about 9,380 tonnes (ECHA, 2008; VECAP, 2009).

With regard to the extent of total releases of HBCDD to the environment from European sources, estimates vary widely. For example, VECAP (2009) estimated total potential emissions (presumably only relating to production of HBCDD and material containing HBCDD) at about 2,017 kg in 2008 and 309 kg in 2009. In contrast, Jensen and Bergman (2009) estimated an annual release from all sources of 8,700 kg (500 kg to air, 6,300 kg to wastewater and 1,900 kg to surface waters). ECHA (2008) estimated that the remaining European production facility released 2 kg to air and 0.73 kg to wastewater and the micronising of HBCDDD released only 0.28 kg to air. These and recently available estimates of other releases from the use of HBCDD – together amounting to some 3,126 kg per year - are summarised in Table A2-2.3.

Table A2-2.3: Summary of Total Environmental Releases to the Environment from the Production and Use of HBCDD

Industrial Activity	**Amount Released (kg/annum)**		
	Air	**Waste-water**	**Surface Water**
HBCDD production (only EU site)	2	0.73	0
Micronising of HBCDD (based on main site of production)	0.28	0	0
Formulation of EPS and HIPS compounds (in 2006)	19.5	48	212
Formulation of XPS compound (in 2006)	11.4	71.2	8.6
Formulation of EPA beads & HIPS compounds (in 2006)	30.4	75	330
Formulation XPS compound (in 2006)	13.5	84	10
Industrial use of EPS in manufacture of flame retarded EPS (EU-15 in 2006)	159	128	31
Professional installation of insulation boards (EU-27 in 2006)	236	0	236
Service life release from building insulation (EU-27)	70	0	0
End of life recycling of building insulation (EU-27 in 2006)	143	0	0
End of life disposal of building insulation (EU-27 in 2006)	85	0	0
Industrial manufacture of flame retardant XPS (EU-15 in 2006)	146	63	16.1
Industrial use of HIPS to manufacture flame retardant HIPS (EU-15 for 2002-04)	6.3	5.0	1.3
Formulation of polymer dispersions for textile use (EU-15 during 2007)	1.4	44	11
Textile backcoating (EU-15 during 2007)	0.12	1130	282
Service life of textiles (UK & Irish Republic in 2007)	0	21.4	5.4
Washing of textiles (UK & Irish Republic in 2007)	0	2.1	0
Total emissions to environment (EU-27 in 2006-07)	649	1553	924

Source: ECHA (2008)
EPS - Expanded polystyrene; XPS - Extruded polystyrene; HIPS - High Impact Polystyrene

2.3.2 Predicted Environmental Concentrations of HBCDD

The RAR developed extensive estimates, using standard models, of the national, continental and local predicted concentrations (PECs) for the aquatic and marine (including sediment) and terrestrial compartments and for secondary poisoning for the various release scenarios that were identified and summarised (not presented here).

Implications of Approach Adopted by the RAR

The information from the RAR was generated using approaches set out in the TGD for the assessment of existing substances. The TGD forms the basis of the EUSES risk assessment tool and is very similar to the approach to risk assessment under REACH. Depending upon the data used and assumptions adopted, very different figures may be generated (see Box 2.1). Whilst use of conservative assumptions is appropriate in risk assessment to ensure the environment (and human health) is adequately protected from harm, it has been argued in the Part 1 report that such assumptions represent a key source of uncertainty in a SEA; as a result, where possible more realistic values should also be considered.

BOX A2-2.1: Example of Implications of the Use of Worst-Case Assessment Factors in Estimating Environmental Exposures

The TGD requires that a low-flow rate (or 10th-percentile of flow rate) should be used. Where only average flows are available, the flow for dilution purposes should be estimated as one-third of this average so as to generate a suitably precautionary 'worst-case' estimate not to represent the actual flows that may occur in a receiving water body. If actual data on flow rates are available, different figures may be generated. For example, the flow rates recorded in the UK National River Flow Archive for the River Thames in 2008[1] is used here to illustrate how default and actual figures may diverge significantly for particular sites.

From the TGD, if no information is available regarding the flow rate of a receiving water, a dilution factor of **10** is applied. However, for the Thames, there are data and, assuming that the flow rate at the point of discharge is the same as that at the measurement site, a more accurate worst case dilution factor could be calculated:

1/3 Average flow = 27.5 m^3/s or 2,380,176 m^3/day

This results in a dilution factor (Dilution) = (5,000 + 2,380,176)/5,000 = **477**.

The lowest flow rate was 16.6 m^3/s (1,434,240 m^3/day) which gives a dilution factor [(5,000 + 1,434,240)/5,000] of **288**.

When the effluent discharge from an STP is unknown, the TGD requires a figure of 5,000 m^3/day to be used. However actual effluent rates may be much less. If the actual $EFFLUENTlocal_{stp}$ were 1000 m^3/day, the dilution factor would be almost five times greater than those shown.

In some instances, the actual dilution factor is known to be greater than 1,000 but in accordance with the TGD, within the case study it was limited to 1,000 as this was the maximum used in risk assessments.

2.4 PBT Exposure Assessment

For a substance found to meet the PBT or vPvB criteria, a partial exposure assessment is conducted in the risk assessment that is limited to emission characterisation. This should include an estimation of the releases to the different environmental compartments during all the identified uses including manufacture and import, as relevant. In addition, all likely exposure routes to humans and the environment should be identified.
HBCDD is present in almost all environmental compartments. It has also been found in remote areas (such as the Arctic regions) although the highest levels are detected close to sites of production or use. In biota, as one would expect given its environmental behaviour, the predominant diastereomer detected is α-HBCDD; this is the least biodegradable of the diastereomers. However, the HBCDD composition in abiotic samples (e.g. sediments) reflects the pattern in technical HBCDD, i.e. there is a predominance of γ-HBCDD with less than 10% α-HBCDD detected.

Measured HBCDD levels in atmospheric samples have been shown to range from a few pg/m^3 in remote areas of Sweden and Finland, to 280 ng/m^3 in outdoor air close to production facilities.

In freshwater sediment, HBCDD can reach concentrations as high as 70 mg/kg dwt (dry weight) close to production facilities. However, the median concentration from the available sample data is 1.5 µg/kg dwt. In estuarine/marine sediments, HBCDD level up to 8.8 mg/kg dwt have been measured, with a median concentration for available sample data of 4.2 µg/kg dwt.

HBCDD concentrations in marine fish have been shown to range from 0.001 to 49 µg/kg close to industrial point sources; the median wet weight (wwt) concentration was 0.38 µg/kg wwt. HBCDD levels in European marine mammals ranged from 0.5 to 6,400 µg/kg wwt, with a median wet weight concentration of 108 µg/kg wwt. For the eggs of marine bird species, levels range from a few µg/kg wwt to around 100 µg/kg wwt. HBCDD has also been detected in samples of many other biota, e.g. plankton, invertebrates, freshwater fish and terrestrial birds.

The biomagnification potential of HBCDD has been assessed by comparing measured levels of α-HBCDD in fish to those of marine mammals. Generally the highest levels of HBCDD are found in marine mammals, such as seals and porpoises, which will be exposed to HBCDD predominantly via their food. The median concentration ratio between marine mammals and fish, on a wet weight basis, is 272. For fish-eating marine birds, a study on herring and guillemot calculated a biomagnification factor of 9.1 based on lipid weight.

In conclusion, the available data suggest that α-HBCDD biomagnifies in the marine and aquatic food webs.

2.5 Overview of Outcome of Step 1 - Scoping the Impact Assessment

Based on the information on uses, physicochemical properties, exposure data and estimates and the hazard profiles, the outputs of Step 1 in the logic framework are summarised in Table A2-2.4 (see below). In particular, potential concerns were identified for aquatic and marine environments and terrestrial organisms (largely relating to food chain concerns).

The potential consequences arising from HBCDD's status as a PBT was also considered to warrant specific consideration.

As a result of the review conducted in Step 1 including consideration of the hazardous properties of HBCDD, the following compartments and sub-compartments were identified as warranting further consideration for the SEA (see Table A2-2.5).

Table A2-2.4: Step 1 - Characterisation and Scoping – HBCDD						
Nature of Effect *(Toxicity; Persistence, Bioaccumulation; Equivalent concern (e.g. endocrine disruption)*	**Risk of Concern** *(Abnormalities Reproduction Growth Survival, vPvB, PBT)*	**Exposure Route for Environment Compartment** *(Freshwater; Marine; Air; Soil; Biota, Secondary poisoning)*	**Risk Group**		**Hazard**	**Exposure**
			Group *(Microbial, Fungal; Invertebrates; Fish; Birds; Mammals; Flora, etc.)*	**Sub-group** *(bottom feeders, predators, young, etc)*	**Basis** *(physico-chemistry, experimental, computational, observations, etc)*	**Basis** *(actual data, hypothetical data, monitoring data)*
Aquatic toxicity		Water and sediment; Secondary poisoning – food chain effects	Immediate risk groups: Algae, fish and invertebrates Risk of secondary poisoning throughout the food chain (including birds and mammals) due to PBT status	Bottom feeding species at risk due to persistence in sediment Secondary poisoning through direct contact or via food chain, especially bottom feeders	Experimental data	Modelling supplemented by monitoring data
Marine toxicity		Water and sediment; Secondary poisoning – food chain effects	Immediate risk groups: Algae, fish and invertebrates Risk of secondary poisoning throughout the food chain (including birds and mammals) due to PBT status	Bottom feeding species at risk due to persistence in sediment Secondary poisoning through direct contact or via food chain, , especially bottom feeders	Experimental data	Modelling supplemented by monitoring data
Terrestrial toxicity	Mammalian organ specific toxicity	Soil and porewater; Secondary poisoning – food chain effects	Soil-dwelling organisms.	Secondary poisoning through food chain, , especially those species feeding on soil-dwelling organisms	Experimental (rodent) data	Modelling supplemented by monitoring data
Persistence	PBT	Persistence of some isomers above P-criterion	General environment	General environment	Physico-chemical & experimental data	Modelling supplemented by monitoring data
Bioaccumulation	PBT	Very high BCFs noted in fish species	Increasing concern for higher trophic levels	Higher trophic levels reliant on bottom feeding species	Physico-chemical & experimental data	Modelling supplemented by monitoring data

Table A2-2.5: Summary of Environmental Effects to be Considered in Step 2		
Compartment	**Sub-compartment**	**Comments**
Aquatic	STP	Applies to some sites with industrial use of XPS with intermittent releases to waste water and for 1 textile backcoating site including the generic textile backcoating scenario
	Surface water	Applies to some sites involved in EPS formulation including the generic scenario, one site involved in formulation of XPS compound and the generic scenario, the generic local scenario for formulation of polymer dispersions for textiles, individual sites involved in industrial use of XPS compound and HBCDD powder including the generic local scenario for industrial use of XPS compound and sites involved in textile backcoating including the generic scenario. Also the professional use of insulation boards containing XPS or EPS
	Sediment	Applies to some sites involved in EPS formulation including the generic scenario, one site involved in XPS formulation including the generic scenario, one site involved in formulation of polymer dispersions for textiles including the generic scenario, individual sites involved in industrial use of XPS compound and HBCDD powder including the generic local scenario for industrial use of XPS compound and sites involved in textile backcoating including the generic scenario
Terrestrial		Applies to the generic scenario for industrial use of XPS compound, three sites using HBCDD powder in the production of XPS and one site involved in textile backcoating including the generic scenario
Marine	Surface water	Applies to some sites involved in EPS formulation including the generic scenario, one site and the generic scenario for XPS formulation, one site involved in formulation of polymer dispersions for textiles including the generic scenario, individual sites involved in industrial use of HBCDD powder in XPS and use of XPS compound including the local generic scenario for industrial use of XPS compound, and some sites involved in textile backcoating including the generic scenario
	Sediment	Applies to some sites involved in EPS formulation including the generic scenario, one site and the generic scenario for XPS formulation, one site involved in formulation of polymer dispersions for textiles including the generic scenario, individual sites involved in industrial use of HBCDD powder in XPS and use of XPS compound including the generic local scenario for industrial use of XPS compound, and some sites involved in textile backcoating including the generic scenario
Other	PBT-assessment	P, vB, T
Non-compartment	Secondary poisoning	For PBT-substances the major concern is that accumulation of such substances in the food chain which may result in effects often difficult to predict in the long term

3. LOGIC FRAMEWORK - STEP 2: QUALITATIVE AND SEMI-QUANTITATIVE ASSESSMENT OF ENVIRONMENTAL IMPACTS

The aim of Step 2 is to ensure that decision makers have a good understanding of the nature of any potential environmental impacts that may be associated with the continued use of the substance, so as to inform on the potential scale of the benefits that would be realised by introducing regulatory measures to reduce or eliminate exposures.

There are essentially 5 phases within this Step:

i) Step 2a: Hazard characterisation;
ii) Step 2b: Exposure characterisation;
iii) Step 2c: Qualitative description of potential impacts;
iv) Step 2d: Benchmarking of environmental hazard; and
v) Step 2e: Assessment of the potential for quantification of impacts.

3.1 Step 2a: Hazard Characterisation

The RAR presents details on the ecotoxicity, environmental fate and behaviour and bioaccumulative potential of HBCDD, as summarised briefly below (as explained above, a more detailed assessment was prepared as part of Step 1 to support the case study but is not presented here).

3.1.1 Ecotoxicological Considerations

Aquatic

Algal EC_{50} 52 µg/L and NOEC >10 µg/l (*Skeletonema costatum*)
Daphnia sp. EC_{50} (48 h) NOEC = 3.1 µg/L
Daphnia sp. 21 d NOEC = 3.1 µg/L

No effect in acute fish test at 1.5-6.8 µg/L
Early life-stage tests in fish at 0.43-6.8 µg/L showed no effect on hatch success
NOEC (measured level) = >3.7 µg/L

PNEC = 0.31 µg HBCDD/L
PNEC intermittent release = 0.52 µg HBCDD/L

Sediment

Amphipod 28 d NOEC = 1000 mg/kg dwt sediment; LOEC = >1000 mg/kg dwt sediment.
Chironimus sp. 28 d egg production NOEC = 13.6 mg/kg dwt sediment.

PNEC = 0.86 mg HBCDD/kg dwt

Soil

Earthworm survival/reproduction test NOEC = 59 mg/kg dry soil

PNEC = 5.9 mg HBCDD/kg dwt

Secondary Poisoning

Significant levels of HBCDD in marine birds such as the Atlantic puffin, Herring gull and Kittywake, particularly in eggs, have been reported. The risk posed to these bird species was considered in the RAR which focused on the potential risks on the basis of rodent evidence with regard to neurotoxicity. More recently UNEP (2010) have considered the evidence for an adverse effect on fertility.

UNEP (2010) identified an association between clutch size (number of eggs per female) and HBCDD exposure in the American kestrel (*Falco sparverius*). Similar evidence of an effect on egg production and, importantly on chick survival was noted to exist for Japanese quail (*Coturnix coturnix japonica*) resulting in an estimated NOEC for reproductive performance of 0.7 mg/kg bw/day. While this data might appear a good basis for estimation of the potential impact on the sustainability of the marine bird species, the American kestrel study referred to above was notable in that hatchling numbers were reported to be similar in treated and control birds. Thus, it would be difficult on the basis of existing data, to attempt to estimate any impact on species sustainability given that perhaps most important reproductive parameters (i.e. offspring survival) appeared unaffected in the most relevant species (the American kestrel) available. Furthermore, although an indicative LOAEL for neurotoxicity in birds was developed in the RAR, attempts to interpret the ecological consequence to bird offspring exposed in ovo would be highly speculative, particularly given the requirement to confirm the neurotoxic findings, as emphasised by the RAR and SCHER. Thus, **it is not considered appropriate to consider the potential reproductive consequences to marine predatory bird species further at this time.**

A particularly important aspect of the hazard data when seeking to characterise the secondary poisoning risk posed by HBCDD relates to studies on mammalian toxicity. The key findings and conclusions reached for each toxic endpoint considered are summarised below.

i) Toxicokinetics

Marked differences in toxicokinetic behaviour were identified for the different diastereomers present in the technical product and these properties probably explain the behaviour of the substances across trophic levels. **It is therefore important that the differences are taken into account during consideration of impacts associated with transmission of the substance within food chains.**

ii) Acute Toxicity

The acute toxicity of HBCDD in mammals is very low, and therefore **this endpoint is considered not to warrant further consideration**.

iii) Irritation & Sensitization

HBCDD is not classified as irritant or corrosive and **this endpoint is considered not to warrant further consideration**.

iv) Repeat Dose Toxicity

Several repeat dose studies in rodents (mainly rats) via the oral (but not inhalation or dermal) route are reported in the RAR ranging from 28 days up to and including carcinogenicity studies and a multigeneration test.

