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

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Final Report

Part 1: Literature Review and Recommendations

Prepared for
DG Environment

RPA

Imperial College London

Universität Stuttgart

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Assessing the Health and Environmental Impacts in the Context of Socio-Economic Analysis under REACH

Final Report – March 2011

Part 1: Literature Review and Workshop Discussions

prepared for

European Commission

Directorate-General Environment

by

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ACRONYMS

ADME	Absorbtion, Distribution (within the body), Metabolism and Excretion (i.e. the toxicokinetic behaviour of the substance in the body)
AEP	Aquatic Ecotoxicity Potential
AF	Assessment Factor or Attributable Fraction depending upon context (i.e. in relation to risk assessment or epidemiology, respectively)
AN	Attributable Number (epidemiological term denoting number of additional cases of a condition due to exposure to an agent)
AR	Attributable Risk (epidemiological term denoting difference in rate of a condition between an exposed and an unexposed population)
BMD	Benchmark Dose
C&L	Classification and Labelling
CBA	Cost Benefit Analysis
CBVI	Comparative Biological Value Index
CEA	Cost Effectiveness Analysis
CLP	Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures
CMR	Carcinogenic, Mutagenic or toxic to Reproduction
CNS	Central Nervous System
COI	Cost of Illness
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
CSTEE	European Union Scientific Committee on Toxicity, Ecotoxicity and the Environment
CUA	Cost Utility Analysis
CVM	Contingent Valuation Method
Cw	Estimated environmental water concentration
DALY	Disability Adjusted Life Years
DCM	Dichloromethane
DIY	Do-It-Yourself
DMEL	Derived Minimum Effect Level
DNA	Deoxyribonucleic Acid
DNEL	Derived No Effect Level
DSD	Dangerous Substances Directive 67/548/EEC
ECHA	European Chemicals Agency
EC	European Commission
$EC(L)_{10}$	Effective concentration 10 is the exposure concentration (level) required to produce a specified effect in 10% of a sample population
$EC(L)_{50}$	Effective concentration 50 is the exposure concentration (level) required to produce a specified effect in 50% of a sample population
ECVAM	European Centre for the Validation of Alternative Methods

ED_{10}	Effective dose that is anticipated as equating to a 10% response over background
EFTA	European Free Trade Association
EPA	Environmental Protection Agency, USA
EQC	Environmental Quality Criterion
ES	Exposure Scenario
ESPREME	Eu 6^{TH} Framework Project intended to estimat willingness-to-pay to reduce risks of exposure to heavy metals and to provide cost-benefit analysis for reducing heavy metals occurrence in Europe
ESR	Existing Substances Regulation (EEC) No 793/93
ETUI	European Trade Union Institute
EU	European Union
FA	Fraction Affected
GDP	Gross Domestic Product
GIS	Geographic Information System
GM	Genetically Modified
GMO	Genetically Modified Organism
HC_5	Hazardous Concentration to 5% of the species within an ecosystem (may be based upon the 5^{th} percentile of the SSD (median HC5) or the lower 90% confidence bound for it (lower limit HC_5)
HELI	Health and Environmental Linkages Initiative of the WHO-UNEP to promote and facilitate action in developing countries to reduce environmental threats to human health, in support of sustainable development objectives.
HLY	Healthy Life Years
HTP	Human Toxicity Potential
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IQ	Intelligence Quotient
IUCLID	International Uniform Chemical Information Database
JEL	Job Exposure Matrix
LC_{50}	Lethal Concentration of a chemical which kills 50% of a sample population
LCA	Life Cycle Analysis - a methodological tool that applies life cycle thinking in an quantitative way on environmental analysis of activities related to processes or products (goods and services)
LCIA	Life Cycle Impact Assessment - the phase of an LCA where inventory data on inputs and outputs are translated into indicators about the product system's potential impact on the environment, human health and availability of natural resources.
LD_{50}	Lethal dose that kills 50% of a sample population
LLNA	Local Lymph Node Assay (performed on mice)
MCA	Multi-Criteria Analysis
MPC	Maximum Permissible Concentration
MS	Member States (Generally used here in respect of members of the European Union)
NESCAUM	Northeast States for Coordinated Air Use Management - non profit organisation of

	six US States working on air pollution issues
N(L)OAEL	No (Lowest) Observable Adverse Effect Level
N(L)OEL	No (Lowest) Observable Effect Level
N(L)OEC	No (Lowest) Observed Adverse Effect Concentration
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit (different limits may be set for various time periods relevant to activities during a working day)
OR	Odds Ratio (a measure of effect derived as the ratio of the odds of an event occurring in one group to the odds in another group)
PAF	Potentially Affected Fraction (the fraction of species exposed to a concentration above their NOEC; suggested by some to be a more meaningful basis for comparison of ecotoxicological risks than the commonly used ratio of environmental concentration to no-effect concentration)
PBT	Persistent, Bioaccumulative and Toxic
PCB	Polychlorinated Biphenyl
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
POD	Point of Departure (the lower confidence bound on the lowest experimental dose that showed an effect)
QALY	Quality Adjusted Life Years
(Q)SAR	(Quantitative) Structure-Activity Relationship
RAC	Risk Assessment Committee - The Committee for Risk Assessment of the European Chemicals Agency
RAR	Risk Assessment Report
RCR	Risk Characterisation Ratio – Ratio of predicted or known concentration versus the DNEL, DMEL or PNEC
REACH	Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
REP	Risk Exposure Period
RR	Relative Risk (or Relative Risk ratio) – The risk of an event (or of developing a disease) relative to exposure; it is the ratio of the probability of the event occurring in the exposed group versus a non-exposed group
SAR	Structure-Activity Relationship (the relationship between a chemical or 3-dimensional structure of the molecule and its biological activity)
SCOEL	European Commission's Scientific Committee on Occupational Exposure Limits
SDS	Safety Data Sheet
SEA	Socio-Economic Analysis
SEAC	Committee for Socio-Economic Analysis of the European Chemicals Agency (Socio-Economic Assessment Committee)
SSD	Species Sensitivity Distribution (mathematical model used to combine dose-response data from multiple species to establish a concentration below which the fraction of species exposed above their no-effect level is considered acceptable (usually based on a 5% effect limit)
SVHC	Substance of Very High Concern (a substance which has been proposed for Authorisation of use within the European Union, because of its CMR or other

	hazardous properties)
TEF	Total Equivalency Factor (a measure of relative toxic potency compared with a 'standard' substance, widely used to indicate potency of single or complex mixtures for some chemical groups, such as doioxins)
TEQ	Total Equivalent (weights the toxicity of less toxic compounds as a fraction of that of the most toxic, e.g. used in relation to dioxins)
TGD	Technical Guidance Document (here generally used in connection with the Guidence Documents produced by ECHA)
TTC	Threshold of Toxicological Concern (a concept used to attempt to establish a level of exposure for a chemical(s) below which there is no appreciable risk, even in the absence of adequate toxicity data)
UF	Uncertainty Factor (used in risk assessment to account for the uncertianties implicit in extrapolating from the data available to other scenarios (e.g. from animal data to human populations)
vPvB	very Persistent and very Bioaccumulative (Terminology used in REACH to indicate a substance possess a certain (high) degree of environmental persistence and bioaccumulation potential)
VOC	Volatile Organic Compound (substances that possess high vapour pressures and hence likely to partition into air)
VOLY	Value of Statistical Life-years Lost
VOSL	Value of a Statistical Life
WTA	Willingness to Accept
WTP	Willingness to Pay
WHO	World Health Organisation
YLD	Years Lived with Disability
YLL	Years of Life Lost

1. INTRODUCTION

1.1 Background to the Study

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH[1]) Regulation (EC No 1907/2006) came into force on 1 June 2007. It aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances while at the same time enhancing the innovative capability and competitiveness of the EU chemicals industry. The regulation applies to all substances manufactured, placed on the market and used in the EU, either on their own, in preparations[2] or in articles, for those aspects which are not already covered by other EU regulations (e.g. manufactured plant protection products, which are covered by Council Directive 91/414/EEC of the European Commission (European Commission, 1991)).

Two titles within the regulation include provisions for the use of socio-economic analysis (SEA):

- authorisation which is aimed at progressively reducing the risks posed by Substances of Very High Concern (SVHC). The aim is to phase out the use of SVHCs wherever possible. The continued use of a SVHC may be Authorised where it is demonstrated that the socio-economic benefits of use outweigh the risks to human health and/or the environment and that there are no suitable alternatives (technologies or substances); and

- the restrictions procedure which can involve the placing of conditions or prohibitions on the manufacture, placing on the market or use of particular substances. In this case, authorities must demonstrate only a balance between costs to industry and the health and environmental benefits of risk reduction as well as provide a justification for the need for community wide action.

Guidance on undertaking socio-economic analysis for restrictions has been published by the European Chemicals Agency (ECHA, 2008a), with similar guidance for authorisations awaited. The Guidance highlights "the need for further development of methodologies for appropriately describing and assessing the changes to health and environmental impacts" of decisions relating to both authorisation and restrictions.

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 200/21/EC (REACH).

[2] REACH uses the terminology 'preparations' whereas the GHS system refers to 'mixtures'. We have used preparations in this proposal in order to be consistent with REACH.

1.2 Study Objectives

The overall aim of this contract is to provide scientific, economic and technical advice for the Commission in its preparatory work concerning regulatory decisions in the framework of REACH authorisations and restrictions which require the comparison of the impacts on health and the environment with other socio-economic impacts, such as the costs to businesses and consumers.