The repeat dose studies identified the liver, thyroid and pituitary as target organs and, when combined with our knowledge of its PBT and POPs characteristics, suggest that there could be a risk of adverse effects on mammalian top predators if sufficiently high body burdens were to accumulate. However, it is unclear how such effects would impact on the overall health and survival of these wild animals. At this time, it is therefore not possible to infer impacts on wildlife, including predators, based on current knowledge. **The risks associated with repeat dose toxicity effects should therefore be recognised but cannot be assessed further within the logic framework.**

v) Mutagenicity and Carcinogenicity

HBCDD was found to be negative for mutagenicity in a number of in vitro and in vivo assays, and the available carcinogenicity evidence base was considered inadequate to establish carcinogenicity. **Therefore this endpoint is considered not to warrant further consideration.**

vi) Reproductive and Developmental Toxicity

Evidence of the reproductive toxic potential of HBCDD is provided by a 2-generation study by Ema et al. (2008) from which the RAR established a NOAEL of 10 mg/kg/day, based on a dose-dependent decrease in fertility-index and a reduced number of primordial follicles. A number of other effects were reported (Table A2-3.1) and the RAR considered findings from developmental studies which suggested a NOAEL of 150 ppm (10 mg/kg/day) for pup mortality (i.e. the same as defined for fertility).

Table A2-3.1: Summary of Key Findings in a 2-generation Reproductive Toxicity Study in Rats					
Effect	**Dietary Level (ppm)**	0	150	1500	15,000
	Dose – Male (mg/kg/day)	0	10	101	1,0081008
	Dose – Female (mg/kg/day)	0	14	141	1363
Fertility index (% - male/female)	F0 gen	100/100	91.7/91.7	90.9/90.9	85.7/86.4
	F1	95.8/95.8	95.8/95.8	87.0/87.5	87.5/87.5
Proportion of pregnant	F0	24/24	22/24	20/24	19/23
	F1	23/24	23/24	21/24	21/24
No. litters/total females	F0	24/24	21/24	20/24	18/23
	F1	23/24	23/24	20/24	21/24
No. ovarian primordial follicles	F1	316.3+/-119.5	294/2+/-66.3	197.9+/-76.9	203+/-79.5
Litter losses	F0	0	0	0	1/23
	F1	1/24	1/24	0/24	8/24
Viability index	F0 (day 4)	95.6	98.7	98.7	95.8
	F1 (day 4)	86.9	87.3	92.1	68.4
	F1 (day 21)	85.0	89.6	71.3	49.7
Note: Source Ema et al. (2008)					

The RAR also considered findings from developmental studies. In a study by Murai et al. (1985), Wistar rats were given 0, 0.01, 0.1 or 1% HBCDD via diet (equivalent to approximately 0, 7.5, 75, or 750 mg/kg/day, respectively) on days 0-20 of gestation, a foetal NOAEL of 750 mg/kg/day (highest dose tested) and a maternal NOAEL of 75 mg/kg/day (liver weight) were established. This lack of fetotoxic or teratogenic potential was noted to have been confirmed in a recent study conducted to OECD Guideline 414 and US EPA Health Effects Test Guidelines OPTS 870.3700 (Stump, 1999). In the previously considered 2-generation study by Ema et al. in rats at 0, 150, 1500 or 15,000 ppm, a dose-dependent pup mortality during lactation was noted, giving a NOAEL of 150 ppm (10 mg/kg/day) for pup mortality in this study (i.e. the same NOAEL as defined for fertility).

Given that HBCDD bioaccumulates in marine ecosystems and has been suggested as a candidate POP, **the possibility that the lower survival of offspring might constitute a risk to the reproduction of high marine predators warrants further consideration in the later steps of this Case Study.**

Studies on developmental neurotoxicity were also considered. Of these, that by Eriksson et al (2006) on neonatal male NMRI mice given a single oral dose on day 10 at 0.9 or 13.5 mg (1.4 - 21µmol)/kg body weight (in a mixture of egg lecithin and peanut oil) found statistically significant changes in spontaneous behaviour and learning and memory defects. Hearing function impairment and other neuro-developmental effects in offspring of exposed rats were also noted by Lilienthal et al (2006) but this was reported in inadequate detail for consideration in the RAR. A

series of mechanistic studies were also noted as providing supporting evidence of neurotoxicity. Overall, an indicative LOAEL of 0.9 mg/kg (based on the Eriksson et al study) was identified for the neuro-developmental effects in the RAR. Although representing a potentially considerably lower POD than identified for other aspects of developmental toxicity, the need for confirmation of findings was strongly emphasised by both the RAR and SCHER. Therefore, we consider that **it is inappropriate to progress the developmental neurotoxicity endpoint further at this time.**

3.1.2 Other Considerations

PBT Assessment

The RAR concluded that HBCDD fulfils both B and vB criteria based on experimental data and measured data from biota. With a NOEC of 3.1 µg/l for *Daphnia*, the T criterion is also met. The available soil degradation simulation data show that the half-life of HBCDD in aerobic soil is >120 d and thus the P-criterion in soil is met. Furthermore, HBCDD has been found to be ubiquitously present in remote areas in abiotic samples and biota, providing evidence that the substance undergoes long-range environmental transport. Based on an overall assessment, the TCNES subgroup has concluded that HBCDD has PBT properties, and this opinion was agreed by the Member States Committee in 2008 (ECHA, 2008a and b).

However, a recent industry-sponsored report by Arnot et al (2009) questioned the estimates used in the RAR, instead adopting environmental half-life values of 1.3 (0.4-4.0) days in air, 85 (8.5-850) days in freshwater, 35 (6.0-210) days for marine sediment and 85 (8.5-850) days in soil.

POP Assessment

Norden (2008) considered HBCDD as a possible POP, focusing on the persistent and bioaccumulative potential of the substance.

Photochemical degradation half-life of HBCDD in the atmosphere was estimated to be 3.2 days. HBCDD is known to be abundant in remote areas in biota and abiotic samples. Several studies were also reviewed on biodegradability and a conclusion was reached that HBCDD was not readily biodegradable. Furthermore, it was noted that the main dehalogenation product of HBCDD, 1,5,9-cyclododecatriene (CDT), is also not readily biodegradable.

HBCDD has a very low volatility and a very high adsorption potential to soil. However, levels have been found in air samples at above detection limits at multiple locations. It is also present in most remote sites of the Arctic region being found in air, sediment, birds, mammals, etc. and there appears to be a temporal trend towards increasing concentrations. Since there is no known local source of HBCDD in Arctic regions, it can be assumed that HBCDD enters these areas via long range transport processes. This is supported by the finding that the atmospheric degradation half-life

of HBCDD is around two days (varies depending on study conditions) and its characteristic travel distance (CTD) in air has been estimated to be around 1500 km.

Measured concentrations suggest that HBCDD is present, and bioaccumulates, in biota in freshwater and marine environments. Moreover, evidence suggests that HBCDD biomagnifies between trophic levels with α-HBCDD being the predominant diastereomer in biota. Several studies have been carried out on the biomagnification potential of HBCDD in different food chains. A summary of the biomagnification factors (BMF) and the trophic magnification factors (TMF) established by these studies, is presented in Table A2-3.2.

Table A2-3.2: **BMF, TMF and Concentration Factors for HBCDD**

Study Information	Factor	Value	Comments
Freshwater Food Chain			
Lake Ontario food web	TMF	6.3	For comparison: BMF for p,p'-DDE 6.1, and for sum of PCBs 5.7
	BMF α-HBCDD	3.5 (Sculpin/*Diporeia*) - 10.8 (Smelt/*Mysis*)	Highest BMF for forage fish/zooplankton
Lake Winnipeg food chain	TMF α-HBCDD	1.4	Concerns about the reliability of the study
	TMF β-HBCDD	1.3	
	TMF γ-HBCDD	2.2	
	BMF α-HBCDD	0.1 - 8.2	
	BMF β-HBCDD	0.3 - 5	
	BMF γ-HBCDD	0.1 - 6.3	
Marine Water Food Chain			
Biomagnification occurs but no factor could be determined			
Fish-marine Bird Food Chain			
Herring muscle and Guillemot eggs collected from the Baltic Proper	BMF	9.1	For comparison: BMF for $PBDE_{sum}$ 5.5, for PCB_{sum} 24.6 and for DDT_{sum} 36
Fish-Marine Mammal Food Chain			
Western Europe	Concentration ratio	272	Marine mammals/fish (wwt bwt/ wwt)
Baltic Sea	Concentration ratio	61	Marine mammals/fish (wwt bwt/ wwt)
Western Scheldt	Concentration ratio	187	Marine mammals/fish (wwt bwt/ wwt)
U.K. Harbour porpoise	Concentration ratio	254	Marine mammals/fish (wwt bwt/ wwt)
Dietary Accumulation Study			
HBCDD for 56 days	BMF α-HBCDD	9.2	Juvenile rainbow trout
	BMF β-HBCDD	4.3	
	BMF γ-HBCDD	7.2	

There is now general agreement that HBCDD generally shows biomagnification in the environment, with α-HBCDD generally found to occur at much higher

concentrations in biota than the other diastereommers, despite being present at a relatively low percentage in the commercially-available substance (ECHA, 2008b).

In the RAR it was noted that the biomagnification factor between herring and guillemot was 9.1 (based on lipid weight), compared with values between forage-fish and zooplankton of 3.5 to 10.8 for α-HBCDD. In contrast, for the fish and marine mammal food web, the overall media concentration ratio between marine mammals and fish was 272 on a wwt basis (or 28 on a lipid weight basis). However, there were clear differences found relating to the study location with lower values generally found in studies at more northerly locations. Perhaps, the most relevant to Arctic ecosystems in the RAR was a study on the Baltic Sea where the median concentration ratio between marine mammals and fish was 61 (on basis of comparison of level on a wwt basis) or 5.8 (when lwt[1]s considered). However, a recent study by Jenssen et al (2007) on polar bears and their major prey species and Atlantic and Polar cod, found a biomagnifications factor of only 2 between fish and ringed seals. Importantly polar bears showed no further increase (rather slightly lower levels were found than their prey) and this apparent lack of biomagnification between their prey and polar bears may reflect, as noted in the RAR, the enhanced ability of polar bears to metabolise many POPs compared with their prey species.

Sørme et al (2004), levels of HBCDD in polar cod range from 5-25 ng/g while levels in ringed seal ranged from 15-35 ng/g. The median concentration ratio between marine mammals and fish is estimated as 61 (on wwt basis) and 5.8 (as lwt) in the RAR for the Baltic Sea but a study by Jenssen et al (2007) on polar bears, their major prey species and Atlantic and Polar cod, showed a biomagnifications factor of only 2 between fish and ringed seal (polar bears showed no further increase, indeed they possibly had lower levels than their prey). Given the apparent high level of uncertainty, it is not possible to estimate the biomagnifications between fish and seals more specifically than as somewhere between about 2 and 60.

Data indicate that in mammals HBCDD can be transferred from mother to offspring during pregnancy via the placenta (e.g. low level transfer reported for humans by Meijer et al (2008) and RIVM Report no. 320100002/2006) and, after delivery, via lactation (Fängströ et al, 2005).

Given the concerns regarding the substance's PBT characteristics, it is appropriate to apply benchmarking techniques to further characterise this substance (this is discussed in Step 2d).

3.2 Step 2b: Exposure Characterisation

Whilst the production, use and emissions data presented above (Step 1) are of value in identifying potential sources of HBCDD, such information does not in itself inform on the fate of HBCDD within the environment, in particular with regard to which compartment(s) the substance may accumulate in, nor does it necessarily assist in

[1] lwt = lipid weight

estimating regional or continental exposures associated with continued use of HBCDD in different applications.

Robust environmental monitoring data would ideally be used to develop non-local exposure estimates but only limited data are available for HBCDD. The data that are available tend to be specific to high risk local sites (e.g. production sites) where concentrations would be expected to be high and not necessarily predictive of the wider environment. The detailed data for different sites are presented in Annexes to this case study. The location of the different facilities could be mapped using GIS tools, for example, to provide an indication of where the sites are located and the associated water bodies at risk. However, this would not really help address questions regarding the wider environmental fate of HBCDD within the environment.

The site specific data that are available are not considered statistically representative of the ultimate fate of the substance in terms of which compartments or species may be subject to exposure, nor the magnitude of any such exposures. In practice, for many chemicals this is likely to be the case. As a result, there is a need to draw on modelling approaches where available to provide information on exposures.

The conclusions regarding the quality of available exposure information (modelled or monitored) are summarised in Table A2-3.3 below.

Table A2-3.3: Qualitative Assessment of Exposure Data

Nature of Concern	Risk Group	Level and Frequency of Exposure	Nature of Exposure Data
Aquatic toxicity	Aquatic species (including benthic feeders and higher trophic levels)	Continuous at various levels depending on location relative to source	Modelled data and limited monitoring data mostly associated with industrial releases
Marine toxicity	Aquatic species (including benthic feeders and higher trophic levels)	Continuous at various levels depending on location relative to source	Modelled data and limited monitoring data mostly associated with industrial releases
Terrestrial toxicity	Particular concerns for higher trophic levels	Continuous at various levels depending on location relative to source	Modelled data and limited monitoring data mostly associated with industrial releases
Secondary poisoning	Particular concern for top predators	Continuous at various levels depending on location relative to source	Limited monitoring data, focusing on particular predator/ prey species in the marine food chain
Persistence	General environment	Continuous at various levels depending on location relative to source	Experimental and modelled data
Bioaccumulation	Particular concern for higher trophic levels (particular for aquatic/marine environments)	Continuous at various levels depending on location relative to source	Experimental and modelled data
POPS	Marine and Arctic biota identified as at risk	Continuous at various levels depending on location relative to source	Limited measurement data

3.3 Step 2c: Qualitative Description of Potential Impacts

The aim of Step 2c is to develop a qualitative assessment of the environmental consequences (impact) of the continued use of the chemical of concern. It is suggested that potential impacts be assessed within a framework based on the concept of ecosystem services. A summary of possible impacts is then prepared against a series of reporting headlines including those relevant to understanding potential impact on different types of ecosystem services and the associated environmental impact.

The hazard characterisation conducted in Step 2a identified a number of potential concerns, as summarised below:

Ecotoxicity

Ecotoxicity testing in aqueous media is complicated by the very low water solubility and the high adsorption potential of HBCDD. However, tests with marine algae and the invertebrate *Daphnia magna* show that HBCDD is very toxic to some aquatic taxa. HBCDD also causes adverse effects in sediment organisms at concentrations of relevance to the environment. Two long term tests are available for HBCDD: a reproduction test on *D. magna* reports a NOEC of 3.1 µg/l; and a fish early life-stage test shows no effect at the highest tested concentration of 3.7 µg/l. A marine algae (*S. skeletonema*) gave an EC_{50} of 52 µg/l (all three diastereomer were tested together at their respective limits of solution).

Secondary Poisoning

In mammalian species, there was no indication of carcinogenicity in the studies considered by the RAR. A NOAEL of 22.9 mg/kg bw/day (based on a 28 day study with rats) for repeat dose toxicity was derived in the RAR for risk assessment purposes. Another relevant NOAEL for neurotoxicity (0.9 mg/kg bw) was also identified but it was suggested that the study findings needed confirmation (RAR). A NOAEL from a 90 days study would normally be preferred as the basis for derivation a PNEC for secondary poisoning but the uncertainties introduced in the evaluation of the 90 days study by the dosing of HBCDD-particles to animals, lead to the choice of a NOAEL from a 28-days study (though this decision was questioned by SCHER). The most recent 28 days study in rats was performed using a benchmark model design and oral administration of dissolved HBCDD. The study shows effects on the liver, the thyroid and the pituitary. Overall, a NOAEL/BMD-L of 22.9 mg/kg/day for liver weight increase was proposed for repeated dose toxicity and was used as the basis for derivation of the secondary poisoning value in the RAR. This BMD-L of 22.9 mg/kg/day was also assumed to be adequately protective of the effects on the thyroid and pituitary system; this was based on an assumption that hepatic enzyme induction was one factor contributing to the effects on the thyroid. Based on the data, the RAR concluded that HBCDD meet the T-criterion.

Reproductive and development studies in rodents also identified impairment of fertility and a lower offspring survival in response to HBCDD exposure. A NOAEL

of 10 mg/kg/day, based on a dose-dependent decrease in fertility-index and a reduced number of primordial follicles, was identified. A dose-dependent lowering of pup mortality during lactation was also noted which established the same NOAEL (10 mg/kg/day).

However, it is unclear how many of the chronic mammalian effects used to characterise hazard in the risk assessment would impact the overall health and survival of wild animals.

Wider Ecosystem Services Considerations

As noted above, the PBT and potential POPs status of HBCDD should also be considered, particularly in respect of the possibility for risks arising relating to transport to remote regions and with regard to the dangers of build-up within the environment or food-chains.