The contract is expected to:

- review and analyse gaps concerning existing methodologies which are applied or potentially applicable to chemical risk management and are relevant to identifying, quantifying and valuing the impacts on health and the environment in order to make them comparable with other socio-economic impacts;

- provide the Commission with general advice as to what should be covered in an assessment of health and environmental impacts in the context of socio-economic analysis under REACH;

- outline a logic framework for identification and assessment of health and environmental impacts and comparing them with other socio-economic impacts, including a discussion of the availability of information and appropriateness and proportionality of using different methodologies; and

- finally, to provide suggestions for a research agenda concerning socio-economic analysis in chemical risk management.

The study findings will also be shared with ECHA, to feed into any further development of relevant guidance documents, and with ECHA's Risk Assessment Committee (RAC) and Socio-economic Analysis Committee (SEAC), who may find it of value as background information when formulating their opinions in the future.

1.3 Study Approach

1.3.1 Overview

Our approach to the study comprises five main tasks:

- Task 1: Start-up meeting and scoping phase;
- Task 2: Experts Workshop;
- Task 3: Advice on health and environmental impact assessment and comparison of impacts;
- Task 4: Practical examples; and
- Task 5: Recommendations on the research agenda concerning socio-economic analysis in chemical risk management.

The Task 1 meeting was held with the Steering Group in January 2010. A number of important comments were made during the meeting that set the context for the rest of the study. Of most immediate concern are the key issues for the literature review, as this task is the focus of this report.

Firstly, from the Commission's perspective the focus of Task 2 should be on public health and the environment, with occupational health issues given lesser priority as these aspects are better understood. The study should also focus on the benefits of risk management, and the processes or methods that are being used to value changes in health and environmental risks and under what conditions quantitative assessments of impacts and valuation can be achieved. In terms of the environment, the identification of impacts should start with a focus on ecosystem services. A number of life-cycle assessment sources were also suggested for the literature review.

1.3.2 Approach to Task 1: Scoping and Literature Review

This report summarises our findings from the literature review. The requirements of the literature review have been wide-ranging. Previous conclusions regarding the need for the further development of SEA methodologies stem not only from issues surrounding the application of economic analysis, but also from the need to bridge the gap that can exist between the outputs of risk assessments and the data requirements of economic analysis.

This bridging requirement relates to the outputs of EU risk assessments, use of data on transport and fate of chemicals in the environment, data on environmental and human exposures, use of toxicologically and/or epidemiologically derived effect information for the estimation of risks, data on populations and subgroups at risk and on relevant valuations for changes in risk.

The project specification set out a comprehensive list of issues to be examined, with these including:

- steps in the identification of the health and environmental impacts of using a chemical of concern;
- availability and quality of emissions and exposure data;
- predicting the magnitude of health and environmental impacts and linkages between this and the chemical risk/safety assessment;
- appropriate economic valuation methods for identified impacts (including secondary impacts);
- specific issues relating to risk in socio-economic analysis relevant for the REACH processes;
- distribution of impacts to different parts of society, geographically (the influence of spatial explicitness) and temporally (short term vs. long term view); and
- typical uncertainties and ways to deal with them.

We also believed it important that the review considered how these issues vary across different types of health and environmental issues. In other words, the sources and availability of emissions and exposure data in relation to public health risks may be

very different from those for assessing environmental impacts. Similarly, different issues are likely to arise in assessing changes in human health risk as opposed to changes in environmental risks, and in particular risks related to different environmental media (air, water, soil, sediment, etc.) and via different exposure pathways.

1.3.3 Approach to Task 2: Experts Workshop

An experts' workshop, hosted by DG Environment, was held in May 2010. The details of the workshop programme, its format and the discussions are presented in Section 8 of this report.

1.3.4 Approach to Task 3 and 4: Advice on Health and Environmental Impact Assessment

Task 3 comprises the development of an integrated Logic Framework for undertaking the assessment of human health and environmental impacts within a SEA. 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.

While some work has been undertaken under Task 3 to develop the Logic Framework, as noted in the project proposal, development of this and the practical examples (case studies; Task 4) are the main focus of the remaining period of the study.

1.4 Organisation of this Report

As a result of the above, we have organised reporting on the above work into two parts.

Part 1 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 (Task 1) and the expert workshop (Task 2), together with a short summary of the research needs that have been identified throughout the study (Task 5).

Part 2 presents the proposed logic frameworks for both human health and the environment (Task 3), together with the two illustrative examples of the application of the logic frameworks using chemicals currently being considered for further risk management (Task 4).

This part of the report has been organised as follows:

- Section 2 presents a review of REACH requirements to establish the context for the study;

- Section 3 examines health risk assessment methods and issues, with environmental risk assessment methods and issues reviewed in Section 4. These sections include a discussion of the key hazard/risk indicators used in these fields and approaches to predicting impacts;

- Sections 5 provides a brief overview of approaches to exposure assessment for health and the environment, including the types of models used traditionally in chemical risk assessment and as part of Life Cycle Impact Assessment;

- Sections 6 and 7 then move on to the methodologies that could be and are used in SEA to assess human health and environmental benefits respectively. This discussion ends with some consideration of a logic framework in relation to health and the environment; and

- Section 8 presents a summary of the discussions arising from the expert workshop;

- Section 9 presents a summary of the progress made in the study to date, including those topic where additional research may be required in order to fully develop the potential of the logic frameworks. This section finishes by providing a summary of the next steps in the development of a logic framework.

The report draws information from a range of scientific disciplines as well as economic theory and therefore contains many technical terms as well as the wide use of acronyms; acronyms are detailed at the front of this report. It should also be noted that the technical language used in the REACH Regulation and associated guidance documents is in some instances highly specific, and may not necessarily always represent that applied to the same concept within other chemical regulatory systems or within the wider scientific literature. However, details of the specific steps, procedures and terminology under REACH are readily available in the extensive Guidance Documents published by ECHA.

2. REACH REQUIREMENTS, SEA METHODOLOGIES AND THE PRECAUTIONARY PRINCIPLE

2.1 General Requirements of REACH

REACH applies to all substances manufactured, imported, placed on the market or used in the EU, either on their own, in mixtures[3] or in articles. A purpose of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances while at the same time enhancing the innovative capability and competitiveness of the EU chemicals industry. This aim is to be achieved through provisions for:

- registration of all substances manufactured or imported in quantities greater than one tonne per year per company;
- movement of information throughout the supply chain;
- identification of Substances of Very High Concern (SVHCs), the use of which should be phased out or continue only under Authorisation; and
- restrictions on the marketing and use of substances.

The remainder of this section sets out the key REACH requirements of relevance to this study, the SEA methodologies identified in the ECHA Guidance for SEA and restrictions (ECHA, 2008a) and a discussion of the legal application of precautionary principle, given its relevance to the authorisation provisions of REACH.

2.2 Registration Requirements

2.2.1 The Registration Dossier

A registration dossier must be submitted to the ECHA for all substances manufactured or imported in quantities greater than one tonne per year per company. There are exemptions from some or all of the provisions of REACH for the substances described in Annex IV or Annex V or where the use of a substance is controlled by more specific legislation, as set out in Section 3.2. Furthermore, the registration requirements under REACH do not apply to substances manufactured or imported in quantities less than one tonne per year per company.

Details of the information to be included in a registration dossier are set out in Annexes VI to XI of REACH. Briefly, each dossier is to contain information regarding:

- identity of the substance, including of the purity of the substance and details of impurities and additives;

[3] REACH originally used the terminology 'preparations'. However, from 20 January 2009 Article 57(11) of regulation 1272/2008 on classification, labelling and packaging of substances and mixtures, required all references to 'preparation/s' in REACH to be replaced by 'mixture/s'.

- manufacture and use including details of uses advised against;
- classification and labelling (details of the relevance of classification and labelling legislation to the preparation of a SEA are considered in Section 3.1);
- guidance on safe use;
- information on exposure;
- physicochemical properties;
- toxicological information; and
- ecotoxicological information.

The level of information required on physicochemical properties, toxicological information and ecotoxicological information increases depending upon the quantity of the substance manufactured or imported by a company per year.

2.2.2 The Chemical Safety Assessment

A Chemical Safety Assessment (CSA) must be undertaken for any substance manufactured or imported by a company in quantities greater than 10 tonnes per year. A CSA must include a hazard assessment. Furthermore, exposure scenarios must be developed, exposure assessments undertaken and risk characterisations carried out as part of a CSA for all substances which meet the hazard classification criteria set out in the EU classification and labelling (C&L) legislation (See Section 3.2 for more details of C&L legislation). A CSA must also be carried out for all substances that meet the criteria for being Persistent, Bioaccumulative and Toxic (PBT) or very Persistent and very Bioaccumulative (vPvB) substances as set out in Annex XIII to REACH.

An overview of the CSA process contained in 'Guidance on Information Requirements and Chemical Safety Assessment' provided by ECHA, is shown in Figure 2.1.

Substances to be placed on the EU market for the first time at above 1 tonne per year must be registered first, and substances already on the market are being registered over a phase-in period which extends until 31 May 2018, as set out in Article 23 and summarised below:

- **30 November 2010**: All substances over 1,000 tonnes per year per company, substances over 1 tonne per year that are carcinogenic, mutagenic or toxic to reproduction (CMR) category 1 or 2 and substances over 100 tonnes per year that are classified as very toxic to aquatic organisms (R50/53)[4];
- **31 May 2013**: All substances over 100 tonnes per year per company; and
- **31 May 2018**: All substances over 1 tonne per year per company.

[4] Classifications in accordance with the Dangerous Substances Directive 67/548/EEC.