Table A2-3.4 below provides a summary of the nature of the risk concerns in relation to ecosystem services, the species at risk and the level and frequency of exposures. The discussion above also highlighted the regional nature of concerns due to HBCDD appearing to meet the criteria for a POP and showing biomagnification across species, together with data on persistence in terms of the half life of HBCDD. This information is built upon in Table 3.4 to provide an indication of the potential impacts on ecosystem services. These impacts may be geographically widespread, as discussed in Section 2.4 and 3.1.2 above (see also Table A2-3.2). For example, impacts on fish populations have been identified for freshwaters (lakes and rivers) in Europe as well as for marine fisheries in European estuaries, the Baltic Sea and Arctic regions. Similarly, both marine and terrestrial bird populations have been identified as being impacted with effects on reproduction (e.g. egg production and chick survival), as have marine mammals found in Northern European and Arctic regions (seals and porpoises) which are also been identified as being potentially at risk due to food chain effects.

3.4 Step 2d: Benchmarking of Environmental Hazard

Given the identified PBT properties of HBCDD, it may be of value to use benchmarking/risk ranking approaches to place the risks posed by the substance into context against other chemical stressors.

A key issue for this case study was the ability of the available tools to rank chemicals with P and B properties and here we have explored use of one such model, the Chemical Scoring and Ranking Assessment Model (SCRAM)[2,3]. SCRAM provides a formalised process to rank-order chemicals based on their physicochemical properties.

[2] Available at http://www.epa.gov/glnpo/toxteam/pbtrept/

[3] Other approaches to the benchmarking of HBCDD have been explored by Arnat et al (2009) but these relate specifically to its POP characteristics.

Table A2-3.4: Qualitative Assessment of Environmental Impacts – Ecosystem Services			
Compartment	**Subgroup at Risk**	**Nature of Vulnerability**	
Aquatic species	**Algae, fish and invertebrates**	**Exposure via sediment and via surface waters**	
	Nature of potential effects	Toxicity, possibly including repeat dose toxicity	
	Nature of exposure	Via discharges to water and concentrations building in sediment; discharges associated with production activities and service use therefore continuous in nature.	
	Ecosystem Service Impact[4]	*Provisioning services: food*	Potential impact on fisheries and other food species
		Regulating services: regulation of biotic environment	Lifecycle maintenance with regard to food chain effects, habitat maintenance, and impacts on fish nursery populations in European estuaries
		Symbolic, Experiential and Cultural services	Possible loss of species important for recreational fishing
	Higher trophic levels - incl. mammals and birds	**Exposure via food chain**	
	Nature of effect	Toxicity (including potential reproductive impairment in marine predators)	
	Nature of exposure	Via food chain (biomagnification)	
	Ecosystem Service Impact	*Provisioning services*	Potential impact on food species
		Regulating services: regulation of biotic environment	Lifecycle and habitat maintenance with regard to food chain effects
		Symbolic, Experiential and Cultural services	Possible impacts on health of or loss in species of symbolic importance and important for ecotourism
General environment and biota	**Particular concerns for sediment and higher trophic levels**	**Exposure of environmental media due to persistence; exposure of biota via sediment and food chains**	
	Nature of effect	Persistence and bioaccumulation	
	Nature of exposure	Environmental transport to sediment and to all levels of biota via food chains	
		Regulating services: regulation of biotic environment	Lifecycle and habitat maintenance with regard to food chain effects
		Symbolic, Experiential and Cultural services	Possible impacts on health of or loss in species of symbolic importance and important for ecotourism

[4] These services are based on the Millennium Ecosystem Approach by the United Nations Environment Programme (UNEP) set out to asses how human-made changes to ecosystems affect human welfare.

3.4.1 HBCDD Data Used for SCRAM Calculations

The following describes the data required and the resultant outputs for HBCDD based on comparisons with several other substances present in the existing SCRAM dataset and with other substances suggested as possible alternatives to HBCDD.

Bioaccumulation

Two studies on bioaccumulation were reviewed in the RAR. The study on fathead minnow revealed a BCF of 18,100 and the quality of this value was considered to be acceptable. In the study on rainbow trout, values ranged from 8,974 to 21,940. These results fall in the category >10,000-100,000 of the bioaccumulation scoring system of SCRAM, leading to a **score of 4**. The uncertainty associated with a measured BCF is **scored as 1** (low).

Environmental Persistence

This score is based on the half-lives of the substance in five environmental compartments. The greatest score from among the five compartments is used as the chemical's score for persistence. The RAR reviewed several studies on persistence but only half-lives for soil and sediments were derived. Results are presented in Table A2-3.5.

Photochemical degradation half-life of HBCDD in the atmosphere was estimated by AopWin v1.91 to be 76.8 hours (3.2 days). The highest score is obtained for sediments since the half-life is greater than 100 days. A **chemical score of 5** is therefore assigned for persistence. Regarding uncertainty, the lack of data for two categories and the estimated half-life for air result in a **score of 5.** Under the SCRAM system, since the chemical score for environmental persistence is above 2, only chronic toxicity was assessed further.

Table A2-3.5: Half-lives for HBCDD in Different Compartments (in Days)

Temperature	Aerobic Soil		Anaerobic Soil		Anaerobic Freshwater Sediments		Aerobic Freshwater Sediments	
	Viable	Abiotic	Viable	Abiotic	Viable	Abiotic	Viable	Abiotic
Simulation Study 1								
12°C	119	>>227	13	155	2.8	19	61	360
20°C	63	>>120	7	82	1.5	10	32	190
Simulation Study 2								
12°C	No degradation				125		191	
20°C					66		101	

Chronic Toxicity

i) Terrestrial Compartment

One NOEC value is required for each of the five subcategories – plants, invertebrates, mammals, birds and reptiles – to minimise uncertainty. The data used for this assessment, together with their chemical scores, are summarised in Table 3.6. Invertebrates **score the highest (4);** this value is therefore used for the assessment. Since toxicity data for birds and reptiles are not available, an **uncertainty score of 2** has been assigned.

ii) Aquatic Compartment

One NOEC value is required for each of the five subcategories – plants, invertebrates, cold water fish, warm water fish and amphibians – to minimise the uncertainties. The data used for this assessment together with their chemical scores are summarised in Table A2-3.6. Both of the studied species **score 5** according to the SCRAM scoring system and **uncertainty scores 3**.

Table A2-3.6: SCRAM Final Environmental Scores	
Chemical Score	39
Uncertainty Score	13
Composite Score	52

iii) Human Toxicity

Using the data on mammalian toxicity detailed in the RAR, the appropriate scores were developed (see Table A2-3.7. below) in order to allow a full characterisation using SCRAM. Of these, it is of note that the study from which a NOAEL for developmental neurotoxicity was derived was not performed according to current OECD guidelines or GLP. This value was not, therefore, included in the dataset resulting in a **chemical score of 4** for human toxicity.

3.4.2 Outputs from SCRAM

In the SCRAM model, for each of environment and human health concerns, a 'chemical score' (representing the nature of the hazard posed) and an 'uncertainty score' (reflecting the robustness of the available database) are combined to give a 'composite' score. An overall score for the chemical is then obtained by combining the environment and health scores. For HBCDD, the resultant SCRAM scores are presented in Table A2-3.8.

Comparison with Other Substances

In order to fully compare HBCDD with other substances using SCRAM, it was necessary to include data relevant to human health hazards (i.e. experimental findings in mammalian species) not just the ecotoxicity information. When including the score

relating to human toxicity into the SCRAM assessment, the total chemical score becomes 43 giving a final composite score, after taking uncertainty into account, of 56.

The first step in the proposed benchmark process is to identify substances with an environmental impact score that is similar to that for HBCDD. The SCRAM database currently comprises a set of 146 substances. Of these, 5 substances were identified as having not dissimilar scoring profiles to HBCDD and, hence, were considered appropriate benchmark comparisons. These are:

- hexachlorobenzene;
- polybrominated biphenyl (PBBs);
- mercury;
- pentachlorobenzene; and
- hexachloro-1,3-butadiene.

The individual SCRAM scores (for chemical, uncertainty and composite) for each of the comparator substances are given alongside those for HBCDD in Table A2-3.7.

Table A2-3.7: SCRAM Scores Based on Combined Human and Environmental Risks for Selected Substances in the Generic SCRAM Database

CAS No.	Chemical name	Chemical Score	Uncertainty Score	Composite Score
118-74-1	Hexachlorobenzene	53	9	62
25637-99-4	*HBCDD*	*43*	*13*	*56*
608-93-5	Pentachlorobenzene	39	14	53
87-68-3	Hexachloro-1,3-butadiene	37	16	53
7439-97-6	Mercury	45	7	52
Class 07-8	PBBs	40	10	50

Table A2-3.8: Summary of Toxicity Data Contributing to overall Human Health and Environmental Chemical Scores in SCRAM[1]								
Category	**Animal**	**Duration**	**Value**	**Type**	**Unit**	**Study**	**Source**	**Chemical Score**
Terrestrial ecotoxicity								
Invertebrates	Worm	28	≥4,190	NOEC survival	mg/kg soil dw	Aufterheide et al, 2002	IUCLID (2005) - RAR	1
	Worm	56	59	NOEC reproduction	mg/kg soil dw	Aufterheide et al, 2002	IUCLID (2005) - RAR	4
Mammals	Rat	28	1,000	NOAEL	mg/kg/day	Chengelis, 1996	ACC (2001)	3
	Rat	90	1,000	NOAEL	mg/kg/day	Chengelis, 1996	ACC (2001)	
	Rat	28	22.9	NOAEL	mg/kg/day	van der Ven et al, 2006	RAR	
Plants		21	≥5000	NOEC	mg/kg soil dw	Porch et al, 2002	IUCLID (2005) - RAR	1
Aquatic ecotoxicity[1]								
Fish	Rainbow trout	88	3.7 - 6.8	NOEC	µg/l	Drottar et al, 2001	ACC (2001)	5
Invertebrates	*Daphnia magna*	21	3.1 - 3.4	NOEC	µg/l	Drottar and Krueger, 1998	ACC (2001)	5
Human Toxicity								
General toxicity	Rat	28	22.9	NOAEL	mg/kg/day	van der Ven et al, 2006	RAR	3
Mutagenicity			No known effects				RAR	1
Carcinogenicity			No known effects				RAR	1
Reproductive toxicity	Rat		10	NOAEL	mg/kg/day	Ema, 2008	RAR	4
Developmental neurotoxicity	Mouse		0.9	LOAEL	mg/kg/day	Eriksson et al, 2006[2]	RAR	5
Developmental toxicity			No known effects				RAR	1

[1] Toxicity- and Ecotoxicity-based Chemical Scores combined as defined by SCRAM methodology with Persistence and Bioaccumulation scores to give overall scores for HBCDD

[2] Study Not performed according to OECD guidelines

Table A2-3.7 indicates demonstrates that the chemical score for HBCDD is not dissimilar to those of a number of important environmental pollutants such as mercury and PBBs, but is lower than that for the fungicide hexachlorobenzene, a suspected human carcinogen and aquatic toxicant. The comparison also demonstrates that the level of uncertainty surrounding the estimation of the toxic profile of HBCDD is not dissimilar to that for several of the other substances considered of environmental concern. This could be taken to indicate that the degree of uncertainty attached to the toxicity profile of HBCDD may be a relatively common issue for substances that may be subject to SEA for REACH regulatory purposes.

On the basis of the combined (composite) scores, it would appear that HBCDD should be regarded as being of high concern.

Interpretation of these finding should be subject to a degree of caution. For example, examination of the datasets show that the apparently low composite score for mercury is largely an artefact of the very low degree of uncertainty in its dataset. Comparing the chemical scores for each substance would suggest that in practice mercury should be regarded as of greater concern as an environmental contaminant, not least because unlike HBCDD it is an element and will not therefore degrade over time but instead will enter the global mercury cycle. This example illustrates the potential limitations and challenges when applying benchmarking systems to chemicals possessing markedly different physicochemical or biological properties.

3.5 Step 2e: Assessment of the Potential for Quantification of Impacts

The aspects considered and the conclusions drawn with regard to the potential for further progression within the overall logic framework are summarised in Table A2-3.9 below. On the basis of our considerations, only the following aspects were judged suitable for exploration in Step 3 (see Section 4):

- Persistence (P) – through use of physicochemical modelling approaches to characterise the risk posed by HBCDD;
- Toxicity (T) – through use of dose-response based quantification methods to characterise the magnitude of potential impact on aquatic ecosystems (in this case using SSD modelling); and
- Combined concerns regarding Bioaccumulation and Toxicity (BT) – in relation to the implications of the reproductive toxicity noted in rodent reproductive studies (intended mainly to inform the human health risk assessment process) on marine predators in the light of concerns regarding possible food chain effects as a result of HBCDD's high bioaccumulative potential.

3.6 Overview of Step 2 - Qualitative and Semi-Quantitative Assessment of Environmental Impacts

During the course of Step 2, the hazardous properties of HBCDD were described, as was the nature of the exposures experienced by various environmental compartments. Based on this understanding, qualitative descriptions of the nature of the potential adverse impacts that might occur in various environmental compartments were elaborated and placed into context against the potential consequences to the environment in terms of impacts on ecosystem services.

Since HBCDD has been identified as a PBT, it was also appropriate to apply benchmarking techniques (Step 2d) to place the risk posed by the substance into a wider context. In this case study, comparisons were drawn against well-known environmental pollutants and also against potential alternative substances for some of the applications for which HBCDD is currently used. While successfully elaborating on the nature of concerns regarding HBCDD, this exercise also highlighted the potential difficulties and limitations of the benchmarking technique, and the need to critically interpret the output from such exercises.

Overall, as a result of the reviews conducted in Step 2, a number of compartments and sub-compartments were identified as potentially suitable for progression to Step 3 (summarised in Table A2-3.9). Thus, in this case study, it was considered possible to progress consideration of several potential impact measures to Step 3.

In some cases, where attempts at detailed quantification (e.g. through use of SSD techniques) is considered not to be feasible, semi-quantification outputs from SSD-type approaches may still be of value in informing policy development as these provide a surrogate indicator of impact that can be used to consider the potential implications, in terms of the nature of the risk posed, of aspects such as the bioavailability and persistence characteristics of a substance and/or trends in the usage pattern for the substance.

Table A2-3.9: Summary of Step 2 Considerations and Possible Progression to Step 3			
Step	**Nature of Data Considered**		**Finding and Implications for Step 3**
2a – Hazard characterisation	Non-vertebrate toxicity	Aquatic, sediment, soil	Very toxic to some aquatic taxa and may adversely affect some sedimentary species. Some studies give good dose response data
	Mammalian toxicity	Toxicokinetics, acute, irritation/ sensitization, repeat dose, mutagenicity/ carcinogenicity, reproductive/ developmental	Several adverse effects identified but ecological consequences of many unclear. Reproductive effects (particularly offspring survival) may directly influence species sustainability. Some reproductive endpoints have dose-response information. Given, PBT/POP concerns (see below) is a need to consider secondary poisoning in Step 2e
	Other	PBT and POP potential	HBCDD meets PBT criteria. Consequences of POP-like behaviour and PBT properties raised concerns regarding environmental persistence (Step 2d) and risk to higher predators (Step 2e)
2b Exposure characterisation	Environmental compartments of concern in Step 1	included Aquatic, Marine, Terrestrial and Secondary poisoning	Data generally limited to modelled estimates; extent of monitoring data low
	Environmental behaviour	Persistence, Bioaccumulation, POPs	Experimental and modelled data on P and B, limited measurement data on POP behaviour also raises concern
2c – Qualitative description of impacts	Ecosystem services		Concerns raised specially for aquatic species and food chains and implications for symbolically important species and ecotourism
2d - Benchmarking of hazard	Benchmarking of HBCDD against important environmental pollutants and some possible alternatives	Explored using US EPA SCRAM model	Comparison with recognised environmental pollutants of concern suggest HBCDD should be a high concern. Against alternatives considered HBCDD appears to lie at the upper end of the concern range but datasets for the alternatives subject to high degree of uncertainty
2e – Potential for quantification	Findings from Steps 2a-d, inclusive		Most concerns identified not suitable for progression. Attempts to be made in Step 3 to quantify: Use of physicochemical modelling Use of dose-response quantification methods Mammalian reproductive effects in marine predators

4. LOGIC FRAMEWORK – STEP 3: QUANTITATIVE DESCRIPTION OF ENVIRONMENTAL IMPACTS

4.1 Introduction

The aim of Step 3 is to provide a more quantitative indication of the benefits of a proposed restriction or authorisation 'no use' scenario (or any other alternatives being considered). Quantification may help justify restrictions as the most appropriate risk management option or help demonstrate that the socio-economic benefits of continued use outweigh risk to the environment. As data availability will determine the path that any quantitative assessment of environmental impacts might take, Step 3 of the logic framework has been broken down into 4 different activities.

i) Step 3a: Detailed description of the baseline and the restriction scenario or the no-use scenario for authorisation;
ii) Step 3b: Expanded use of physical indicators;
iii) Step 3c: Dose-response based quantification; and
iv) Step 3d: Assessment of potential for valuation.

Each step is considered here to illustrate how the assessment was attempted in this case study.

4.2 Step 3a: Detailed description of the baseline and the restriction scenario or the "no use" scenario for authorisation

Although having a clear understanding of the baseline is important for the previous steps, it is more critical to this step in terms of accounting for future trends in use, etc. However, for the purpose of this case study, we have simply assumed that applications for authorisation are made by all current users and that the trend in use would remain constant.