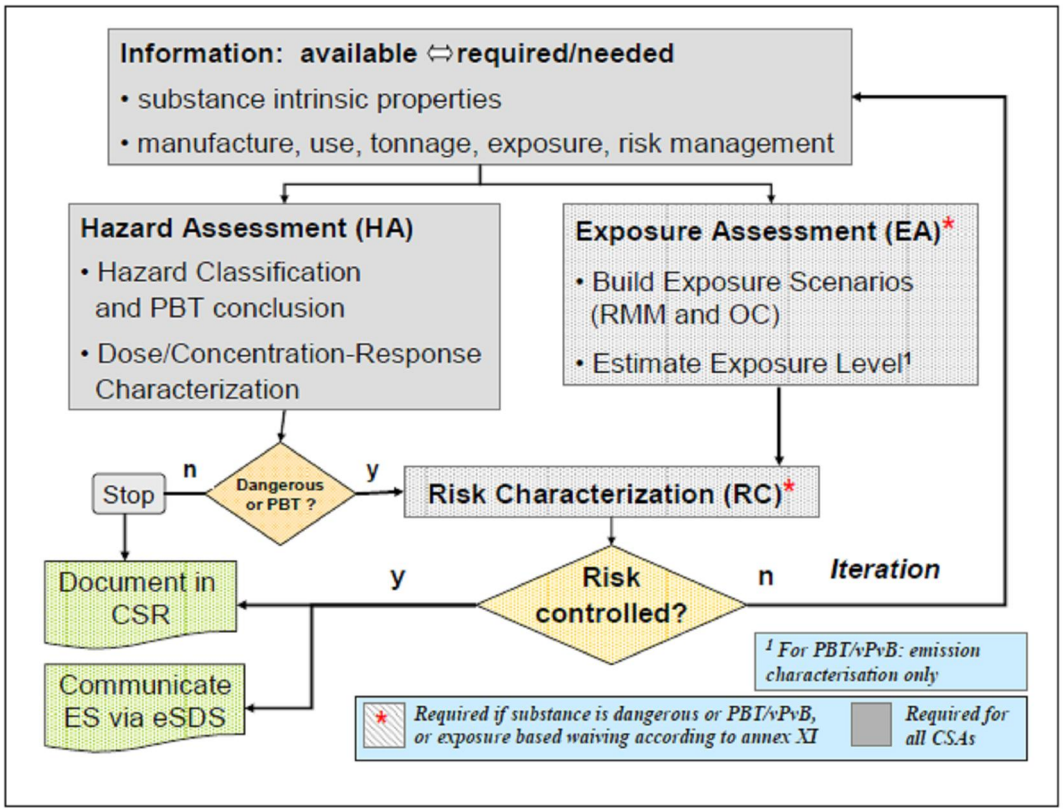

Figure 2.1: An Overview of the CSA Process

It is important to note that a substance may be subject to authorisation or restriction without that substance having been registered under REACH. It is possible therefore that information from a REACH registration dossier will not be available for an SEA. However, as some of the more hazardous and all of the high volume substances should be registered by 30 November 2010, it is likely that registration data will be available to support the preparation of restriction or authorisation dossiers.

The substance assessment must be documented in a Chemical Safety Report (CSR) for all substances manufactured or imported in quantities greater than ten tonnes per year per company.

2.3 Outputs from a REACH Registration

2.3.1 Summary

REACH requires registration dossiers to clearly identify the substance concerned and the dossiers should include a range of descriptive data (see also Annex VI of REACH) including: the name or other identifier of each substance; information related to molecular and structural formula of each substance; and the composition of each substance. Currently, any classification under the Dangerous Substances Directive 67/548/EEC (DSD) should be included in the registration dossier. However, from 1 December 2010, classification details must be according to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures (CLP).

Each registration dossier must include hazard information and a hazard assessment based on that information. The hazard information requirements are set out in Annexes VII to X to REACH, where the level of information required increases depending upon the quantity manufactured or imported:

- 1 tonne or more (Annex VII);
- 10 tonnes or more (Annex VIII);
- 100 tonnes or more (Annex IX); and
- 1,000 tonnes or more (Annex X).

Exposure data and details of risk management measures should included in exposure scenarios for each use of a substance. However, in many instances default values may be used with these corresponding to generic use conditions [as summarised for use and release descriptors in "Guidance on Information Requirements and Chemical Safety Assessment" Part D and Chapter R.12, published by ECHA (2008 b and c)].

The technical guidance on risk assessment under REACH is set out in "Guidance on Information Requirements and Chemical Safety Assessment"[5]. Importantly, all hazard and exposure estimates developed in support of a registration will have been based on the use of conservative safety factors (known as "assessment factors") and generally represent a 'worst case' estimate. The resultant risk assessments will therefore also be based upon precautionary assumptions.

REACH incorporates the principle of avoiding or minimising tests involving vertebrate animals wherever possible (for example, see recital 47 and Article 25). There are therefore options to avoid animal testing by applying exposure based waiving[6], grouping approaches, (quantitative) structure-activity relationships ((Q)SARs) and expert systems.

Exposure based waiving allows for test data to be omitted from a registration dossier where exposure scenario(s) show such data to be unnecessary for risk assessment or where exposure to a substance can be shown to be absent, unlikely, not relevant or not significant.

Grouping approaches, (quantitative) structure-activity relationships ((Q)SARs) and expert systems each estimate data for a substance based on data generated for other, similar substances. These approaches may be used to generate estimates of physicochemical, toxicological and ecotoxicological properties of a substance which may be used in place of test data or provide information to supplement test data. The development and application of these non-testing based methods for generating data is based on the principle that similar compounds should behave in similar ways and may be used to:

5 Available from the ECHA internet site: http://guidance.echa.europa.eu/guidance_en.htm.

6 Detailed guidance on the use of non-test methods is set out in "Guidance on information requirements and chemical safety assessment" Chapter R.6 to Chapter R7, available from the ECHA internet site: http://guidance.echa.europa.eu/guidance_en.htm.

- inform priority setting for risk assessment;
- guide the design of a test or testing strategy;
- inform the assessment of available test data; and
- fill data gaps for hazard and risk assessment, classification and labelling activities, and PBT or vPvB assessment.

Ideally, documentation accompanying 'non-test data' will be sufficient to demonstrate such data to be relevant, reliable and adequate for the purpose. However, there may be a great deal of uncertainty associated with non-test data that should be taken into account before it is used and when evaluating risk assessments undertaken using such data.

Where a registrant determines animal testing[7] to be necessary they must submit a testing proposal to ECHA who will publish the proposal for consultation before agreeing or disagreeing with the necessity of conducting such testing.

2.3.2 Outputs Relating to Human Health Hazards

Any human health hazard classification of a substance under DSD or CLP will give an indication of the human hazards that may form the focus of subsequent hazard and risk characterisation assessments. The human health hazard data that must be included in a registration dossier are set out in Table 2.1.

Table 2.1: Human Health Hazard Requirements, Units and Tonnage Thresholds

Properties	Units	Tonnage Threshold/s
Toxicological Information		
Skin irritation or skin corrosion	Grade, category or indication of severity	1 & 10
Eye irritation	Dose (e.g. ml or g), grade, category or indication of severity	1 & 10
Skin sensitisation	Dose (e.g. ml or g), incidence or category	1
Mutagenicity	Highly variable (in vivo and in vitro)	1 & 1,000
Acute toxicity	LD_{50}[8] (mg/kg, mg/m^3 or mg/m^2) or indication of DSD/CLP classification only	1 & 10
Repeated dose toxicity	N(L)OEL in terms of mg/kg body weight/ day, mg/ m^3 (inhalation), g/m^2 (dermal), ppm (diet) or mg/ml (water)	10, 100 & 1,000
Reproductive toxicity	As for repeated dose toxicity in terms of parental and developmental effects	10, 100 & 1,000

[7] Under REACH these provisions relate to the conduct of tests on vertebrate animals (see Guidance on Data Sharing, available at: http://guidance.echa.europa.eu/docs/guidance_document/data_sharing_en.pdf

[8] LD50 (Lethal Dose 50) is the dose which kills 50% of a sample population.

Table 2.1: Human Health Hazard Requirements, Units and Tonnage Thresholds		
Properties	**Units**	**Tonnage Threshold/s**
Toxicokinetics	Absorption in terms of mg/time, mg/ kg body weight/ time, mg/m2 surface area, rate or percentage. Distribution in terms of mg/ g tissue or mg/ ml blood Excretion - variable units including mg/ml of urine, mg/m^3 for exhaled substances, half-life in body	10
Carcinogenicity study	As for repeated dose toxicity	1,000

For all registration dossiers, the human health hazard data are assessed by the registrant to determine the dose or exposure level representing the point of departure (POD)[9]; this may be expressed variously by terms such as No (Lowest) Observed Adverse Effect Levels (N(L)OAELs), No (Lowest) Observed Adverse Effect Concentrations (N(L)OAECs) and/or Derived Benchmark Dose (BMD) (see also Section 3 to this report). Comparisons of these dose descriptors (across study types and endpoints) are applied to determine the critical (key) toxic endpoint(s) of concern. Key endpoints are further developed through use of uncertainty/safety factors (known as "assessment factors" under REACH) to derive a dose which is considered to be safe, expressed as a Derived No Effect Level (DNEL), as set out in Figure 2.2.

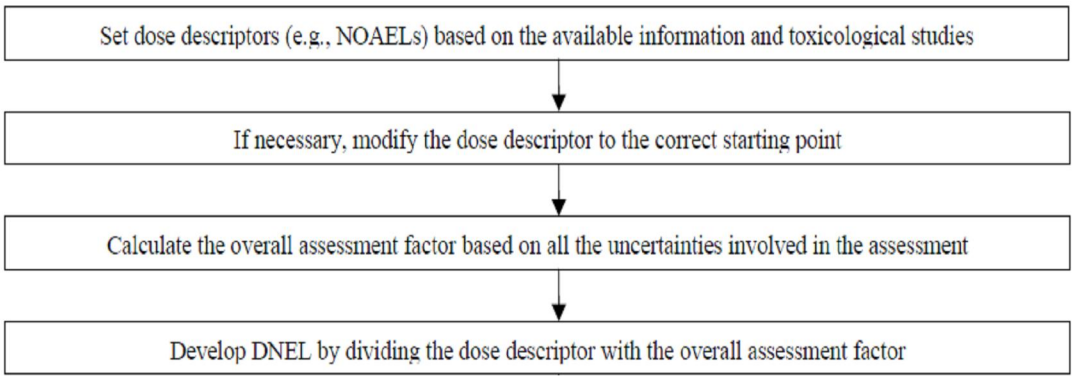

Figure 2.2: Hazard Assessment Process under REACH[10]

[9] Point of Departure is the lower confidence bound on the lowest experimental dose that showed an effect.