Thus, the data as presented above are assumed to hold under the continued use scenario; the 'no use' scenario then equates to a total ban in use across all current applications and hence a reduction in emissions to zero with the exception of any emissions from articles already in service.

4.3 Step 3b: Expanded Use of Physical Indicators

4.3.1 Impacts of Spreading Sludge Containing HBCDD to Land

An important consideration in a SEA of the impacts of an environmentally persistent substance is to establish how long it might take for current environmental releases into the environment to be eliminated or for levels in a particular compartment to fall below a concentration at which there would be no concern. Information on this can help identify the consequences of a delay in action during which further releases would occur leading to the potential build-up of higher concentrations within the

environment. This might be of particular importance for substances only classed as being vPvBs and for which the main justification for a restriction or authorisation is the prevention of the risk of unforeseeable effects in the future.

In this case study, we have chosen to illustrate the potential removal rate of the substance from the environment by looking at degradation rates following the spreading of STW sludge contaminated with HBCDD to agricultural land. However, it is important to note that the degradation rate and the substance's potential speed of removal or its potential for build-up in the environment can be difficult to determine accurately.

γ-HBCDD (the diasteromer present in the highest concentration in technical HBCDD) has an estimated half-life in soil of around 190 days. Based on this estimated value, Figure 4.1 demonstrates how concentrations in soil might be anticipated to vary over time if it is assumed that γ-HBCDD is applied to soil through the spreading of sludge.

From the RAR, concentrations of HBCDD in sludge from a municipal sewage treatment plant have been shown to vary from 0.3 µg/kg dwt to 9120 µg/kg dwt. Levels are highest in Ireland and the UK, with median values of 1439 and 1256 µg/kg dwt, respectively. The highest figure of 9,120 µg/kg dwt relates to one particular UK sewage treatment plant. The pattern illustrated in Figure 4.1 assumes an initial concentration of 1400 µg/kg (or 1.4 mg/kg) dwt and addition of a further 1400 µg/kg (or 1.4 mg/kg) dwt once every year (i.e. taking the median value for Ireland).

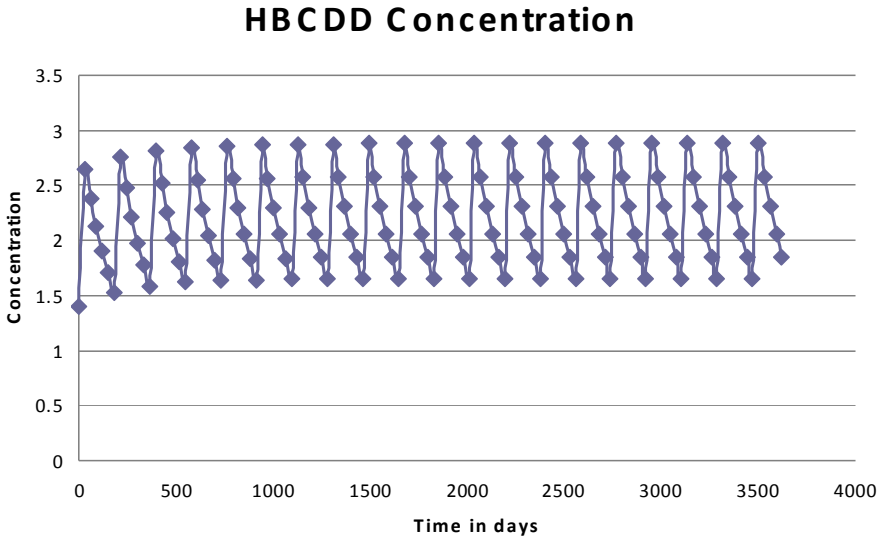

Figure A2-4.1: Soil Concentrations of HBCDD Assuming Annual Application

These results suggest that – for the assumed half-life and a once-per year frequency of application – concentrations in soil would be expected to stabilise at a maximum of just under 3 mg/kg dwt shortly after application of sludge containing HBCDD but would then return to the base level before the time of next application. As the RAR

established a PNEC for HBCDD in the terrestrial environment of 5.9 mg/kg dry soil, this would indicate that repeated annual application of sludge containing HBCDD even at a relatively high concentration would be unlikely to represent a particular cause for concern. Other modelling (not presented here) showed that a build-up of HBCDD in soil would only start to occur if application of sludge was undertaken at a frequency of 3 or more times each year (which would be in contravention of some national legislation and interfere with growing cycles).

As previously noted, the different diasteromers of HBCDD show different degradation rates. α-HBCDD (present at less than 10% in technical HBCDD) has a half-life of about 210 days. γ-HBCDD (the substances present at the highest concentration in the technical material) shows a half-life of <197 days (depending on concentration). Within an SEA prepared for formal use, possible different application frequencies (reflecting differences in agricultural practice) and the implications of the physicochemical behaviour of the diastereomers would need to be considered before reaching an overall conclusion.

Using LCIA Models to Estimate Environmental Concentration

Where monitoring data are not available, Life Cycle Impact Assessment (LCIA) models may provide a potential means of estimating the environmental distribution and concentrations (both geographical and compartmental) of substances. Several models are available but the one most appropriate for this case study would appear to be USETox[5], as HBCDD is already implemented in the model in relation to human health impacts.

The overall goal of LCIA models is to look at the whole life cycle of a chemical and to estimate its impact on human health and the environment; they are not currently designed to assess a chemical's dynamic trend in the environment over time. Predicting actual impacts due to future emissions etc. also lies outside the scope of current LCIA models[6]. The models rely on emissions data to be input and the models only allow for one set of emissions data to be used at any one time.

There are multimedia models available which give a dynamic solution[7], mostly focussing on classical air pollutants or POPs, such as dioxins. These models are designed for predicting impacts, e.g. in the context of environmental health impact assessment (EHIA), and are highly complex. In particular, they require an immense

5 www.usetox.org

6 The models are mostly built on matrix algebra, where they have to inverse the initial matrix of transfer rate coefficients (which represent the transfer processes between the involved environmental compartments including removal, e.g. via degradation), which gives a fate factor matrix, where the residence times for each compartment (expressed as mass in receiving compartment per unit emission per day in source compartment) are stored. This may serve as a starting point to manually extract the relevant matrices and compute a dynamic solution by means of numerical treatment of the set of ordinary differential equations behind these matrices in Matlab or something similar, but this has not yet been done.

7 Models include those by Gerhard Lammel at MPI in Germany and Oleg Travnikov at MSC-East in Moscow.

amount of spatially and temporally explicit data for meteorology, substance degradation, re-emission, run-off, etc. As far as we are aware, none of these have implemented HBCDD yet in relation to the environment.

PANGEA is foreseen as also including a dynamic solution (i.e. evolution of a chemicals' concentration in the environment over time), as it is supposed to be applied in both LCIA and EHIA but this model will not be ready until the end of 2011, at the earliest.

Since dynamic models are not yet available, for the purposes of a SEA at present it would therefore be necessary to run models repeatedly using revised emission data to represent the likely emissions scenarios that may result from HBCDD use not being authorised (and to take into account that there would still be emissions from products in use, or undergoing recycling and disposal).

If disaggregated emissions data for different source sectors were available, it might also be possible to consider each source sector individually in order to determine the relative contribution of each. An important limitation is, in any case, that the resulting output data from a LCIA model would only be as detailed as the emissions data available to support the model.

Given the current stage of development of LCIA models and their limitations, it was not considered feasible to progress such a modelling exercise within the context of the current case study. However, it is interesting to note that global models which have a European Continental version nested in them (such as USEtox) can be used to investigate the contribution of an emission (e.g. within Europe) to the other continents or globally. This may in future be useful for indentifying contribution loads to more sensitive geographic areas such as the Arctic, which might be particularly beneficial when considering the behaviour of persistent chemicals such as HBCDD that are likely to undergo long-range transport. Indeed, most global models of LCIA consider long-range transport as a particular process.

4.4 Step 3c: Dose-response Based Quantification

4.4.1 Modelling Species Sensitivity Distributions Based on the TGD approach

The first approach illustrates the use of SSD-methodology based on the guidance in the TGD (where SSD modelling is noted to require the availability of at least 10 long-term NOECs from across 8 taxonomic groups).
The initial step is thus to consider the possibility of developing a SSD for HBCDD using the data available on the aquatic compartment. For this, exposure and toxicity data on HBCDD were drawn from the RAR wherever possible. However, for HBCDD the available dataset does not meet minimum data requirements as specified in the TGD (i.e. there are insufficient test data quoting NOEC values for this compartment). This is likely to be an issue for many substances considered under REACH and highlights the difficulties that may be experienced if attempting to derive

SSD estimates in full accordance with the assessment methods documented in the TGD.

For illustrative purposes only and solely within the context of this case study, additional NOEC values were generated for other species by use of linear extrapolation regression techniques from the EC_x values available in the RAR for these species, to generate a EC_0 value. This EC_0 was assumed to correspond to the LOEC and a NOEC value was then generated by applying the NOEC/LOEC ratio that had been established in the RAR for *Daphnia magna*. Even including these additional 'generated' data points, there were only 6 NOECs from 3 taxonomic groups (fish, invertebrate and algae) available to support a SSD; this would again fail to meet the TGD recommendations for the minimum dataset with which to construct an SSD. In order to generate a more accurate SSD, it would be necessary therefore to generate further NOECs, for example by conducting additional laboratory tests on other relevant species/taxonomic groups. However, the available data were considered adequate to proceed with this illustrative example within the context of a case study (see Table A2-4.1).

In using this dataset to derive the fraction affected (y-axis), the lowest log_{NOEC} was taken to be:

1/6 (total number of NOEC values used)/2 = 16.7%/2 = 8.3%

Table A2-4.1: NOECs Used in SSD Modelling

Raw Data from HBCDD RAR					**NOECs for SSD**		
Type	**Value (µg/l)**	**Hours**	**Species**	**Type**	**Retained from RAR or Derived**	**NOEC (µg/l)**	**log (NOEC)**
NOEC	3.7		Rainbow trout	Fish	Retained	3.7*	0.568
NOEC	3.1	504	*Daphnia magna*	Invertebrate	Retained	3.1*	0.491
LOEC	5.6	504					
LOEC	>2.5	96	*Selenastrum capricornutum*	Algae	Derived	2.5**	0.398
EC_{10}	40.6	72	*S costatum*	Algae	Retained	20.8*	1.318
EC_{50}	52	72					
NOEC	>10	72					
EC_{50}	40-380	72	*Thallassiosira pseudonana*	Algae	Derived	107**	2.029
EC_{50}	1500	96	*Chlorella sp.*	Algae	Derived	765**	2.884

Note:
EC*x* is the estimated concentration causing an effect of *x* % compared with controls

Table A2-4.2: Cumulative Values				
NOEC µg/L	**Log(NOEC)**	**Fraction Affected**	**Species**	**Type**
2.5	0.398	0.083	*Selenastrum capricornutum*	Algae
3.1	0.491	0.250	*Daphnia magna*	Invertebrate
3.7	0.568	0.417	Rainbow trout	Fish
20.8	1.318	0.583	*Skeletonema costatum*	Algae
107	2.029	0.750	*Thallassiosira pseudonana*	Algae
765	2.884	0.917	*Chlorella sp.*	Algae

All $\log_{NOEC}$ values and the associated fraction affected are shown in Table A2-4.2 above.

Fitting a normal distribution to the log of the toxicity data resulted in the SSD presented in Figure 4.2[8].

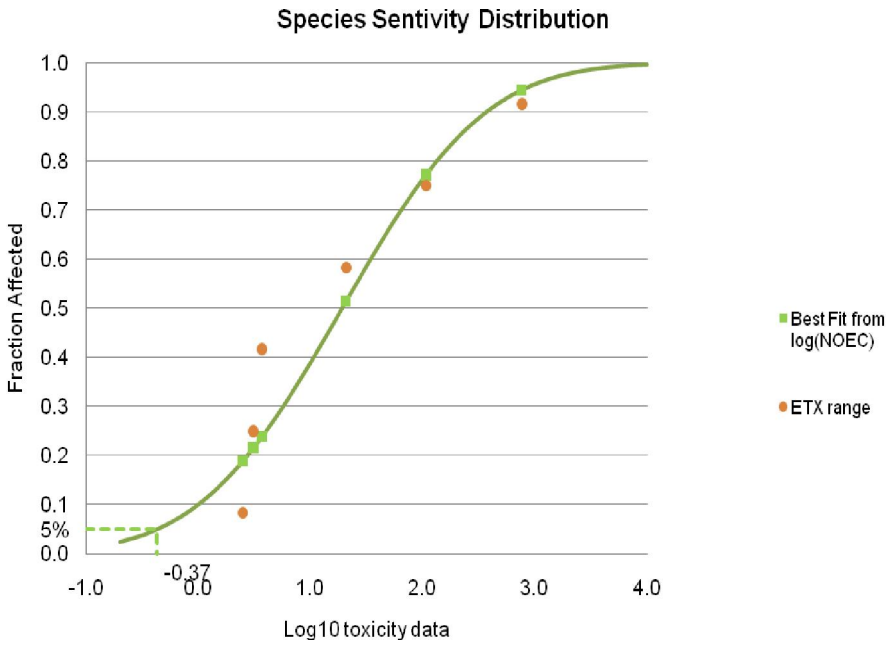

Figure A2-4.2: Species Sensitivity Distribution for HBCDD Using Limited Dataset

Using this dataset, SSD modelling indicates that the HC_5[9] obtained from the curve is 0.43 µg/l[10] (N.B. the model passed all goodness of fit tests at a significance level of 0.05).

[8] The distribution parameters (calculated using mean and standard deviation of the toxicity data logarithmic values) were $\mu = 1.28$ and $\sigma = 1.00$.

[9] i.e. hazardous concentration for 5% of species

Once a SSD has been generated for HBCDD, the next stage is to compare this with measured or predicted environmental concentration data. The objective is to identify what proportion of the species present in the compartment of concern might be 'affected' at current environmental concentrations. This is demonstrated by overlaying a probabilistic model of the HBCDD concentrations in a relevant environmental compartment, in this case 'rivers', against the scale of effect anticipated at particular concentrations.

In order for this type of analysis to be robust, actual monitoring data should be used. In the case of HBCDD, surface water monitoring data are included in the RAR but these relate to multiple sample data from only a few sites including several identified as of particular concern. For example, the dataset includes historic information on two HBCDD production sites (one in the UK and the other in the Netherlands). As such, the available data does not constitute a truly representative picture of levels of HBCDD across the entire EU surface water system. To develop a robust SEA suitable to inform regulators, more comprehensive monitoring data drawn from a range of representative sites would be used ideally[11]. Nonetheless, the limited data currently available (see Table A2-4.3) can be used here to illustrate how monitoring data might be used in practise.

Table A2-4.3: Concentration Data for UK and NL Rivers (All Samples are Surface Water)

Location	Value (µg/l)
UK	0.025*
UK	0.025*
UK	0.057
UK	0.08
NL	0.16
UK	0.2*
UK	0.2*
UK	0.2*
UK	0.2*
UK	0.2*
UK	0.21
NL	0.25*
UK	0.884
UK	1.52
UK	4.81**

10 $10^{-0.37}$

11 This type of analysis could also be undertaken for a single site, to predict the likelihood of exceeding specified concentrations using all sampling data across a one year period. This would be more relevant for an application of an authorisation covering a single site; furthermore consideration of the data for individual sites will be important in relation to toxicity considerations. The approach adopted above has been chosen so as to also reflect and take into account the P and B properties of HBCDD.

Table A2-4.3: Concentration Data for UK and NL Rivers (All Samples are Surface Water)	
Location	**Value (µg/l)**
UK	4.97**
UK	6.61**
UK	10**
UK	14**
UK	16**
Notes: * Indicates that the concentration is below the detection limit. In such cases, the concentration is assumed to be one-half the detection limit ** These samples were taken at a major European manufacturing plant producing HBCDD over different points in time. As these concentrations are relatively high and the total number of samples is low, the mean of these values for this one site was used in the assessment.	

A lognormal probabilistic distribution was fitted to the monitoring data[12] and the resulting distribution of concentrations compared graphically with the SSD data in a single graph (Figure A2-4.3).