[10] From Guidance on Information Requirements and Chemical Safety Assessment, Part B: Hazard Assessment, Figure B.7.1, European Chemicals Agency, 2008.

2.3.3 Outputs Relating to Ecotoxicology and Physicochemical Hazards

Any physicochemical or ecotoxicological hazard classification of a substance under DSD or CLP will give an indication of the hazards that may be the focus of subsequent hazard and risk characterisation. The physicochemical and ecotoxicological hazard data that must be included in a registration dossier are detailed in Table 2.2.

Table 2.2: Physicochemical and Ecotoxicological Hazard Requirements, Units and Tonnage Thresholds

Properties	Units	Tonnage Threshold/s
Physicochemical Properties		
Physical state of substance	At 20°C and 101.3 kPa	1
Melting/freezing point	°C	1
Boiling point	°C	1
Relative density	N/A	1
Vapour pressure	Pa	1
Surface tension	dyne/cm or mN/m (milli-Newton per meter)	1
Water solubility	g/l	1
Partition coefficient (at least octanol-water ratio)	N/A	1
Flash-point	°C	1
Flammability	At 20°C and 101.3 kPa	1
Explosive properties	N/A (may be °C or kPa)	1
Self-ignition temperature	°C	1
Oxidising properties	N/A	1
Granulometry (solids only)	distribution of particle diameter (cm, mm, µm) by weight (g, mg, µg)	1
Stability in organic solvents and identity of relevant degradation products	g/l	100
Dissociation constant	moles/l	100
Viscosity	kg m^{-1} s^{-1}, Pa s or N s m^{-2}	100
Ecotoxicological Information		
Aquatic toxicity	Many possibilities including LC_{50}[11], LD_{50}, $EC(L)_{50}$[12], N(L)OEC as mg/l	1, 10 & 100
Degradation	Half-life in one or more media	1, 10, 100 & 1,000
Fate and behaviour in the environment	Including adsorption/ desorption and bioaccumulation (may be log Kow only)	10, 100 & 1,000
Effects on terrestrial organisms	Many possibilities including LC_{50}, LD_{50}, $EC(L)_{50}$, N(L)OEC as mg/g, mg/kg or mg/m^3	100 & 1000
Long-term toxicity to sediment organisms	Many possibilities including $EC(L)_{50}$ as mg/l, mg/g or mg/kg	1,000
Long-term or reproductive toxicity to birds	Many possibilities including $EC(L)_{50}$ as mg/g, mg/kg or mg/m^3	1,000

[11] LC50 (Lethal Concentration 50) is the concentration which kills 50% of a sample population

[12] EC(L)50 (Effective concentration (Level) 50) is the concentration (level) required to produce a specified effect in 50% of an animal population

For all registration dossiers, the ecotoxicological hazard data for each study are assessed by the registrant to determine appropriate POD; dose descriptors can be expected to include terms such as No (Lowest) Observed Adverse Effect Concentrations (N(L)OAECs) and/or derived benchmark dose (BMD). The endpoints and study dose descriptors are further developed using appropriate assessment factors to derive a dose which is considered to be safe, expressed as a Predicted No Effect Concentration (PNEC), in a process similar to that set out in Figure 2.1.

Furthermore, all substances must be assessed for their Persistent, Bioaccumulative and Toxic (PBT) properties, as well as for very Persistent and very Bioaccumulative (vPvB) properties using criteria set out in Annex XIII to REACH[13]. Where PBT or vPvB properties are identified, these are likely to be a major focus for subsequent risk assessment.

However, it is of note that a Chemical Safety Assessment must be provided together with all applications for an authorisation, regardless of the tonnage in which the substance is manufactured or imported (unless already submitted together with a registration dossier).

2.3.4 Outputs Relating to Exposure

All registration dossiers must include information on the manufacture and uses of the substance and guidance on safe use, as well as the identification of receptors and target media where these occur within the EU (as set out in Annex VI to REACH and summarised below).

Of most relevance to this study are the data available on exposures. Exposure information is required for all registrations, whether or not an exposure assessment is undertaken, including:

- an indication of whether the substance is for industrial use, professional use and/or consumer use;
- an indication for all industrial and professional uses, whether it is used in a closed system, its use results in inclusion into or onto matrix, non-dispersive use and/or dispersive use;
- an indication of significant routes of human exposure (oral, dermal and/or inhalation) and of environmental exposure (water, air, solid waste and/or soil); and
- patterns of exposure (including accidental/infrequent, occasional and/or continuous/frequent exposure).

[13] See Guidance on information requirements and chemical safety assessment. Part C: PBT Assessment, available at:

http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_c_en.pdf?vers=20_08_08

For substances manufactured or imported by a registrant in quantities greater that 10 tonnes per year, the human health exposure assessment should include exposure estimates for site specific, local, regional and EU wide emissions. Each such exposure estimate may also be subdivided into estimates to workers (industrial and professional), consumers and humans via the environment for dermal, oral and/or inhalation exposure routes.

The environmental exposure assessment should as appropriate include exposure estimates to air, water (surface, dissolved, fresh, marine, sediment, soil pore water for different soil types, groundwater and/or total), soil (agricultural soil, grassland soil, natural soil, industrial soil) and/or sewage sludge. Concentrations in specific organisms are rarely available. However in the case of secondary poisoning (food chain assessment), estimates of generic concentrations in plants, fish and earthworms are generally produced although these are not necessarily based on consideration of purely local exposure source(s) and are likely to be subject to a relatively large degree of uncertain in the absence of actual monitoring data.

For both health and environment, the level of detail included in the exposure assessment is likely to be greater for exposure pathways that are significant for the uses of a particular substance.

Where a Chemical Safety Report is not required (e.g. for substances manufactured/ imported in quantities less than 10 tonnes per year), the following information is required:

- details of exposure controls/personal protection;
- stability and reactivity information;
- details of disposal considerations; and
- details of recycling and methods of disposal for industry and for the public.

However, it is of note that a Chemical Safety Assessment (CSA) must be provided together with all applications for an authorisation, regardless of the tonnage in which the substance is manufactured or imported.

2.3.5 Outputs Relating to Risk Assessment

The risk assessment will provide outputs in the form of Risk Characterisation Ratios (RCRs):

- Human health RCR = Estimated exposure level ÷ DNEL; and

- Environment RCR = PEC[14] ÷ PNEC.

The purpose of risk assessment for REACH registration is to demonstrate that all uses of a substance are safe in terms of human health and environmental effects. Therefore, **risk assessment under REACH is not primarily to determine actual**

[14] Predicted Environmental Concentration

risk (or impacts) to human health or the environment. Values are chosen to represent the worst case for the hazard and exposure assessments. Hence, the purpose of risk assessment is to demonstrate safe use by showing that the RCR either demonstrates an adequate margin of safety in relation to human health or is less than one in the case for all uses, receptors and target media.

Where uncertainty exists over the quality of hazard data under REACH, assessment factors[15] are applied to the point of departure (POD)[16] to produce a DNEL or PNEC that is then used as the basis for the risk assessment. Similarly, generic scenarios made up from precautionary exposure estimates often represent the worst case in place of actual release or exposure measurements.

In general, the risk assessment is initially undertaken using only generic exposure scenarios (known as a Tier 1 assessment). It is only where the RCRs produced by this Tier 1 assessment indicate a risk that should be reduced will more accurate exposure scenarios be developed drawing on, for example, actual release and exposure data and in the light of additional site specific risk management measures.

2.4 Restriction and Authorisation

2.4.1 Restriction

The restrictions procedure acts as a safety net and can involve the placing of conditions or prohibitions on the manufacture, placing on the market or use of particular substances. The restrictions process can be triggered by concern about risks resulting from the use of substances with almost any specific hazards that can only be addressed through Community-wide action. Restrictions may include the use of a substance in articles, may refer to specific uses of a substance but may extend to a complete ban on the marketing and use of a substance.

Restriction dossiers adhering to the requirements set out in Annex XV to REACH, are prepared either by ECHA (at the request of the Commission) or by Member States. The authority preparing the restriction dossier has to demonstrate that there is an unacceptable risk to human health or the environment and that the risk needs to be addressed on a Community-wide basis. It must also be demonstrated that a restriction is the most appropriate risk management measure in terms of effectiveness, practicality (implementation, management, and enforcement) and monitorability.

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15 REACH defines such factors within the term ‘assessment factors’ (see REACH Guidance on information requirements and chemical safety assessment – Chapter R.19: Uncertainty analysis - available at Internet site:

http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r19_en.pdf?vers=20_08_08), however other regulations relating to risk assessment and, wider academic circles, may refer to these in somewhat different terms, such as uncertainty or safety factors.

16 Point of Departure; this is the lower confidence bound on the lowest experimental dose that showed an effect.

Consideration of the socio-economic impacts of the restriction is an important factor in providing this justification and involves demonstrating that there is balance between the health and environmental benefits associated with the reduction of risks arising from continued manufacture or use of the substance and the costs to industry, together with any change in other health or environmental impacts. In other words, the net benefits of a proposed restriction to society as a whole are compared to its net costs to society as a whole.

Again, the decision on whether or not to adopt a proposed restriction is taken by the Commission following receipt of opinions from the RAC and SEAC.

Restrictions on manufacture, placing on the market and use of substances under legislation that proceeded REACH are transferred to the list of restrictions detailed in Annex XVII.

2.4.2 Authorisation

The authorisation procedure is aimed at progressively reducing the risks posed by substances of very high concern (SVHCs) and ensuring that they are properly controlled and progressively replaced by suitable alternatives where these are technically and economically feasible. A substance may be identified as a SVHC if it meets the criteria set out in Article 57, which are summarised here:

- Carcinogenic, Mutagenic or toxic to Reproduction Category 1 or 2, in accordance with Directive 67/548/EEC;
- Persistent, Bioaccumulative and Toxic (PBT) or very Persistent and very Bioaccumulative (vPvB) substances, as defined by Annex XIII to REACH; or
- substances of equivalent concern to CMR and PBT/vPvB substances, such as endocrine disrupting substances.

Authorisations for the continued use of such substances by a company will be granted if the risks to human health or the environment from the use of the substance are demonstrated as being adequately controlled, as documented in the substance's chemical safety report. Where an applicant cannot demonstrate adequate control, then the company is required to demonstrate that the socio-economic benefits of use outweigh the risks to human health or the environment and that there are no suitable alternatives (technologies or substances). Although applications are submitted to ECHA, decisions on authorisations are taken by the Commission following receipt of opinions from the RAC (Risk Assessment Committee) and the SEAC (Socio-Economic Analysis Committee).

2.5 REACH and Socio-Economic Analysis (SEA)

2.5.1 Annex XVI

Annex XVI outlines the type of information that may be included within a SEA, with the level of detail and scope of a SEA being the responsibility of the interested parties. With specific reference to the health and environmental benefits of risk management, Annex XVI identifies the following types of information:

- impacts of a granted or refused authorisation, or a proposed restriction, on consumers. For example, product prices […], as well as effects on health and the environment to the extent these affect consumers;

- availability, suitability and technical feasibility of alternative substances […]. In the case of an application for an authorisation, the social and/or economic impacts of using any available alternatives identified in the substitution plan; and

- in the case of a proposed restriction or refused authorisation, the benefits for health and the environment, as well as the social and economic benefits of the proposed restriction. For example, worker health, environmental performance and the distribution of these benefits, for example, geographically, or for some population groups.

There are no requirements within Annex XVI as to the form that a SEA should take, and the ECHA Guidance makes little reference to the different methodologies within the main body of the text (although the methodologies are discussed in Appendix 7).

However, it is important to note that the burden of proof varies between restrictions and authorisation. With respect to restrictions, the authority preparing the dossier has to justify that the proposed restriction reduces the identified risk and that the restriction is the most appropriate measure. There is no requirement to demonstrate that benefits outweigh costs; only to provide an indication of the balance between costs and benefits. In contrast, for authorisation, the continued use of a SVHC can only be granted in those cases where an applicant cannot demonstrate adequate control if the applicant can demonstrate that the socio-economic benefits of use outweigh the risks to human health or the environment and that there are no suitable alternatives (technologies or substances).

2.5.2 Information Feeding into the SEA

Authorisation

The information to be provided as part of an application for an authorisation includes the CSA addressing the properties that led to the need for authorisation (specified in Annex XIII: CMR, PBT, vPvB etc), as well as an analysis of alternatives and a substitution plan. This information is mandatory (see also Section 4). However, the level of detail at which this information is provided is relevant to the framing of the SEA, as the exposure scenarios, including existing and recommended risk management measures are important inputs to the assessment.

In contrast, an applicant may submit a SEA of the impact of a granted or refused authorisation, if he/she considers this to be appropriate. The decision to do so is up to the applicant although it will normally be in the interest of the applicant to submit a SEA. If the applicant does decide to submit this, he/she needs to provide enough information, details and justification to allow the SEA Committee to form its opinion and the Commission to take a decision. The level of detail needed for these purposes may vary from case to case.

Restriction

With regard to restrictions, Annex XV lays down the general principles for the contents of a dossier justifying proposals for restrictions. The dossiers will include the following:

- evidence that implemented risk management measures are not sufficient;
- justification for action on a Community-wide basis;
- identification of the available options for addressing the risks;
- identification of the means for implementing the available options; and
- justification for the option and implementation method selected, with this analysed in terms of effectiveness, practicality and monitorability.

Member State Authorities are encouraged to prepare a SEA of the impacts of the proposed restrictions but this is not a mandatory component of the dossier. Nonetheless, the MS (or the Agency) will want to ensure that any dossier provides a good basis for decision making, including the need for a SEA; again, though, the level of detail needed within the SEA may vary from case to case.

2.5.3 The SEA Methodologies

Guidance has been published by ECHA on preparation of SEAs for Restrictions (ECHA, 2008a). As indicated in Section 1, the aim of this study is not to revise this guidance but to build upon on it. It is therefore important that we consider the methodologies and associated techniques identified in the Guidance.

The most commonly discussed methodological frameworks or decision aiding tools relevant to the assessment of the health and environmental benefits of risk management and referenced in the ECHA Guidance are:

- cost-effectiveness analysis (CEA);
- cost-benefit analysis (CBA) for example based on impact pathway analysis (IPA); and
- multi-criteria analysis (MCA) techniques: simple and complex scoring and weighting methods, including for example, approaches such as the eco-efficiency assessment tool.

Both CEA and CBA-based approaches have been widely used in support of policy development. For example, since its development in the early 1990s in projects such as the ExternE Project (Bickel and Friedrich, 2005) and the CAFE – Clean Air For Europe Programme (see Holland et al, 2005), CBA based on impact pathway analysis has been used to inform European environmental legislation and international agreements such as the National Emission Ceilings Directive setting emission limits for a number of atmospheric pollutants and the related Gothenburg Protocol to the UNECE Convention on Long-Range Transboundary Air Pollution. For further information on these approaches see the ECHA Guidance document on SEA under Restriction[17].

More detailed discussions on the current use of such methodologies for assessing health and environmental impacts follows in Sections 6 and 7 respectively; this includes their potential role in any logic framework developed as part of this study. However, there may also be other relevant methods, including life cycle impact assessment, risk ranking techniques, etc. which are also relevant to examining economic versus health or environmental risk trade-offs.

Life Cycle Analysis and Life Cycle Impact Assessment

Life Cycle Analysis (LCA) is a technique that can be used to assess the potential environmental impacts that might arise in relation to a substance, product, process, or service. The analysis consists of four main phases that include:

- goal and scope definition, where the identification of the boundaries and environmental effects to be reviewed for the assessment is completed;
- life cycle inventory analysis, compiling of an inventory of relevant inputs and environmental releases;
- evaluating potential environmental impacts, life cycle impact assessment; and
- interpreting the results.

The evaluation phase of LCA is also referred to as Life Cycle Impact Assessment (LCIA), which is aimed at assessing the human health and environmental impacts of

[17] see http://guidance.echa.europa.eu/docs/guidance_document/sea_restrictions_en.pdf

the relevant substances. LCIA is comprised of the following steps (Jolliet et al, 2003):

- identifying and selecting impact categories as well as the indicators for each impact category;
- classifying impact categories;
- characterisation - modelling life cycle inventory impacts within impact categories using science-based conversion factors;
- normalisation - expressing potential impacts in ways that can be compared;
- grouping - sorting or ranking the indicators;
- weighting - emphasizing the most important potential impacts; and
- evaluating and reporting results.

While the main focus of the assessment is human health and environmental impacts, LCIA also looks at resource depletion and aims to establish a connection between the substance or the product and its impacts. It does so by using generalised models that are suitable for relative comparisons as opposed to an actual risk analysis.

When selecting impact categories to be included in a LCIA, aspects of the environment or health are chosen that are potentially affected by the product/substance that is being evaluated. Frequently selections are made based on pre-defined lists or recommendations.

In the characterisation phase contributions to the selected impact categories are modelled quantitatively and then expressed as an impact score in a unit common to all contributions within the selected impact categories. The characterisation portion of the LCIA phase allows for the contributions from all emissions and resource extractions within each impact category to be totalled.

Currently, there are several methodologies, models, and assumptions available for LCIA (e.g. refer to Jolliet et al, 2003; Pennington et al, 2005; Rosenbaum et al, 2008; Hauschild et al, 2008; van Zelm et al, 2009). In comparison to traditional risk assessment methods, LCIA requires more innovation to deal with the additional impact categories. Therefore, modelling within LCIA depends on a variety of factors such as: impact categories, indicators, the level of acceptable uncertainty, use of expert judgement, available data along the whole life cycle, etc.

An optional element in the LCIA phase of an LCA study is a weighting component, where the results from the different impact categories are weighted against each other. This can be useful in order to reach an overall ranking of 'impacts' in comparative assessments.

LCIA as a framework is suitable to assessing the impacts of chemicals at various locations and with various levels of impacts. The assessment will provide a basis for comparing options based on a procedure for the classification and characterisation of different types of impacts. It is also of note that LCIA outputs can be combined with monetary valuations (and other impact measures such as DALYs – see Section 6) to provide cost-benefit analyses at the policy level.

Non-Economics Based Methods

The final set of methods that are considered here are those that do not stem from an economics background. This includes methods developed for risk ranking purposes or to create comparative risk indices. Such methods have been applied by the safety industry for example to provide a means for distinguishing lower risk accidents from higher risk accidents, and in the fields of environmental and health risk assessment.

These types of approach may be the most relevant to assessing the benefits associated with restrictions on or refused authorisations for substances such as PBTs and vPvBs and those with non-threshold properties. They may also be relevant to other contexts, such as substances possessing mutagenicity and reproductive toxicity, neurological effects, etc. where it may be hard to quantify the nature of the end health effect. Further, more detailed, discussion of the application of this type of method is included in Section 7.