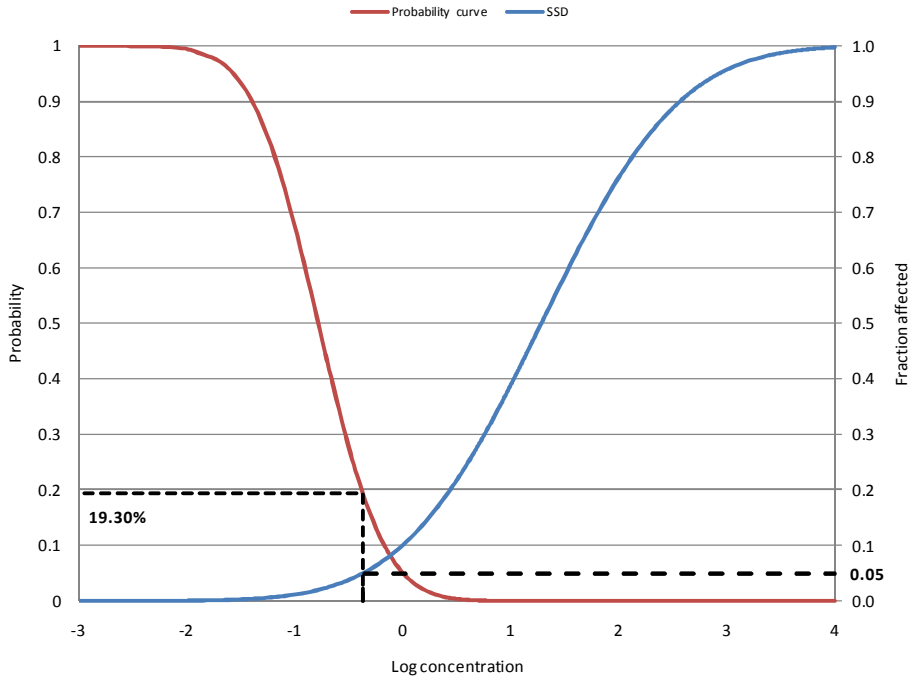

Figure A2-4.3: Probability of Exceeding a Specific Fraction Affected in a River

As Figure A2-4.3 illustrates, based on what should be regarded as a 'worst case' estimate of the distribution of exposures in European rivers, it is possible to generate a predicted probability of the proportion of rivers that may exceed the NOEC for 5% of

12 The distribution passed all goodness of fit tests (Kolmogorov-Smirnov, Anderson-Darling and Chi-squared) for a significance level of 0.05. The parameters of the lognormal distribution were $\mu = -1.80$ (mean of the log concentration values), $\sigma = 1.1$ (sample standard deviation) and $n = 14$ (sample size).

species (i.e. >0.43 µg/l or a log concentration of -0.37); the derived estimate is 19.30% of rivers.

The estimate of percentage of rivers affected would probably decrease if exposure data were available to give a more representative sample of water bodies including pristine, non-industrial and other industrial water bodies across the EU.

It should be appreciated that the level of '5% of species affected' (which equates to the HC_5 criteria) adopted here is purely a nominal metric which reflects existing conventions within ecotoxicological risk assessment. The proportion of species for any given ecosystem that can be adversely impacted without there being a significant challenge in the ecosystem's sustainability is currently unknown and an aspect of ongoing ecotoxicological debate. In particular, this approach does not inform on which might be the 5% of species adversely affected (or to what extent this may have wider ecological consequences). Hence, as an indicator of impact, this estimate carries with it considerable uncertainty.

During use in risk assessments, HC_5-type estimates are subject to application of various assessment factors (AFs) which are intended to adjust for the uncertainties surrounding the resulting ecological consequences. The extent to which such assessment factors might be appropriate in the context of a SEA has not, however, been defined. Until such time as a scientific consensus emerges as to the correct interpretation of a particular %-loss of species that can be tolerated by particular types of ecosystem, choice of 'cut off' criteria to denote an 'adverse consequence' must be regarded as essentially a policy-based (nominal) value.

As shown in the above example, the fact that datasets may be limited for many SVHC chemicals may lead to difficulties in utilising a fully TGD compliant approach when undertaking SSD estimations for SEA purposes under REACH. However, in developing this approach for SEA purposes, consideration might be given to the use of a range of estimate values within a sensitivity analysis. As can be seen from this case study, comparison of the SSD curve against a probabilistic based estimate of the distribution of environmental exposure levels for the relevant compartment can inform on the likelihood of a particular level of impact occurring at a particular concentration.

4.4.2 Use of SSD and LCIA Models to Estimate Implications of Draft Proposals for Environmental Quality Standards

Initial working draft proposals for environmental quality standards (EQSs) are under development for HBCDD by the EC (version supplied by DG Environment dated 18 August 2010, Reference 20100816). Therefore, as an illustrate exercise, these unpublished proposals were examined using the SSD and river exposure models as developed above and using a LCIA-based approach, in order to inform on the possible extent to which the envisaged draft QS values might be protective of the European environment.

Use of SSD Model and Probabilistic Estimates of River Concentrations

SSD models of the type developed in the section above could be of particular value when attempting to develop environmental quality standards (EQSs); they can provide an indication of the proportion of a compartment that might be exposed to environmental concentrations above the proposed quality standard.

In this case, the potential scale of impact was assessed in terms of both the proportion of rivers that might exceed various draft EQS standards[13] and the rigor of species protection that the proposed EQS might provide (in terms of the equivalent HC_x value). The draft EQSs that are relevant here are an acute-based MAC-EQS of 0.52 µg/L for freshwater and an annual average value for direct toxicity for chronic exposures (AA-EQS-direct toxicity) of 0.31 µg/L. A tentative MAC of 0.052 µg/L was also proposed for transitional and marine waters. A tentative QS for freshwater of 0.92-4.6 ng/L was also back calculated from a biota standard of 167 µg/kg w/w based on secondary poisoning; this was developed based on the NOEC of 5 mg/kg feed established in a study on quail. It is understood that refinement of this QS to a single value of 1.6 ng/L may be a possibility but, as further consideration is being given within the ongoing proposal process, further consideration of this aspect was not undertaken in detail here.

Comparing the proposed MAC (acute poisoning) of 0.52 µg/L and the AA-EQS (direct toxicity) of 0.31 µg/L with the predicted profile for river concentrations (see Figure A2-4.3) indicates that there might be between 15% to 29% of rivers that exceed each of these respective standards. The level of species protection associated with either the acute-based MAC-EQS (freshwater) of 0.52 µg/L or the direct toxicity value for chronic exposure (AA-EQS-direct toxicity) of 0.31 µg/L using the SSD equates to a HC value of the range 3.7-6.0, i.e. the HC_5 value falls within the range of values under consideration for EQS purposes.

Use of LCIA Models

An alternative approach to illustrating the potential scale of impacts that might be associated with the draft EQSs being considered by the Commission is the application of a LCIA-based model to derive estimates of exposure levels to various media. This exercise was undertaken using the USEtox model (described in Part 1 of the report) that was developed as part of the UNEP-SETAC Lifecycle initiative to characterize human and ecotoxic impacts and facilitate comparative assessment of substances based on their inherent hazard characteristics.

The USEtox model incorporates a database for HBCDD that is customisable to allow the exploration of alternative assumptions. This facility proved essential since the USEtox generic dataset contained some important differences in input parameter

[13] This exercise was conducted using information extracted from a draft EQS dossier (Reference 20100816) dated 18 August 2010, supplied by the Commission

assumptions compared with the approach used when drafting the EQS (see Table A2-4.4).

Table A2-4.4: Input Parameters Used for USEtox Estimations		
Input Parameter	***Data Source***	
	USEtox[a]	***Draft EQS[b]***
BAF [kg_{water}/kg_{fish}]	3.55E+06	6.00E+03[c]
Kow [--]	5.50E+07	4.17E+05
$K_{H,25°C}$ [Pa·m³/mol]	6.88E+01	7.50E-01
$P_{vap,25°C}$ [Pa]	2.24E-06	6.30E-05
$Sol_{25°C}$ [mg/L]	2.09E-05	2.10E-03
Koc [L/kg]	9.11E+04	4.57E+04
$k_{deg,air}$ [1/s]	4.59E-06	6.00E-08
$k_{deg,sediment}$ [1/s]	1.49E-08	9.44E-08
Note *a USEtox substance Database default data* *b From draft EQS dossier 20100816* *c A revised estimate for the BAF has since been adopted in a revised draft EQS dated 19 January 2011 (see discussion on Uncertainty below)*		

The resultant estimates of predicted concentration in the abiotic and biotic (fish) environmental compartments considered by the UStox model are presented in Table A2-4.5, for each set of assumptions.

Table A2-4.5: Estimated Concentrations in Various Compartments			
Concentration in	**Compartment**	**Based on generic USEtox scenario**	**Based on draft EQS scenario**
Environmental Media (as kg/m^3)	urban air	8.02E-16	7.35E-16
	continental air	8.21E-16	7.53E-16
	continental freshwater	**6.49E-10**	**8.30E-10**
	continental seawater	2.05E-12	2.86E-12
	continental natural soil	1.56E-11	1.38E-10
	continental agric. soil	1.56E-11	1.38E-10
	global air	4.79E-18	8.85E-18
	global freshwater	1.36E-15	3.97E-14
	global seawater	7.70E-16	1.94E-15
	global natural soil	9.08E-14	1.62E-12
	global agric. soil	9.08E-14	1.62E-12
Concentration in Fish (as kg/m^3)	**Fish**	**2.31E-03**	**4.98E-06**

By comparing the Usetox estimates with the draft EQS, the likelihood of exceedence of the various draft EQS values under consideration for European rivers can be estimated (please note that concentrations below are expressed as µg/L units since these are more naturally used when considering water body exceedences).

The modelled estimates of continental freshwater concentration ranged from 0.000649 to 0.00083 µg/L based on generic USEtox or draft EQS assumptions respectively, indicating that the proportion of rivers that might exceed either the proposed acute-based MAC-EQS (freshwater) of 0.52 µg/L or the direct toxicity value for chronic exposure (AA-EQS-direct toxicity) of 0.31 µg/L would be expected to be very low.

In sharp contrast, if the predicted estimates for fish concentrations are considered, levels are estimated to range between 2,308 µg/L and 4.98 µg/L, based on the USEtox and draft EQS data respectively. These estimates are generally higher than the potential range of values that have been considered with regard to an EQS for freshwater biota; the marked difference between the estimates was identified as largely attributable to different assumed extent of bioaccumulation (i.e. the BAF value used) and the resultant accumulation patterns within relevant food chains. Caution would be warranted, however, if attempting to interpret this finding since the focus of the fish concentration estimates derived by the LCIA model is to define an input into the human food chain, rather than necessarily informing on either fresh or marine water levels per se.

Uncertainty

The very large variations in the estimated environmental concentrations and consequently in the extent of predicted exeedence of the draft EQS in many of the compartments, according to the basis of the estimate, is notable. In this particular example, the critical importance to the LCIA model of the value assumed for BAF can be illustrated by consideration of data from a revised version of the draft EQS dossier (Reference 20110119) dated 19 January 2011, that amends the average BAF to 105,000 L/kg fw[14]. Adoption of this revised BAF to generate an LCIA estimate of the concentration in fish would be anticipated to lead to a much closer agreement with the generic USEtox estimate.

The sensitivity of the estimates to changes in input parameters, and the differences between them, highlight the difficulty of conducting any quantification of impacts based on such data. If only one source of data (be it a draft EQS document or USETox defaults) had been available for consideration, then the level of uncertainty attached to the estimates might not have been fully appreciated.

This example illustrates the need for extreme caution to be exercised before developing impact assessments, even when based upon data from reputable sources.

[14] Revision of EQS necessitated by publication of corrections to the source paper; for details see Harrad S et al., (2010) Environ., Sci. Technol. 44, 5318

4.4.3 Potential Extension of SSD Modeling Beyond the TGD Approach

As a possible approach to make full use of the available datasets, consideration was given to the potential for combining available toxicity data on species from the aquatic compartment with those for sedimentary species; the rational for this was that these represent sub-compartments that could be considered – at least to some extent - to be essential for the sustainability of freshwater ecosystems. It could also be argued that equilibrium between these compartments – in terms of both toxic effects on species, the environmental levels of the substance and inter-species interactions – might exist at least to some extent. Based on these assumptions, the combined dataset for each compartment might be of sufficient size to enable a more robust SSD to be developed.

As noted above, the RAR quotes 3 NOECs for the aquatic compartment across 3 taxonomic groups. There are also 3 NOECs relating to invertebrates in the sediment compartment. Combining these gives a total of 6 NOECs which, although insufficient to comply fully with TGD requirements on number and spread of data, would allow an indicative analyses to be undertaken without the need to generate additional NOEC estimates (as illustrated above). However, it must be stressed that the uncertainty surrounding the output should still be regarded as quite significant.

In the HBCDD dataset, in order to derive combinable NOECs for species from the aquatic and sediment compartments, NOEC units must be comparable. In this case, the available sediment values were therefore transformed into the units used for aquatic species.

One approach by which this may be achieved is to apply the equilibrium partitioning method (EPM; described in TGD document R10). This uses values for aquatic organisms and the suspended matter/water partitioning coefficient as the inputs. The formula is given by equation R.10-2 of the TGD:

$$PNEC_{sed} = \frac{K_{susp-water}}{RHO_{susp}} . PNEC_{water} . 1000$$

where:
RHO_{susp}: Bulk density of wet suspended matter [$kg.m^{-3}$] = 1150
$PNEC_{water}$: Predicted No Effect Concentration in water [$mg.l^{-1}$]
$PNEC_{sed}$: Predicted No Effect Concentration in sediment [$mg.kg^{-1}$ of wet sediment]
$K_{susp-water}$: Partition coefficient suspended matter water [$m^3.m^{-3}$].

This last metric may in turn be calculated using TGD Equation R.16-7:

$$K_{susp-water} = Fair_{susp} . K_{air-water} + Fwater_{susp} + Fsolid_{susp} . \frac{Kp_{susp}}{1000} . RHO_{solid}$$

where:
$Fair_{susp}$: Fraction air in compartment comp (only relevant for soil) [$m^3.m^{-3}$] = 0

$K_{air\text{-}water}$: Air-water partitioning coefficient [-]
$Fwater_{susp}$: Volume fraction water in susp. matter [$m_{water}^3.m_{susp}^{-3}$] = 0.9
$Fsolid_{susp}$: Volume fraction solids in susp. matter [$m_{solid}^3.m_{susp}^{-3}$] = 0.1
RHO_{solid}: Density of the solid phase [$kg.m^{-3}$] = 2,500
Kp_{susp}: Solids-water part. coeff. in susp. matter [$l.kg^{-1}$].

Kp_{susp} is given by TGD Equation R.16.-6:

$$Kp_{susp} = Foc_{susp}.Koc$$

where:
Foc_{susp}: Weight fraction organic carbon in susp. solids [$kg_{oc}.kg_{solid}^{-1}$] = 0.1
Koc: Partition coefficient organic carbon-water [$l.kg^{-1}$] = $4.54x10^4$

Therefore,

$$Kp_{susp} = 4.54.10^3\ l.kg^{-1}$$
$$K_{susp-water} = 1{,}125.9\ m^3.m^{-3}$$
$$PNEC_{sed} = 979.PNEC_{water}$$

Unfortunately, the values for sedimentary species for HBCDD in the RAR are quoted only in terms of 'dry weight' but the above formula applies to 'wet weight' units. However, TGD Chapter R16 cites a formula for soil to convert dry weight to wet weight. Applying this formula to sediments (since it is indicated as equivalent to suspended matter according to the TGD), gives:

$$CONV_{sed} = \frac{RHO_{susp}}{Fsolid_{susp}.RHO_{solid}}$$

where:
RHO_{susp}: density of wet sediment [$kg.m^{-3}$] = 1,150
$Fsolid_{susp}$: volume fraction solids in sediment [$m_{solid}^3.m_{sed}^{-3}$] = 0.1
RHO_{solid}: density of the solid phase [$kg.m^{-3}$] = 2,500

Hence,

$$CONV_{sed} = 4.6\ kg_{wwt}.kg_{dwt}^{-1}$$

The results of applying the above equation are given in Table A2-4.6; this includes the available toxicity data for sediments and the derived estimates in terms of mg/kg wwt. These data are then used together with those for the aquatic compartment (see Table A2-4.7) to develop a SSD.

Table A2-4.6: Ecotoxicity Data for Sediments			
Species	**Duration (Days)**	**NOEC (mg/kg dwt)**	**Adjusted NOEC[1] (mg/kg wwt)**
Hyalella azteca	28	1,000	217.39
Lumbriculus variegatus	28	8.6	1.87
Chironomus riparius	28	37.8	8.22
Note: [1] Using above formula			

Table A2-4.7: Ecotoxicity Data for Aquatic and Sedimentary Species		
Taxonomic group	**Species**	**NOEC (µg/l)**
Aquatic Compartment		
Fish	Rainbow Trout	3.7
Invertebrate	*Daphnia magna*	3.1
Algae	*Skeletonema costatum*	10
Sediment Compartment		
Invertebrate	*Hyalella azteca*	220
Invertebrate	*Lumbriculus variegatus*	1.87
Invertebrate	*Chironomus riparius*	8.22

The resulting SSD derived by the ETX software is plotted in Figure A2-4.4. This was obtained by fitting a normal distribution to the toxicity data logarithmic values (N.B. again the model passed a goodness of fit tests at a significance level of 0.05).