2.6 The Precautionary Principle

2.6.1 Introduction

Several of the requirements of REACH are based on the precautionary principle. This is particularly true in relation to the potential for controls to be placed on vPvBs for which no damages can yet be established and to a lesser degree for PBT substances based on the identification of hazard properties rather than on risks due on predicted exposures.

This sub-section provides a brief overview of the application of the precautionary principle in environmental and health protection policy-making in the EU. This is achieved by first introducing and defining the precautionary principle as a concept and subsequently by providing examples of its application in EU legislation and policy documents, as well as in the relevant case law, i.e. in judgements delivered by courts belonging to the Court of Justice of the European Union.

Several sources confirm that a broad approach involving the review of both the relevant legislation as well as of case law is necessary. For example, the Commission Communication on the Precautionary Principle (EC, 2000) confirms the importance of judicial interpretation by stating that as the principle is only adumbrated rather than defined in the legislation "it is for the decision-makers and ultimately the courts to flesh out the principle. In other words, the scope of the precautionary principle also depends on trends in case law."

It is not possible though to provide an exhaustive review of all legislation, policy documents and case law relevant to the precautionary principle within this study. According to Marchant & Mossman (2004), "the EU has applied the precautionary principle in hundreds of regulatory decisions, opinions, resolutions, and reports,

ranging from severe restrictions on genetically modified foods and bans on various chemical products to [….] REACH." In addition, our research indicates that the precautionary principle is referred to in approximately 130 judgements delivered by courts belonging to the Court of Justice of the European Union. Therefore, it is clearly outside the scope of this study to present an exhaustive overview of the application of the precautionary principle in the EU; rather, we focus on providing examples of the principle's application (with a particular focus on the fields of environmental and human health protection) in order to illustrate its importance in EU policy.

2.6.2 EU Legislation and Policy

EU Primary Legislation

In 1992, the Maastricht Treaty introduced an explicit reference to the precautionary principle (Alemanno, 2007). This was incorporated in Article 130r(2)[18] of the EC Treaty. Following the amendments introduced by the Lisbon Treaty, the reference to the precautionary principle has been transferred into Article 191(2) of the Consolidated Treaties on European Union and on the Functioning of the European Union (2008)[19], which states that EU *"policy on the environment [...] shall be based on the precautionary principle..."*. However, no further definition of the principle is provided.

Policy Documents

The most significant policy document relating to the precautionary principle is the 2000 Commission Communication on the Precautionary Principle (EC, 2000). While this document does not have a legally binding status, it provides the most comprehensive EU level policy guidance on the application of the principle and provides useful insights to issues relating to both the scope of the principle's applicability in EU law, as well as into conditions for its invocation.

According to EC (2000), while the principle can only be found in the environment section of the EC Treaty, its applicability should not be seen as restricted to the environment; "the Commission considers that the precautionary principle is a general one which should in particular be taken into consideration in the fields of environmental protection and human, animal and plant health".

The guidelines for the application of the precautionary principle given in EC (2000) include the following principles:

- proportionality;

[18] This later became Article 174(2) under a subsequent legislative amendment of the treaties of the European Union.

[19] Council of the European Union (2008): *Consolidated versions of the Treaty on European Union and of the Treaty on the Functioning of the European Union*, available from the Europa Internet site, http://register.consilium.europa.eu/pdf/en/08/st06/st06655.en08.pdf, accessed on 24th March 2010

- non-discrimination;
- consistency;
- examination of the benefits and costs of action or lack of action; and
- examination of scientific developments (following the adoption of the measure).

Secondary Legislation

A large number of examples of application of the precautionary principle can be found in secondary EU legislation, mainly in the fields of environmental and health protection. These include both instances where the precautionary principle is explicitly referred to in the legislation, as well as instances where the principle may only be implied.

Historic examples in relation to the Existing Substances Regulation include, risk management measures taken in relation to both penta- and octa-bromodiphenyl ether flame retardants, for which the precautionary principle was invoked as providing a basis for action. However, this approach was adopted after the assessments were conducted and prior to the introduction of the REACH requirement to assess a substance's persistence and bioacumulative potential. Hence, since both substances are now known to meet the REACH Annex XIII criteria, it can be concluded that had the assessment of these substances been undertaken today, it would have been unnecessary to explicitly invoke the precautionary principle, as aspects of that principle have been built into REACH (see below).

More generally, while in EU food safety legislation the principle is 'expressly defined', explicit references to the precautionary principle in other operative sections of EU environmental legislation are rather rare (De Sadeleer, 2009)[20].

<u>The REACH Regulation (Regulation (EC) 1907/2006)</u>

EC (2007) provides examples of provisions in REACH which are based on the precautionary principle. These are reproduced in Table 2.3 below.

The extent to which REACH is seen as being underpinned by the precautionary principle depends on the definition of the principle used. For example, Hansen et al (2007)[21] argue that REACH is based on the precautionary principle as it includes burden of proof being placed on industry to assess the hazard/risk and to prove that the substance in question is safe compared to an assessment of alternatives (due to their definition of the precautionary principle, Hansen et al (2007) see this as a key component of the precautionary principle).

[20] However, there is still a commitment on Member States arising from Articles 10 and 174 of EC Treaty which extends to their interpretation of secondary EU law. According to de Sadeleer (2009), this is borne out in EU case law.

[21] Please note that some of the analysis in Hansen *et al* (2007) is based on discussing proposals for the REACH regulation rather than its final version.

However, even under less extensive definitions of the principle, REACH still contains components that are underpinned by the precautionary principle. A key example would be the focus on substances which meet the criteria for being vPvB. According to Lokke (2006), the vPvB criterion in REACH is precautionary as it "shortcuts the risk assessment on the basis of inherent properties that indicate irreversibility of possible adverse effects which have not been proved in the strictest of terms".

Table 2.3: Examples of requirements in REACH which are underpinned by the precautionary principle
Safety assessment: If there is uncertainty over scientific evidence (e.g. conflicting data exist), the safety assessment should normally be based on the evidence that gives rise to highest concern. The principles laid down in the PP communication should also be reflected in the guidelines being developed to support industry and authorities with implementation of REACH. **Risk management measures:** While a company is awaiting further test data on a particular hazard it should make sure that the risk management measures appropriate for the potential risk are in place and describe these measures in the safety assessment; in the case of PBTs and vPvBs, industry is requested to minimise exposure at all times (cf. Annex I, Section 6.5). **Authorisation:** Industry is required to seek authorisation for uses of substances of very high concern, regardless of the measures taken to control the risks. **Restrictions:** Member States and the Commission can suggest immediate restrictions in case there are indications of severe risks associated with the use of a given chemical. In this way the PP could be implemented in cases where it would take too long to establish the data necessary for a scientific evaluation or where data does not allow the risk to be determined with sufficient certainty.
Source: Reproduced from EC 2007

General Food Law Regulation (EC) No 178/2002

Article 7 of this Regulation states that the precautionary principle may be invoked (i.e. preventive measures may be adopted) in a situation of scientific uncertainty where a food might have harmful effects on human health. The measures adopted should be proportional to the risk and should be subject to a review "within a reasonable period of time".

EU Legislation on GMOs (Directive 2001/18/EC, Directive 2008/27/EC, Regulation 1830/2003)

According to Herrera (2007), the EU approach to GMOs is based on the "assumption that if GMOs are used in the production process, the final product requires separate regulation, even if it exhibits no risks different from the conventional product." Directive 2001/18/EC thus requires environmental risk assessment prior to authorisation (which according to Annex II of the Directive is to be elaborated in accordance with the precautionary principle) and Regulation 1830/2003 requires tracing of GM products to facilitate their removal from the production chain should harmful effects be identified (Herrera 2007 and Article 3 of Regulation 1830/2003[22]).

Other legislation

Table 2.4 provides examples of recent (2004-2009) legislation which contain explicit references to the precautionary principle.

[22] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32003R1830:EN:HTML

Table 2.4: Examples of Recent Secondary Legislation Explicitly Mentioning the Precautionary Principle	
Legislation	**Provisions Mentioning the Precautionary Principle**
Regulation (EC) No 66/2010 on the EU Ecolabel	Introductory remarks
Regulation (EC) No 1223/2009 on cosmetic products	Introductory remarks
Directive 2009/127/EC amending Directive 2006/42/EC with regard to machinery for pesticide application	Introductory remarks: in cases of scientific uncertainty Member States should apply the precautionary principle as outlined in EC 2000 when taking measures under this Directive.
Directive 2009/128/EC establishing a framework for Community action to achieve the sustainable use of pesticides	Operative provisions: Article 3: "The provisions of this Directive shall not prevent Member States from applying the precautionary principle in restricting or prohibiting the use of pesticides in specific circumstances or areas."
Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC	Introductory remarks: "The precautionary principle should be applied and this Regulation should ensure that industry demonstrates that substances or products [...] do not have any harmful effect on human or animal health or any unacceptable effects on the environment." Operative provisions: Article 1: "The provisions of this Regulation are underpinned by the precautionary principle [...]." Article 13: Precautionary principle is listed as one of the factors for future decision making.
Commission Regulation (EC) No 606/2009 implementing Regulation (EC) No 479/2008 on the categories of grapevine products and oenological practices	Operative provisions: Appendix 11: a requirement on wine filtering is also based on the precautionary principle.
Directive 2009/48/EC on the safety of toys	Introductory remarks: in cases of scientific certainty Member States should apply the precautionary principle as outlined in EC 2000 when taking measures under this Directive. Operative provisions: Article 39: Member States take measures as provided for in this Directive [...] they shall take due account of the precautionary principle.
Directive 2008/101/EC amending Directive 2003/87/EC so as to include aviation activities in the scheme for greenhouse gas emission allowance trading	Introductory remarks
Regulation (EC) No 1334/2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods	Introductory remarks: "The approval of flavourings should also take into account other factors relevant to the matter under consideration including [...] the precautionary principle."
Regulation (EC) No 1333/2008 on food additives	Introductory remarks: "The approval of food additives should also take into account other factors relevant to the matter under consideration including [...]the precautionary principle."
Regulation (EC) No 1332/2008 on food enzymes	Introductory remarks: "The approval of food enzymes should also take into account other factors relevant to the matter under consideration including [...] the precautionary principle and the feasibility of controls."