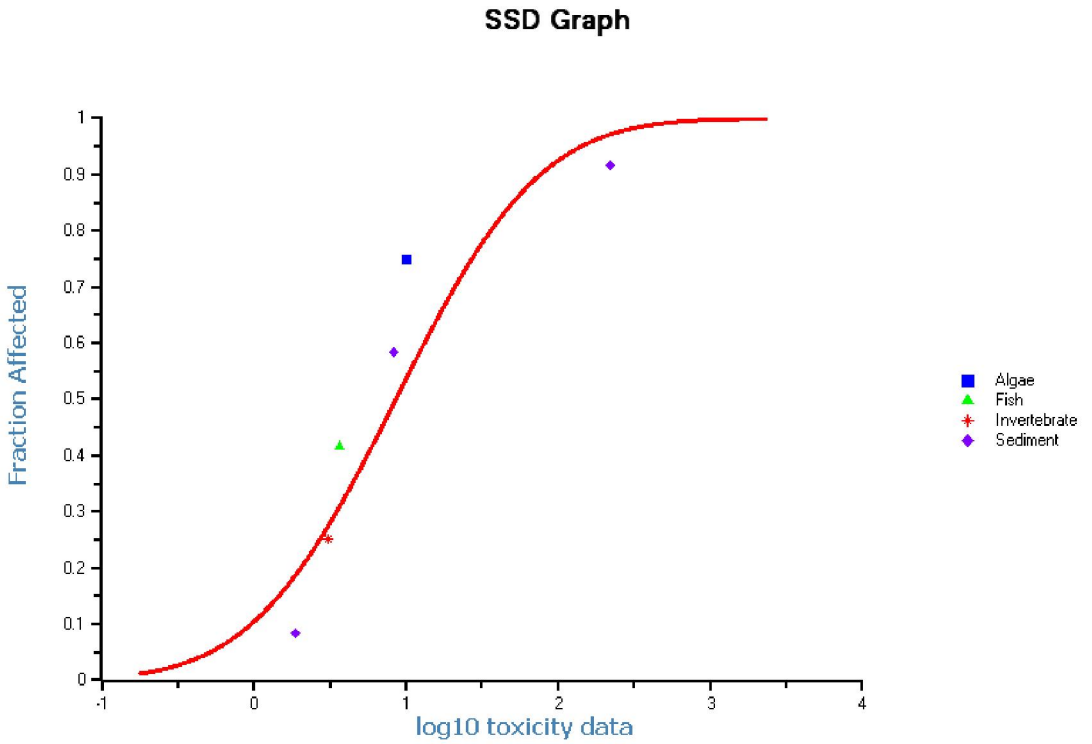

Figure A2-4.4: Species Sensitivity Distribution (SSD) Using a Combined Dataset for Aquatic and Sediment Species

The distribution parameters are calculated using the mean and standard deviation for the toxicity data (as logarithmic values) and are μ =0.93 and σ =0.74. Based upon the approach that is used by ETX, the same analysis was realised using Microsoft Excel to facilitate ease of subsequent calculations. The HC_5 value derived using Excel was found to equal 0.52 µg/l ($10^{-0.29}$ – see Figure A2-4.5).

As highlighted above, one of the particularly attractive possibilities that is offered by the use of the SSD approach is to determine the fraction of affected species that might occur at any given environmental concentration. To illustrate this, we therefore used the data available from this example to derive an estimate of the percentage of species that might be affected at the production site in the Netherlands and for various industrial sites where HBCDD is used as a back-coating agent for textiles (Table A2-4.8).

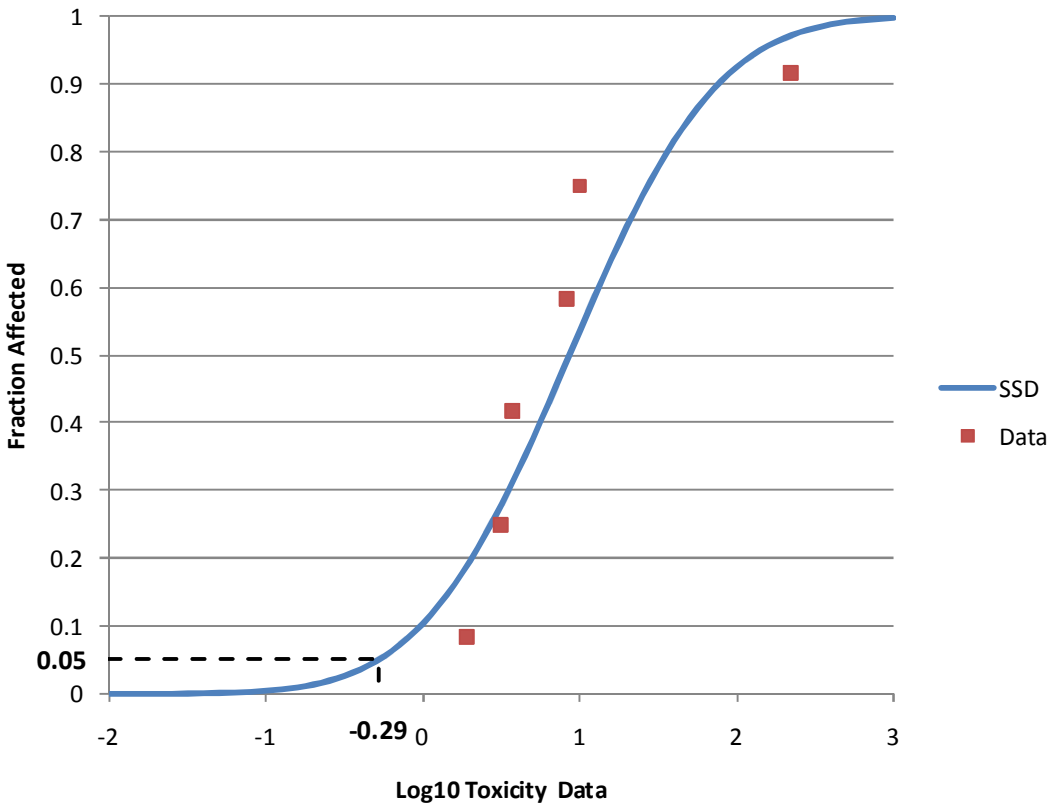

Figure A2-4.5: Species Sensitivity Distribution Using Combined Datasets of Aquatic and Sedimet Species – Including Estimated HC_5 Value

Table A2-4.8: Percentage of Species Affected based on Combined Datasets for Aquatic and Sedimentary Species						
Site	**Connected to Municipal STP**	**Dilution in the Recipient**	**PEC_{water} During Emission Period**	**% of Species Affected**	**PEC_{water} Annual Average**	**% of Species Affected**
Production						
ProdB	Yes	1000	0.028	0.04%	0.028	0.04%
Industrial Use of Textile Back-Coating Agent						
Backcoat.1	Yes	10	0.33	2.82%	0.21	1.49%
	No		1.5	15.37%	0.93	9.67%
Backcoat.2	Yes	10	0.33	2.82%	0.073	0.26%
	No		1.5	15.37%	0.24	1.81%
Backcoat.3	Yes	10	52	85.44%	12	57.81%
	No		250	97.59%	58	86.85%
Backcoat.4	Yes	10	0.029	0.04%	0.028	0.04%
	No		0.031	0.05%	0.03	0.05%
Backcoat.C	Yes	10	0.13	0.71%	0.04	0.08%
	No		0.5	4.81%	0.083	0.33%

As can be seen from Table A2-4.6, on the basis of the assumptions used there do not appear to be significant concerns with regard to the environmental impact on the local freshwater environment for the production site. In contrast, some sites involved in the industrial use of HBCDD as a textile back-coating agent appear to be at significant risk in terms of loss of species. It should however be noted that - as previously discussed – the PECs used for this example may be overly conservative and therefore may constitute only a poor indicator of the actual environmental concentrations associated with these sites.

4.4.4 Considerations on the Use of SSD-based Impact Assessments

These examples illustrate the use of the SSD approach to identify the fraction of sites that might be affected, showing in this case that the proportion of rivers subject to adverse impacts could be potentially significant. Such information might allow the targeting of those types of sites considered to be of particular concern for further investigation and monitoring. However, for those cases where the predicted fraction affected is considered negligible using conservative assumptions, it might be suggested that the risk of significant adverse impacts would be relatively low, although this conclusion would clearly be based on consideration of toxicity alone and would not take account of the P or B nature of the chemical.

The examples above also demonstrate that even if the available data are insufficient for SSD modelling within the strict terms of the TGD on risk assessment, the SSD may in some circumstances provide valuable insight into the extent of impacts in particular ecosystems. However, the accuracy and predictive reliability of any such assessment is crucially dependent on the quality and quantity of information available.

Also, the above examples illustrate that to produce more meaningful estimates of the likely magnitude of any impact on the European environment would require use of more robust environmental monitoring data. In the case of HBCDD, only data from the UK and Netherlands (relating to locations in the vicinity of potential emission sources) were available and these are unlikely to be representative of the general European environment. Ideally, more information would be available on chemical exposures across the EU - including both high and low risk sites.

There would still remain a key limitation for the SSD methodology as to the degree of uncertainty that surrounds a central assumption concerning the ecological relevance of impacts measured in terms of '% species affected'. It is also noted that the traditional use of SSD has been to assess toxic effects under 'steady-state' exposures. In order to better inform on the potential consequences of changes in levels over time for a PBT chemical, there may be a need to modify the assumptions used to address temporal changes in environmental levels in the abiotic and biotic environment. Also the SSD approach is clearly unhelpful when considering a vPvB substance for which toxic concern has not been defined.

4.4.5 Use of Dose-response Data for the Most Sensitive Species

In situations where the dataset on a substance contains only NOEC estimates (or these are derivable only) for a very small number of species (i.e. 4 or less) and so construction of a meaningful SSD is not possible then, providing appropriate dose-response data are available from the risk assessment, the TGD on risk assessment specifies that a single species dose-response approach may constitute an alternative approach. In such cases, some comparative measure of toxicity such as the $EC_{1,}$ $EC_{2.5}$, EC_{10} or other value for the most sensitive species in a given environmental compartment might be assumed to provide a 'representative' indictor of the susceptibility of the overall compartment from which that species is drawn.

To illustrate the use of single-species methods, we have considered species from the aquatic compartment. As previously noted, only 3 values for 3 taxonomic groups are presented in the RAR. Of these, the most sensitive species (i.e. that with the lowest NOEC) is the invertebrate *D. magna* which gave a NOEC of 3.1 µg/l, based on a 21 day study. The RAR also included detailed dose-response data on various endpoints from this study and the data can therefore be used to construct a dose-response curve, in this example relating to cumulative mortality (Table A2-4.9).

Table A2-4.9: Mortality in *Daphnia magna* Exposed to HBCDD for 21 Days			
Mean Measured Concentration of HBCDD (µg/l)	**% Mortality**	**Total Number of Animals**	**Total Number of Animals Dying**
Negative control	5.0%	40	2
Solvent control	2.5%	40	1
0.87	2.5%	40	1
1.6	2.5%	40	1
3.1	0.0%	40	0
5.6	7.5%	40	3
11	12.5%	40	5
Note: Data from Drottar and Kruger, 1998, as reported in the RAR			

The dose response curve developed from these data was fitted using a probit model using XLSTAT[15]; the natural mortality was taken as 2.5% (i.e. 1/40 as reported for the solvent control group). The response curve generated is presented in Figure 4.6 (confidence in this dose-response curve is good since the model passed all goodness of fit tests). The EC_5 derived using this curve is 7.4 µg/l , the $EC_{2.5}$ is 5.5 µg/l and the EC_1 is 3.9 µg/l.

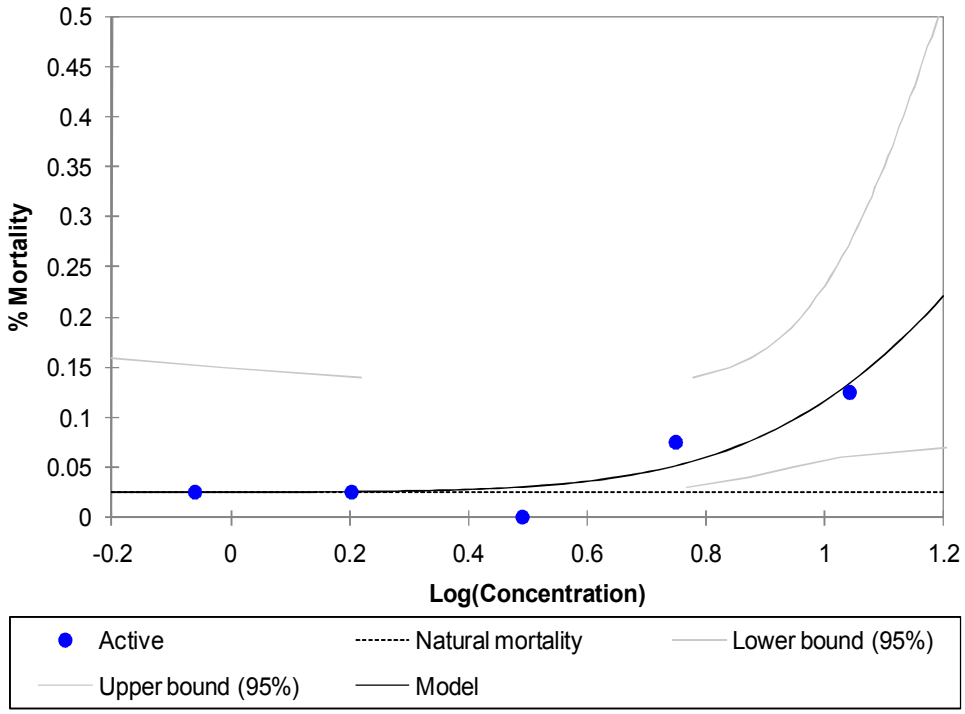

Figure A2-4.6: Dose Response Curve for *Daphnia magna* (Probit Model)

15 XLSTAT. Free trial available at www.xlstat.com

As an alternative, a logit model was fitted to the mortality data; this model also passed the goodness of fit tests. The dose response curve (Figure A2-4.7) allowed estimation of EC_{10}, $EC_{2.5}$ and EC_1 values of of 7.7, 5.6 and 3.7 µg/l respectively.

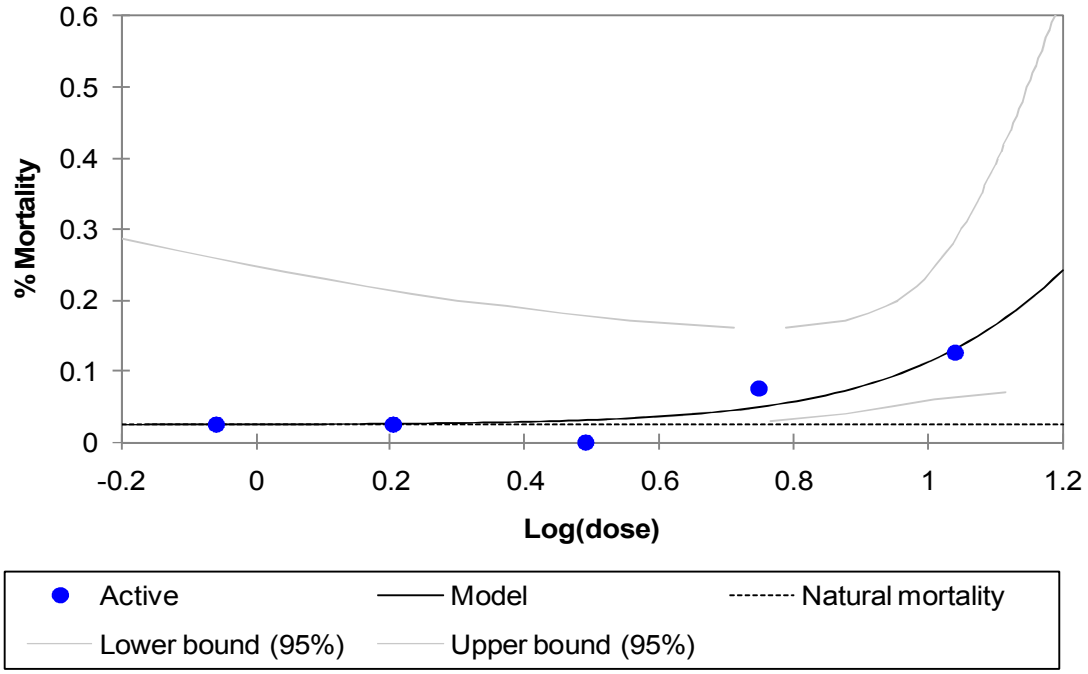

Figure A2-4.7: Dose Response Curve for *Daphnia magna* (Logit Model)

If we compare these response curves with the distribution developed for environmental concentrations of HBCDD in surface waters (as previously done in the SSD examples, see Figure A2-4.3), we can estimate the corresponding percentage of rivers where concentrations are predicted to be at risk of exceeding various levels of toxicity, in this case based on EC_x criteria. For example, if an EC_1 value of 3.7 µg/l were adopted as the threshold for unacceptable environmental risks, then based on the pattern of European river concentrations as predicted earlier, it would be estimated that about 0.5% of rivers would be at risk of exceedence. Note this figure is significantly different from that found for the HC_5 due to the differences in the way the latter is derived.

The RAR for HBCDD included data on long-term toxicity for a number of sediment-dwelling species including *Hyalella azteca, Lumbriculus variegates* and *Chironomus riparius.* The most sensitive was *L. variegate* (NOEC of 3.1 mg/kg dwt) and it would be of interest, given that dose-response data are available, to derive comparable EC_x estimates for this oliogochaete (after conversion to units of ug/l) to establish if this was a more sensitive indicator of aquatic ecosystem sensitivity; however this aspect was not progressed because of resource constraints.

4.4.6 Considerations On the Use of Single Species-based Impact Assessments

The interpretation of this type of impact estimate requires great caution given the high degree of scientific uncertainty as to the ecological relevance of single-species EC_x values. In particular, estimates that are based on a single species for which suitable data are available may not be particularly representative of risk to the ecosystem. The difference in predictivity that may be anticipated between SSD and single species approaches can be illustrated by reference to the scale of the assessment factor applied in risk assessment when deriving PNEC values according to TGD-R10. An assessment factor of up to 5 is considered sufficient for a fully-compliant SSD but a value of between 10 and 1000 may be appropriate for single species estimates (depending on study duration and the strength of evidence). The difference in sensitivity is further demonstrated in this example by comparing the derived EC_1 value of 3.1 μg/l with the HC_5 of >0.43 μg/l from the SSD-based approach (see above).

4.4.7 Use of Mammalian Dose-response Data to Estimate Secondary Poisoning Impacts

As previously discussed, for HBCDD there is evidence of abiotic contamination and biotic accumulation extending to remote geographical regions, such as the North Polar area. This has given rise to concerns that accumulation may lead to toxic levels being attained in marine predatory birds and mammals. The possible estimation of impacts in bird species has previously been discounted (see above) however the potential consequences in marine predators warrant further consideration.

Although the top Arctic predator, the polar bear, appears able to metabolise HBCDD substance and therefore avoid biomagnifications, it is important to note that the polar bear is regarded as a 'flag-ship' species so it would be of particular importance if HBDCC were to adversely affect the reproductive capacity of its prey species. The ringed seal (*Pusa hispida*) accounts for about 80% of the bears' diet (with 8-44% of seal pup production lost to bear predation); other prey include bearded seal, harp seals, spotted seals, hooded seals, walrus, beluga whales and narwhals (Smith, 1991; Thiemann et al, 2008). Given the critical importance of the ringed seal to the bear's diet, the case study therefore focused on the possibility of HBCDD causing adverse effects on ringed seal populations (further background information on ringed seals is given in Box A2-4.1).

Box A2-4.1. The Ringed Seal

The ringed seal (*Pusa hispida*) has a circumpolar Arctic distribution and comprises 5 subspecies: *P. h. hispida*, Arctic Ringed Seal; *P. h. botnica*, Baltic Sea Ringed Seal; *P. h. ladogensis*, Lake Ladoga Ringed Seal; *P. h. saimensis*, Lake Saimaa Ringed Seal, and *P. h. ochotensis*, Sea of Okhotsk Ringed Se (IUCN, 2010). Although the global population was estimated at about 2.3-7 million in the late 1980's, the current population is uncertain (Krafft, 2005). However, about 5500 *P.h.botnica* are thought to occur in the northern and central Baltic (Seal Conservation Society, undated). It is a small seal (50-90 kg in weight, averaging about 70 kg in adults of either sex) and

reaches sexual maturity by around 5-7 years, possibly living to 45 years of age. It is an opportunist feeder consuming various fish species as well as amphipods, decapods and squid, and generally reproduces annually. Although a high ovulation rate (about 86%) is found for reproductively active females, there are reports that there may significant variation in the numbers progressing to normal pregnancy (28% according to Helle, 1980 while other suggest yearly variations of 42.9% to 100%). A single pup is normally born weighing about 4.5 kg. In Norway, birth occurs in April and is followed by a 40 day lactation period during which the mother loses about 27% of bodyweight. This is the period when young are at particular risk from polar bears and other predators (Krafft, 2005).

Regional ringed seal production rates show great variability since this is highly dependent on factors including: level of predation; food availability; stability of ice; and amount of snow accumulation at time of breeding (IUCN, 2010). Nonetheless, the estimated proportion of young-of-the-year (YOY) is unexpectedly low; yearly estimates were 4.1-23% for a population with pregnancy rates of 46.7-70.9% in the period 1991 to 2000 (Stirling, 2005). On this basis, it might be anticipated that a substance that results in a significant reduction in late pre-weaning viability could elicit a significant adverse impact on population sustainability.

Experimental study of mammalian reproductive function has provided evidence of several dose-related effects; many of the changes appear to have similar dose-response characteristics and, in some cases, share a common NOAEL.

Of the effects seen in rodents, reduction in ovarian primary follicle number is important since, in mammals, primordial follicles do not proliferate or grow. As a consequence, the primordial follicle population represents a female mammal's total reproductive potential. It is therefore possible, based largely on human evidence (Wallace and Kelsey, 2004; Zaidi et al, 2007), that a reduction in follicle number could bring forward an individual's time of reproductive senescence. Depending on the life-cycle of the species, this might result in adverse demographic consequences. There is however insufficient information on ovarian function in the seal to progress this aspect.

Effects in rodents on fertility index and Day 21 pup viability also both point to a potential reduction in the ability of dams exposed to HBCDD to produce viable young and their capacity to rear offspring to a stage of independence. This could have adverse implications on the sustainability of populations depending on a species' reproductive strategy. Importantly, an effect on the overall viability index of the offspring could have important consequences on a species' reproduction capacity, particularly in species that bear only small numbers of young. Therefore, in this example, the possible scale of impact on offspring survival rate was investigated for the ringed seal using cross-species extrapolation of data from a rodent reproductive study, using allometric scaling.

Taking the rodent data on day 21 viability and extrapolating to the ringed seal (using the approach adopted by the TGD with regard to allometric extrapolation from

rodents to humans based on bodyweight) indicates a dose-response as set out in Table 4.10.

Table A2-4.10: Extrapolation of Dose-response Data on Offspring Viability in the Rat to the Ringed Seal				
HBCDD concentration in diet (ppm)	0	150	1,500	15,000
HBCDD dose in female rodent (mg/kg bw/day)	0	14	141	1363
Equivalent dose in ringed seal bear (mg/kg bw/day)	0	3.423	34.474	333.252
Day 21 viability index (F1 generation)	85.0	89.6	71.3	49.7
Notes: Source of rodent data was Ema et al (2008) Extrapolation of dose-equivalents to ringed seal based on a allometric scaling factor of 4.09, assuming bodyweight of 70 kg for a typical adult female seal and 0.250 kg for a rat (equivalent value for extrapolation from mouse data would be 7.274 assuming a bodyweight of 0.025 kg)				

To only take into account the 'additional' compound-related burden, the percentage of animals showing reproductive deficiency in the controls was subtracted from the incidence rates for each treated group. Since the control suffered up to 15% loss of offspring numbers, the 'additional' burden across study groups was thus modelled on basis of: values of 0, 0, 13.7 and 35.3 for seal equivalent doses of 0, 3.423, 34.474 and 333.252 mg/kg bw/day respectively.

Applying a Bench Mark Dose (BMD technique) using a US EPA model[16] approach to the data gave a BMD of 26.50 mg/kg bw/day and a $BMDL_{10}$ of 14.47 mg/kg bw/day for a logprobit model (extra risk). The model results are presented in Figure 4.8; this passed the goodness of fit test and has a p-value of 27%.

As discussed in Section 3.1.2, given the conflicting evidence on biomagnifiaction, it is not possible to estimate the extent to which this occurs between fish and seals more specifically than somewhere between about 2 and 60. Even so, using this range to highlight the degree of uncertainty, the extent of potential exposure of seals via their food chain could be explored if adequate data were available on likely changes in the level of HBCDD in fish in Arctic regions for the "no use" and "continued use" scenarios. Unfortunately, such information is not available and the dietary habits of the seal in relation to the daily quantity of fish eaten is also uncertain.

Nonetheless, on the basis of the current body burden estimate for ringed seals of 15-35 µg/ kg lwt (equating to whole weight values of approximately 5-11.7 µg/kg bw, based on a conversion factor of level in blubber/3' established for marine mammals in the RAR) and assuming this is a reasonably surrogate with which to compare to the BMD dose-response function (which is based on daily intake, it is of note that there is approximately a 1000-fold difference between the body burden and the BMDL value suggesting that an adverse impact on reproductive function appears unlikely.

[16] Benchmark Dose Software (BMDS) Version 2.1.2. Available at http://www.epa.gov/ncea/bmds/

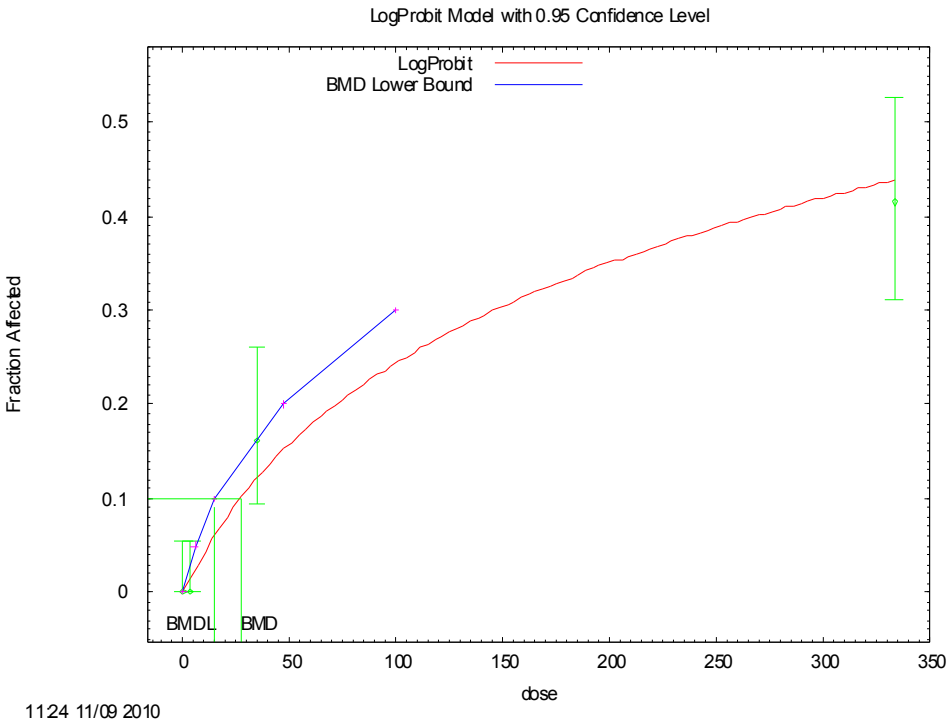

Figure A2-4.8: Ringed seal Dose Response Curve (LogProbit model)

There are, however, many uncertainties surrounding such a prediction. For example, the comparative metabolic capacities and toxic susceptibility of the species in question are uncertain as are the actual exposures experienced by seal mothers during the pre-natal period and by the cubs during the early post-natal period (when mothers are surviving/lactating using energy released from adipose stores). There is also a lack of knowledge as to the demographic parameters of this species, in particular what is the critical replacement level necessary for population sustainability.

To establish the impact of substances such as HBCDD on seal populations, the critical 'p' value (i.e. the survival rate for weaned seals) necessary for sustainability of populations would need to be established, and an estimate made of the extent to which this might be affected by chemical exposure. If these aspects were established, predictions could be made as to the sustainability of the ringed seal populations.

Although it had been hoped that it might be possible to use the LCIA models to generate exposure estimates for this case study, current LCIA models – even the LCIA model that includes HBCDD in its substance dataset –are designed to consider whole economies (rather than point sources causing impacts on e.g. predators in the polar region) and are intended to be used as tools to compare the impact of numerous chemicals with respect to various midpoint and damage categories (e.g. Jolliet et al., 2004). Hence, a single modelling framework for assessing the exposure and related impacts of predators by following the whole food chain through the environment in a spatially explicit and dynamic way is not available using LCIA as of now. However, ideas from LCIA could be of use to establish such a framework in the near future.

4.5 Step 3d: Summary of Results and Assessment of Potential for Valuation

Table **A2-4.11** provides a summary of the results of the assessment carried out above as part of Step 3.

Of the estimations attempted in Step 3 of the case study, that relating to the use of contaminated sludge on land (Step 3b) was successfully progressed through to establishing the frequency of application at which accumulation of HBCDD to toxic levels would be anticipated. This exercise provides valuable information to policy makers on the context in which this source of exposure could become of concern. Had this been found to be within a pattern of use common within agriculture, then the potential economic implications of restricting use of such sewage sludge could have been investigated as part of Step 4 of the framework.

Use of SSD-modelling and single species extrapolations and comparison of the resultant dose-response curves with estimates of environmental exposure patterns in the relevant compartment (in this case European rivers) successfully allowed the prediction of the percentages of rivers that might show an adverse impact on river quality. However, the exercise also demonstrated the sensitivity of the method to the dose-response assumptions made and the definition of a 'critical effect' criterion. In determining the scale of rivers impacted, the need for representative estimates of 'real world' exposure patterns was also highlighted. Thus, in this case, the predicted scale of impact on rivers affected in Europe varied markedly, from approx 20% of all rivers to <1% for other more-specific scenarios investigated. This high level of uncertainty and problems in interpreting these outputs in terms of impacts on ecosystems lead to a decision not to progress this aspect of the assessment to Step 4 (valuation) (see also Table A2-4.11). Nonetheless, in some circumstances, estimates of the likelihood of the extent of risk based on toxicity may act as an acceptable surrogate indicator of impacts. As noted elsewhere, other potential surrogate indicators might draw upon consideration of bioavailability, persistence or trends in usage.

Estimates were also derived for the potential implications of draft environmental quality standards, in terms of the proportion of rivers that would exceed the proposed quality standards, using the SSD approach and a LCIA model.

The impact on the reproductive success of ringed seal could also not be fully progressed because of limitations in data availability including, critically, a lack of basic scientific information on the species. Nonetheless, a simple comparison of the dose-response function established using a BMD-approach and the known body burdens of the seal indicate that it is unlikely that there are any quantifiable impacts on this critical reproductive endpoint at current exposures. It should be noted, however, that data from only one of several rodent reproductive effects was suitable for extrapolation. Hence, other adverse impacts through other pathways cannot be discounted.

Similarly, the use of cross-species extrapolation from rodent to the species of particular concern, the ringed seal, successfully allowed the generation of a dose-

response function applicable to an important reproductive parameter of direct relevance to the sustainability of the seal. Again, however, a lack of basic scientific knowledge on food-web patterns and population biology for the species, precluded the derivation of a robust impact assessment in this example.

Table A2-4.11: Summary of Considerations in Step 3 and Possibility for Progression to Step 4			
Step	**Nature of Data Considered**		**Finding and Implications for Step 3**
Step 3b – Use of physical indicators	Risk from contamination of sludge	Analysis of consequences of spreading HBCDD-contaminated sludge to land, using decay rate modelling	Build-up of HBCDD in soils only a risk if sludge applied 3 or more times a year. f
	Other environmental transport concerns	Use of LCIA	Current stage of LCIA development precluded progression
Step 3c – Dose-response modelling	Impact on aquatic ecosystem	Estimate proportion of European rivers exceeding a HC5 estimate, based on SSD using expanded SSD dataset for aquatic species	Illustrative 'worst case' estimate of 19.30% of European rivers exceed HC_5 value of >0.43 µg/l
		Impact on ecosystems at production site and from backcoating use in textiles, based on SSD using combined aquatic and sedimentary species datasets	Estimate of 0.04% of species affected at production site, and range of 0.04-86.85% of species at backcoating facilities Of the 4 specific (and one generic) backcoating sites considered, 2 appear to exceed the HC5 estimate of 0.52 µg/l
		Estimation of proportion of European rivers exceeding a EC_{10} value estimate using dose-response data from one species	Use of EC_1 values of 3.7-3.9 µg/l, gives estimate of 0.3-0.5% of rivers at risk of exceedence
	Impact on marine predators (seals)	Extrapolation from rodent reproductive data to ringed seal using BMD modelling and allometric scaling	BMD of 26.50 mg/kg bw/day and a $BMDL_{10}$ of 14.47 mg/kg bw/day established for extra risk of offspring survival to weaning. Compared with current estimate of HBCDD levels in ringed seals of 15-35 µg/ kg lwt (or 5-11.7 µg/kg bw whole weight), shows about 1,000-fold safety factor, suggesting adverse effect unlikely to occur
Step 3d – Potential for evaluation	Contamination of sludge		No impact found hence no valuation (Step 4) appropriate. However, if concern had been identified then Step 4 processes could have been applied to outputs from Step 3
	Impact on aquatic ecosystem		Worst-case scenarios suggested effects of up to 20% of rivers affected but other scenarios suggest impact at <1%. Inadequate information on exposure levels in rivers across Europe to allow generation of robust estimates of scale of impact, suitable for use in Step 4
	Impact on marine predators (seals)		No reproductive impact established for marine predator considered at current level. Hence no valuation (Step 4) necessary

5. LOGIC FRAMEWORK - STEP 4: VALUATION OF IMPACTS

5.1 Summary of Impacts

The previous Steps have identified concerns relating to the physicochemical properties of HBCDD and its potential for causing aquatic and marine (including sediment) toxic effects, as well as for terrestrial toxicity. Risk of secondary poisoning developing through food chain bioaccumulation was also identified.