Table 2.4: Examples of Recent Secondary Legislation Explicitly Mentioning the Precautionary Principle	
Legislation	**Provisions Mentioning the Precautionary Principle**
Directive 2008/105/EC on environmental quality standards in the field of water policy, amending	Introductory remarks
Directive 2008/98/EC on waste and repealing certain Directives	Introductory remarks
Directive 2008/56/EC (Marine Strategy Framework Directive)	Introductory remarks
Council Regulation (EC) No 708/2007 concerning use of alien and locally absent species in aquaculture	Operative provisions: Article 9(4): "Any refusal of a permit must be duly motivated on scientific grounds and, where scientific information is as yet insufficient, on the grounds of the precautionary principle." Article 12: same as above for withdrawal of permit. Annex II: in case of scientific uncertainty in environmental risk assessment, the precautionary principle should be applied."
Regulation (EC) No 1923/2006 amending Regulation (EC) No 999/2001 on transmissible spongiform encephalopathies	Introductory remarks
Commission Directive 2006/141/EC on infant formulae and follow-on formulae and amending Directive 1999/21/EC	Introductory remarks
Commission Directive 2006/134/EC to include fenarimol as active substance	Introductory remarks
Commission Directive 2006/133/EC to include flusilazole as active substance	Introductory remarks
Commission Directive 2006/132/EC to include procymidone as active substance	Introductory remarks
Commission Directive 2006/125/EC on processed cereal-based foods and baby foods for infants and young children	Introductory remarks: "in cases where the relevant scientific evidence is insufficient, the precautionary principle allows the Community to provisionally adopt measures on the basis of available pertinent information, pending an additional assessment of risk and a review of the measure within a reasonable period of time."
Commission Directive 2004/1/EC as regards the suspension of the use of azodicarbonamide as blowing agent	Introductory remarks
Regulation on Persistent Organic Pollutants (Regulation (EC) No 850/2004 on persistent organic pollutants	Operative provisions: this Regulation refers to the precautionary principle in Article 1 detailing the objectives of the Regulation.
Source: http://eur-lex.europa.eu *Note:* Commission and Council decisions and Commission recommendations are not included in this table.	

2.6.3 EU Case Law

The key importance of EU case law in defining the scope and applicability of the precautionary principle has been highlighted by several sources, such as Alemanno (2007), de Sadeleer (2009), EC (2000) and Marchant & Mossman (2004).

This section provides a brief overview of case law by the Court of Justice of European Union (both the European Court of Justice and the Court of First Instance – which was renamed in 2009 as the General Court) and of the EFTA Court. This includes a number of different types of case, including cases against Member States (in particular where Member States adopted national restrictions on importation of goods from other Member States in accordance with Article 30 of the EC Treaty), as well as cases where the claimant requested nullification of European legislation.

On the basis of categorisation developed by Alemanno (2007), EU case law on the precautionary principle can be divided in the following stages:

- **the obiter dictum stage** - Alemanno (2007) notes that EC case law referred to the precautionary principle (albeit as obiter dictum only) even before its formal introduction in the Maastricht Treaty in 1992. Such cases related mainly to Member States restricting importation of foodstuffs on public health grounds in the 1980s, thus restricting the principle of free movement of goods;
- **early judicial shaping** of the precautionary principle - the precautionary principle was used in judicial reasoning in a growing number of cases in the 1990s but its invocation had not been systematised; and
- **recent case law** which attempts to better define the conditions for invocation of the principle.

Table 2.5 provides an overview of EU and EFTA case law on the precautionary principle[23]. It is not an exhaustive review of all cases, with a search for explicit references to the precautionary principle in Court of Justice of European Union case database returns approximately 130 judgements. It is also of note that the role of the precautionary principle in these cases can vary from a relatively minor one to a major one. Marchant & Mossman (2004) identified approximately 60 cases dating before 2004[24] of which the precautionary principle played a major role in 14 (in half of which the court delivered a judgement agreeing with the application of precautionary principle) and 46 in which it played a minor role (in approximately 75 percent of cases its application was upheld by the Court).

[23] A full list of cases seen by the ECJ and CFI can be accessed via: http://curia.europa.eu/jurisp

[24] Search conducted at http://curia.europa.eu returns approximately 80 cases where the precautionary principle was mentioned (potentially only as obiter dictum) between 1996 and 2004.

Table 2.5: Overview of EU and EFTA Case Law on precautionary principle		
Case name	**Field**	**Summary and verdict**
Obiter dictum stage		
Kaasfabriek Eyssen (ECJ) Case C83/80 1981	Public health	The Netherlands banned the use of nisin as a preservative in processed cheese but scientific evidence underpinning this measure was not clear-cut. Due to the fact that risk depended on 'indeterminable eating habits in Member States', the ECJ granted Member States the space to implement national measures.
Sandoz (ECJ) Case 174/82 (1983)	Public health	Due to scientific uncertainty over the hazard associated with a certain additive, the Member States were allowed to implement national measures protecting human health (in the absence of full harmonisation and in the situation of specific national eating habits).
Heijn (ECJ) Case 94/83 (1984)	Public health	National restrictions are justified in a situation of scientific uncertainty about the potential intake of pesticide residues.
Mirepoix (ECJ) Case 54/85 (1986)	Public health	
Case C-405/92 (ECJ) Armand Mondiet (1993)	Environment	Regulation (EC) No 345/92 aimed at protecting cetaceans (adopted in a situation of scientific uncertainty) banned certain fishery practices. A ship owner argued that this Regulation was not based on the only information available. The ECJ upheld the regulatory decision.
Early judicial shaping (implicit and explicit use of the principle)		
Judgements of 5 May 1998, cases C-157/96 and C-180/96 (this case is often referred to as the UK BSE case)	Public health	**APPLICATION OF PRECAUTIONARY PRINCIPLE UPHELD:** Due to the BSE outbreak, the European Commission imposed a temporary ban on exports of bovine products from the UK (pending more detailed scientific information). The ban was challenged by the UK and by the UK National Farmers' Union. The ECJ held that: "Where there is uncertainty as to the existence or extent of risks to human health, the institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent. […] Article 130r(2) provides that that policy is to aim at a high level of protection and is to be based in particular on the principles that preventive action should be taken and that environmental protection requirements must be integrated into the definition and implementation of other Community policies."
Case C-352/98 Laboratoires pharmaceutiques Bergaderm v. Commission (2000) (ECJ) and T-199/96 (CFI)	Public health	**APPLICATION OF PRECAUTIONARY PRINCIPLE UPHELD:** The initial case seen by the CFI concerned a company claiming that it was damaged by the application of Directive 95/34/EC. In a subsequent appeal to the ECJ, the appellants disputed the reference to the precautionary principle in Paragraph 66 of the contested judgment which stipulated that "if uncertainties regarding the existence or extent of risks to the health of consumers exist, protective measures may be taken without having to wait until the reality and seriousness of those risks become fully apparent." The appeal was dismissed.
C-6/99 Greenpeace France (ECJ)	Public health and environment	Greenpeace France invoked the precautionary principle when it sought the annulment of a French decree including genetically modified maize in a list of species grown in France. However, such a move had ramifications for the implementation of Directive 90/220/EEC on genetically modified organisms. The judgement of the ECJ did not primarily concern the precautionary principle but rather the right of the Member State to withdraw its consent with a product being placed on the market when new information on risk to human health becomes available in the course of

Table 2.5: Overview of EU and EFTA Case Law on precautionary principle		
Case name	**Field**	**Summary and verdict**
		the product authorisation process.
Case C-473/98 Toolex (2000) ECJ	Occupational health	**APPLICATION OF PRECAUTIONARY PRINCIPLE UPHELD:** There is no explicit mention of the precautionary principle in ECJ's judgement but the principle is still upheld. Following a ban on occupational health grounds by the Swedish authorities of trichloroethylene (classified as Cat. 3 carcinogen under Directive 67/548/EEC) taken scientific uncertainties relating to the its effects (the relevant EC scientific committee was unable to agree on the assessment of the substance), the ECJ upheld that decision.
Case C-67/97 Bluhme (1998) ECJ	Environment	**APPLICATION OF PRECAUTIONARY PRINCIPLE UPHELD:** Despite absence of conclusive evidence, Denmark banned the import to one of its island of any bee species other than the species native to this territory. The ECJ upheld this measure.
EFTA case law		
Case E-3/00 Efta Surveillance Authority v. Norway (Kellog's Case) 2001 EFTA Court	Public health	**APPLICATION OF PRECAUTIONARY PRINCIPLE REJECTED:** Norway banned the import and marketing of fortified corn flakes on the grounds that its population has no nutritional need for fortified corn flakes and contended that the lack of scientific information warrants the application of the precautionary principle. The EFTA Surveillance Authority launched infringement proceedings against Norway and claimed that the risk to human health has not been substantiated. The judgement of the EFTA Court dismissed Norway's restriction for the reason that Norway at the same time allowed fortification of cheese and due to the fact that "it had not been demonstrated that a comprehensive risk assessment had been carried out by the Norwegian authorities in response to Kellogg's submission of its application for authorization" (Alemanno 2007). The Court further stipulated that "[…] measures taken […] must be based on scientific evidence [… and a] purely hypothetical or academic consideration will not suffice. […What is required is] a comprehensive evaluation of the risk to health based on the most recent scientific information" (Alemanno 2007).
Recent case law		
Case T-13/99 Pfizer v. Council (2002)	Public health	**APPLICATION OF PRECAUTIONARY PRINCIPLE UPHELD:** Pfizer requested the annulment of Regulation (EC) 2821/98 which withdrew authorisation for certain antibiotics used in feedstuffs. Following a ban by Denmark on the use of an antibiotic virgiamycin, the Scientific Committee on Animal Nutrition (SCAN) was requested by the European Commission to evaluate the risk from the use of these antibiotics as growth promoters. SCAN concluded that this product did not represent an "immediate risk to public health in Denmark" but due to the uncertainty associated with the evaluation of this product, the EU moved to ban this product. This was challenged by Pfizer but Pfizer's request was rejected by the Court. The Court's judgement, however, reiterated some of the conditions for the application of the precautionary principle: "[…] a preventive measure cannot properly be based on a purely hypothetical approach to the risk, founded on mere conjecture which has not been scientifically verified … Rather, it follows from the Community Courts' interpretation of the precautionary principle that a preventive measure may be taken only if the risk, although the reality and extent thereof have not been 'fully' demonstrated by conclusive