The potential risks associated with the persistence HBCDD were considered in relation to the terrestrial environment and the spreading of contaminated sludge and with respect to the risk to higher predators (particularly in aquatic environments) from HBCDD's reproductive toxic and bioaccumulative potential. The potential risks that might arise from the presence of HBCDD in sewage sludge from STP works associated with industrial sites using HBCDD (particularly those associated with the textile backcoating industry) were modelled but found not to present a significant concern.

The risk associated with the fresh water toxicity of HBCDD was also subject to modelling using SSD and single-species approaches and the dose-response functions developed compared with probabilistic estimates of levels of HBCDD in European rivers. Although the data supporting the modelling of river concentrations were considered unsuited for full quantification of impacts (because the exposure dataset related only to sites associated with industrial emissions of HBCDD), the estimates of rivers potentially at risk (up to around <20%) were nonetheless considered of value as a surrogate descriptor of impact for this compartment. This analysis found that potentially 19% of EU rivers may face hazardous concentrations at which more than 5% of species may be affected. [Comparisons with draft values suggested in the draft EQS document currently under consideration by the Commission were also made using this and a LCIA based approach; these identified that there might be future issues with regard to establishing a secondary poisoning standard and also demonstrated that the LCIA model outcome was strongly influenced by the choice of bioaccumulation factor].

Concerns for higher predators relating to impairment of reproductive performance, were confirmed in Step 2. The principal risk is that HBCDD might show bioaccumulation through aquatic food chains including transport to remote sensitive areas such as the Arctic regions, to an extent that reproductive success of predators might be adversely affected. Although data indicated that the highest Arctic predator, the Polar Bear, was not at particular risk because of its metabolic capacity, concerns were identified but could not be quantified for lower predators such as the ringed seal and several avian species.

Experimental evidence suitable for detailed modelling was available for mammalian species, allowing exploration of the possible impact in the ringed seal. The database on avian species was, however, insufficient for even semi-quantitative impact estimation on these important species. Use of cross-species extrapolation from rodents to ringed seals allowed development of a dose-response function for an

important reproductive parameter of direct relevance to sustainability. However, a lack of basic scientific knowledge on food-web patterns and population biology in this species precluded estimation of ecological impact in our example.

Thus, in summary, the potential impacts on the environment from the continued use of HBCDD considered relate to (see also Table 3.3 and 3.10):

- toxicity effects to aquatic species (algae, fish and invertebrates) through exposure to HBCDD via sediment;

- toxicity effects to higher trophic levels including fish, mammals and birds through exposures via the food chain (i.e. through biomagnification), with this including the potential for reproductive impairment in marine predators; and

- exposure of biota via sediment and food chains to HBCDD due to its persistence and bioaccumulation potential.

Of these, three aspect were progressed - with varying success - to Step 3, implications for the use of sludge contaminated with HBCDD on land (using physical indicators); estimation of the proportion of European rivers suffering a fall in quality (based on comparison of SSD or single-species dose-response data and exposure estimates) and impacts on marine predator species (by applying cross-species extrapolation of rodent data to the reproductive outcome for ringed seals). These effects may also reflect different types of vulnerability within the context of ecosystem services, with these relating to:

a) potential impacts on fisheries and food species;

b) potential impacts on lifecycle maintenance with regard to food chain effects, habitat maintenance (in terms of ecosystem support) and impacts on fish nursery populations; and

c) the possible impacts in relation to the health (including loss) of populations of species important for symbolic reasons or for ecotourism purposes, and possible impacts on the quality of recreational fisheries.

The logic framework defines 4 possible steps for achieving valuation of impact:

i) Step 4a: Development of market based estimates;
ii) Step 4b: Application of transferable willingness to pay estimates;
iii) Step 4c: Review of revealed preferences literature;
iv) Step 4d: Aggregation of valuations and check for double-counting.

Had it had been possible to generate outputs from the consideration of the above risks that were identified, it may have been feasible to also put an economic value on the environmental impact, for example based on loss of river quality or fisheries status. Although this was not possible because of limitations in data and scientific

knowledge, it is useful to consider below what types of valuation approaches might have been applicable.

We start this discussion by looking at fisheries as a food species, and then look at the potential valuation of changes in ecosystem quality in terms of 'lifecycle maintenance' and food chain effects. We finish by considering the potential valuation of impacts on the ringed seal, including consideration of the potential implications for the top Arctic predator, the polar bear which is a symbolic species. For this species particular focus is also given to ecotourism.

5.2 Fisheries Production

HBCDD has been found to bioaccumulate in fish, with elevated concentrations found in a range of species and in a range of locations. For example, Gerecke et al, (2008)[17] report elevated concentrations of HBCDD in fish from Swiss mountain lakes, plateau lakes and rivers heavily impacted by waste water discharges, and provide a comparison of these concentrations against those for other European and North American waters.

A multi-national study on extrinsic drivers into fisheries management (Frid et al, 2006)[18] examined the impact that pollution in the Baltic has had on stock recruitment for a range of different fish species. HBCDD concentrations were one of the anthropogenic drivers considered in the analysis (together with PCBs, mercury, total nitrogen and total phosphates).

The assumption underlying the analysis is that the enclosed nature of the Baltic Sea means that species within it may be more liable to demonstrate impacts from chemical contaminants than the species resident in open, oceanic regions. Running an analysis of pollutants against the pelagic species in the Baltic (i.e. sprat and herring) would allow inferences to be drawn about the species found in the more open, oceanic regions (e.g. herring in the North Atlantic region). The results of the analysis, however, suggested that no relationship with species' stock dynamics appeared to exist in the Baltic region. The authors go on to suggest that from this it could also be "cautiously inferred that toxins do not affect industrial and pelagic species in the other regions (e.g. North Sea and North Atlantic waters)" (Frid et al, 2006).

Note that similar analyses were run for cod and flounder, with no significant relationships found. Given the above, the authors conclude that there would appear to be no economic impact from current HBCDD concentrations in fish on the value of key commercial fisheries.

[17] Gerecke et al (2008): Brominated Flame Retardants – Endocrine-Disrupting Chemicals in the Swiss Environment, Chimia 62, 352-357.

[18] Frid et al (2006): The role of anthropogenic and non-anthropogenic forcing factors on the biology of exploited species. WP1 Deliverable: Incorporating extrinsic drivers into fisheries management, Contract No. FP6-022710.

However, a study by Lower & Moore (2007)[19] concluded that exposure to HBCDD appeared to disrupt plasma thyroid hormone levels as well as olfactory functions, with this possibly having impacts on marine survival and the successful homing of adult salmon.

5.3 Valuation of Lifecycle Maintenance Using SSD or Single Species Extrapolation Techniques

Generally, freshwater ecosystems are known to offer a number of different ecosystem services, which include not only the human use-related ones (such as food provision through aquaculture, or enjoyment through recreational fisheries), but also lifecycle maintenance, habitat provision and protection, gene pool protection, biological control, etc. (see Table 3.3 in the environment logic framework).

As noted in Section 4.4, the percentage of rivers where 5% of species could be affected could be up to around 20%. However, this estimate is based on SSD modelling using a 'worst case' scenario. Other SSD modelled estimates using less conservative assumptions place the impact at around 5% while use of a single species approach gave a very low (<1%) estimate of impact.

As indicated above, interpretation of such estimates is extremely difficult if not impossible at this time. This reflects the limited state of current scientific understanding on ecosystem behaviour, in particular because the proportion of species in any given ecosystem that can be adversely impacted without there being a significant challenge in the ecosystem's sustainability is not known. Furthermore, the methods used here do not provide sufficient information on what particular species would be adversely affected and to what extent such an impact would result in ecological consequences.

For valuation to be carried out using the data generated through Step 3, linkages would need to be made to existing valuation studies regarding the health of the aquatic environment, for example. There are potential data sources for this via the AquaMoney Project and the willingness to pay studies carried out in the various case study countries. These provide an indication of individuals' or households' willingness to pay for surface water quality improvements equating to changes from 'poor' to 'good' or 'moderate' to 'good' or 'very good' as determined by Water Framework Directive standards covering chemical and biological quality.

Although some of the studies would appear to produce converging valuations for improvements in ecological quality, this is clearly measured in different terms than the data generated through Step 3. In addition, the outputs of the studies are either for specific water bodies or regions, and it is not clear how reliably they could be

[19] Lower, N and Moore, A (2007): The impact of a brominated flame retardant on smoltification and olfactory function in Atlantic salmon smolts. Marine and Freshwater Behaviour and Physiology, 40(4), pp 267-284.

transferred to all water bodies across the EU. The studies are also general in the sense that the reflect a combination of pressures rather than a single pressure such as HBCDD.

5.4 Valuation of Potential Symbolic Effects through Impacts on Marine Predators

As discussed above, it is not possible based on available data and methods to establish a meaningful estimate of the potential scale of the reproductive effect of HBCDD on any of the marine predators considered.

However, in the case of the ringed seal, one can gain some insight as to its economic value. Also, given its key role as the major prey source of the polar bear, a decline in seal numbers due to chemical toxicity would be expected to have secondary consequences for polar bear population sustainability.

Ringed Seal

The circumpolar Arctic distribution of ringed seals has led to their harvest in many northern territories including Canada, Greenland, Russia and Norway for hundreds or possibly thousands of years (NAMMCO, undated). The ringed seal has traditionally been used by Inuit peoples for food, fuel and clothing and newly moulted ringed seal pups are often hunted by fur traders for their pelts. IUCN (2010) states that they are a "*fundamental subsistence food item for most coastally dwelling northern peoples*". Ringed seals also provide a range of other, newer products, such as omega-3 fatty acids, protein concentrate and other fatty acids used as or within health food supplements (Canadian Governement, 2008a). The economic value of this species has been recognised as particularly important within the Canadian Central and East Arctic region, where their harvest has the potential to account for up to 71% of utilisable biomass and 54% of harvest related cash income (Notzke 1994, citing Wenzel, 1986).

In the Nunavut province of Canada, the heart of Inuit territory, the food value of ringed seals is estimated at Can$5 million and the associated value-added products are estimated as Can$1.5 million by the Canadian Government (2008b). The Canadian Government (1999) had previously derived a higher figure, stating that the replacement food value of ringed seals in Nunavut was estimated to be as high as Can$10 million and the skins from the seal used in arts and crafts also have a value of Can$1 million.

Seal skin exports contribute to about 5% of the Canadian fur industry, which in 2001 was valued at Can$335 million, thus giving seal skin exports an economic value of Can$16.75 million in this year (Industry Canada, 2001). The proportion of these exports which were ringed sealskins is unknown. However, in 2010 the average value of a ringed seal pelt (from approximately 2000 pelts sold in a Canadian auction) was Can$19.54 (NNSL, 2010).

In Europe, Norway is the only country which still hunts ringed seals commercially. The Norwegian Polar Institute (2008) states that the numbers of ringed seals taken annually are "quite low" (giving no precise figure), but adds that "Their hides have been an important item for making clothing and other household items and have at various times been an important source of cash income for people in the Far North".

In addition to the value of the ringed seal in the context of the ecosystem services it provides, willingness to pay estimates would also be relevant in providing an indication of their symbolic and wider nature conservation importance to people. A review of the academic literature identified no specific studies with regards to ringed seals, although there are willingness to pay values for similar seal species, which may be of relevance. These values are summarised within Table 5.1 (along with values for some other threatened, endangered and rare species). These values should be interpreted with caution as they are based on an extinction scenario (avoiding 100% loss), and thus they are likely to be an overestimate in the context of a potentially declining population, which may be associated in part with HBCDD. Within the context of this case study, a more accurate willingness to pay value may be that derived in a study by Kaval et al (2007), which reports a WTP value of €30.92 (lump sum) for the conservation of monk seals in Greece.

Polar Bears

In terms of symbolic values, the polar bear is highly valued by the Inuit (Wenzel, 2004). The tourism related value in terms of commercial sports hunting and more generally has also been examined by Heinzerling (2008). However, neither author established clear estimates suitable for use in comparative economic evaluations.

Symon et al (2005) estimated the economic value of hunting 500-600 polar bears each year in Canada to be of the order of $1,000,000 (i.e. $1,667-2,000$1667-2000 per animal). However, Dowsley (2010) noted that the value of a sports hunt for a polar bear was somewhat greater at $19,000, approximately 20 times that associated with a subsistence hunt by Inuit; and Freeman and Wenzel (2006) reported that the economic benefits totalled an estimated $814,000/year to the local community from sports hunting of polar bears in North America.

An alternative approach to valuing polar bears might be based on their perceived monetary value in terms of the costs that society may be willing to bear in order to safeguard the habitat of a species from non-chemical threats. In this respect, a recent economic analysis has considered potential direct and indirect costs that could arise if a proposal by the US Fish & Wildlife Service in 2008 to establish a critical habitat designation for 200,541 square miles of territory in the USA was to proceed. The intention of the US Fish & Wildlife Service proposal is to ensure polar bear population sustainability in North America by protecting their environment. Various scenarios and associated costs to the State of Alaska were considered. Of these, the impacts associated with a reduction in current oil production of $9.9 billion and a further cost of $98.9 million per year associated with delays in developing new oil production, are of particular note.

The size of the US population of polar bears is highly uncertain but appears unlikely to comprise more than 4000 individuals (US Fish & Wildlife Service, 2009). The above estimates of the potential cost to safeguarding the habitat of the species could therefore be expressed per bear. Based on the above, the cost would be around $2,475,000 (from loss of current oil production) and a further $24,725 (from delays in new oil production) per bear to the State of Alaska.

General Considerations

Some of the other species in which HBCDD has been found can be described as "charismatic" species. Richardson & Loomis (2008)[20] provide an updated meta-analysis of studies carried out using the contingent valuation method to place an economic value on threatened, endangered and rare species. This research examines the potential for developing a benefit transfer model by comparing studies carried out prior to 1995 and those carried out after 1995.

Willingness to pay values developed using contingent valuation surveys are given for a range of relevant species, with the average economic value reported in Table A2-5.1. In total 31 studies were identified, with all of these being US based. It is important to note that all of the studies are US based, with this limiting the degree to which the resulting valuations are likely to be validly transferred to the EU situation.

Table A2-5.1: Summary of Average Economic Value per Household of Threatened Endangered and Rare Species (US $2006)

Species	Size of Change	Low Value	High Value	Average of All Studies
Studies reporting annual WTP				
Dolphin	Avoid 100% loss			$36
Gray whale	50% to 100% gain	$24	$46	$35
Sea lion	Avoid 100% loss			$71
Seal	Avoid 100% loss			$35
Studies reporting lump sum WTP				
Arctic grayling	33% improvement in habitat	$20	$26	$23
Peregrine Falcon	87.5% gain			$32
Humpback whale	Avoid 100% loss			$240
Monk seal	Avoid 100% loss			$166

More importantly in the context of this case study is an understanding of what changes were being valued. As can be seen from Table 5.1, several of the estimates relate to prevention of a 100% loss of a species from a particular habitat. Where this was the case, it limits the degree to which the study is relevant to valuing the protection of a species from exposure to and bioaccumulation of a chemical such as HBCDD. As HBCDD is not currently found at concentrations within the different species leading to losses, the original valuation scenarios are not directly applicable.

[20] Richardson, L and Loomis, J (2009): The total economic value of threatened, endangered and rare species: An updated meta-analysis. Ecological Economics, 68, 1535-1548.

If HBCDD concentrations could be linked to some level of species loss, it would be important to consider what other chemical, climatic and habitat related pressures may also be leading to losses in order to consider the relevant proportion of willingness to pay that could be allocated to removing the influence of HBCDD alone.

Various EU studies have also been carried out which have derived valuations for protection of different species, but these have generally been related to protection of habitats or increasing the level of habitats available[21]. Again, they do not relate to chemical exposures; the one key exception to this would be a study carried out into people's willingness to pay an increase in the price of a loaf of bread to reduce the impacts on farmland bird populations of pesticides applied to wheat crops in the UK. Use of the outputs of this study in a more general hazardous chemicals context would be difficult given the specific nature of the policy issue being addressed and the payment vehicle adopted.

5.5 Summary of Step 4 – Valuation of Environmental Impacts

Although a number of impact estimates were generated in Step 3, none of these were judged to be sufficiently robust (because of data limitations, gaps in current scientific understanding and the degree of uncertainty) to warrant progression to Step 4. Nonetheless, the considerations above have indicated that there exist methodologies and data on the valuation of environmentally relevant aspects that may be suitable for use in developing valuations of environmental impact where adequate estimates of impact can be generated.

[21] For example, there have been European studies deriving willingness to pay values for improving or providing habitats to support red squirrel, otters, voles, badgers (UK), the griffon vulture (Israel), amongst others.

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