Table 2.5: Overview of EU and EFTA Case Law on precautionary principle		
Case name	**Field**	**Summary and verdict**
		scientific evidence, appears nevertheless to be adequately backed up by the scientific data available at the time when the measure was taken" (Alemanno 2007).
Case T-70/99 Alpharma v. Council	Public health	**APPLICATION OF PRECAUTIONARY PRINCIPLE UPHELD:** Similar to the above case, Alpharma requested the annulment of Regulation (EC) 2821/98 which withdrew authorisation from certain antibiotics used in feedstuffs, including bacitracin zinc. Alpharma's argumentation included the contention that the EU wrongly applied the precautionary principle. Alpharma's motion was rejected.
Case T-74/00, Artegodan GmbH v. Commission, CFI (2002)	Public health	This case concerned an application for annulment of a Commission decision concerning the withdrawal of authorisation for certain medical products. The Court annulled the relevant Commission decision in relation to applicants' products and in the course of its deliberations also focussed on conditions for the application of the precautionary principle stating that "where scientific evaluation does not make it possible to determine the existence of a risk with sufficient certainty, whether to have recourse to the precautionary principle depends as a general rule on the level of protection chosen by the competent authority in the exercise of its discretion. […] That choice must, however, comply with the principle that the protection of public health, safety and the environment is to take precedence over economic interests, as well as with the principles of proportionality and non-discrimination." (also quoted in Marchant & Mossman 2004)
Vitamin Cases (Case 192/01 Commission vs. Denmark, C-24/00 Commission vs. France, C-270/02 Commission vs. Italy, C41-02 Commission vs. Netherlands)	Public health	**APPLICATION OF PRECAUTIONARY PRINCIPLE REJECTED:** Infringement proceedings were initiated against Denmark, France, Italy, Netherlands in relation to national restrictions on the sales of fortified foodstuffs. The Danish and Dutch governments stated that these restrictions were based on the precautionary principle. The ECJ ruled that Denmark, France and Italy were in breach of the EC Treaty (the judgement on Commission v. Netherlands appears not to be available). According to Alemanno (2007), the Commission also set the conditions for the application of the precautionary principle: "when it proves to be impossible to determine with certainty the extent of the alleged risk because of the insufficiency, inconclusiveness or imprecision of the results of studies conducted, but the likelihood of real harm to public health persists should the risk materialise, the precautionary principle justifies the adoption of restrictive measures."
T-229/04 Sweden vs. Commission (2007) CFI	Environment	**LEGISLATIVE DECISION ANNULLED DUE BASED ON PRECAUTIONARY PRINCIPLE:** Following a decision to include paraquat (active substance used in plant protection products) in Annex I of Directive 91/414/EEC thus allowing it to be sold and used, Sweden contested the decision and succeeded in having it annulled by the CFI. The judgement ruled that "interpreted in combination with the precautionary principle, that, in the domain of human health, the existence of solid evidence which, while not resolving scientific uncertainty, may reasonably raise doubts as to the safety of a substance, justifies, in principle, the refusal to include that substance in Annex I to Directive 91/414/EEC" (De Sadeleer 2009).

Table 2.5: Overview of EU and EFTA Case Law on precautionary principle		
Case name	**Field**	**Summary and verdict**
C-219/07 Nationale Raad van Dierenkwekers en Liefhebbers VZW (2008), ECJ	Environment	In relation to national restrictions on trade in certain species, the ECJ referred the decision to national courts but also reiterated the conditions for the application of the precautionary principle: "where it proves impossible to determine with certainty the existence or extent of the risk envisaged because of the insufficiency, inconclusiveness or imprecision of the results of the studies conducted, but the likelihood of real harm to human or animal health or to the environment persists should the risk materialise, the precautionary principle justifies the adoption of restrictive measures."
Sources: EC 2000, Alemanno 2007, de Sadeleer 2009, Marchant & Mossman (2004), texts of individual cases accessed via http://curia.europa.eu		

2.6.4 Summary

While the precautionary principle is not defined in detail in primary EU legislation and can thus be seen as a guiding principle rather than a well defined set of rules, the reasoning given in the policy documents and case law reviewed above appears to provide more detail on the conditions for its application. The two main conclusions that can be drawn on the basis of the information presented above are that: while primary EU legislation only mentions the precautionary principle in relation to environmental protection, the scope of its applicability is much broader and includes health and consumer safety; and there are no definitive criteria on when the principle may be invoked: the conditions for its application have to some degree been defined by case law and other documents; for example, it appears that a risk assessment (albeit inconclusive) is required and that a potential risk has to be identified. However, no criteria have been defined and the assessment of whether this has been fulfilled is left to the courts.

3. HUMAN HEALTH IMPACTS

3.1 Introduction

Assessing the risks of adverse health effects involves both knowledge of the source and nature of the environmental hazard and an understanding of the relationship of the exposure to the disease (Rushton & Elliott, 2001). It is dependent on an understanding of several important issues, including:

- the hypothesised health outcome or toxic effect (acute/chronic, reversible/ irreversible, local/systemic, immediate/delayed);
- the nature of the exposure;
- the relationship between dose and response;
- the relevant time period of exposure, for example many cancers have a long latency and do not occur until many years after first exposure; and
- the variability and susceptibility of the potentially exposed population. For example, sub-groups of the population might be at special risk due either to the pattern and distribution of exposure in the population or to non-environmental behavioural or phenotypic factors that might influence the risk of disease.

There are five main methods for identifying human health risks, with each of these providing different types of outputs for use in a risk assessment and also potentially having implications for how any exposure assessment is undertaken. These are:

- epidemiological approaches;
- human experimental studies;
- mammalian toxicity and toxicokinetic studies;
- in vitro studies on toxicity and toxicokinetics; and
- computation models on toxicity and toxicokinetics.

In addition, under the REACH legislation, it is also acceptable to seek to develop an understanding of the hazard potential for a substance based upon use of 'read-across' or the development of 'groups' or 'categories of substance' although this will normally require one to draw on several lines of evidence to justify their establishment. These approaches allow for the use of data and information on other substance(s) and thereby act to limit the use of animals in toxicity tests (ECHA, 2010a).

An overview of the type of methods that may be applied under each of these approaches is provided below. The aim here is not to provide detailed descriptions of how these methods are carried out, or to present the detailed requirements and terminology for these methods as defined within REACH; such aspects are better described within the extensive REACH guidance documents. It is rather intended to provide an indication of what the output from particular types of study are, and to indicate how these may feed into subsequent stages of an assessment process. Consideration is also given to the metrics that may be available from such studies for quantification of impacts in a SEA.

3.2 Epidemiological Approaches and Human Experimental Studies

3.2.1 Epidemiological Studies

Environmental research includes studies to identify causal relationships between environmental hazards and ill health in general populations and specific subgroups, the evaluation of changes in health with environmental changes and the provision of evidence for the setting of 'acceptable' standards for known environmental contaminants. Observational studies are widely used for this research but have a number of limitations, especially where excess risks of any adverse health effect are small, as will be the case with most environmental exposures encountered today within the EU.

The three most common types of human studies are cross-sectional, cohort and case-control studies. A further common design is an ecological study in which observations are made on a group basis.

3.2.2 Cross-sectional Studies

Cross-sectional studies describe the frequency of the disease of interest in a population at a particular period of time, with the variations between subgroups defined in terms of personal characteristics, time, place and, where available, relevant exposures. They represent a 'snapshot' of a population and are useful for generating hypotheses about the aetiology of a disease. They are particularly useful when dealing with health data that are continuously distributed in the population, such as blood pressure or serum cholesterol. For categorical health outcomes, the cross-sectional study is in fact similar to the case-control study (see below) except that sampling is based on *prevalent* rather than *incident* cases (Rothman and Greenland 1998). Their drawback is that information on exposure and effect is collected simultaneously, thus making it more difficult to attribute causation to any associations identified.

3.2.3 Cohort Studies

Cohort (or prospective) studies follow over time a group of people, the cohort, with particular characteristics in common (including level of exposure to one or more agents) to observe the development of disease. The rate at which the disease develops in the exposed people in the cohort is compared with the rate in a similarly constituted non-exposed group or in a standard group such as the national population:

- If the effect of exposure is multiplicative, the Relative Risk (RR) is estimated as the ratio of the risk of disease in the cohort (exposed population) over the risk in the comparison control or unexposed population; while

- If the effect of exposure is assumed to be additive, then the Attributable Risk (AR) can be estimated as the difference between the risk of disease in the exposed and the risk of disease in the unexposed groups.

The two measures, the RR and AR, have different interpretations when evaluating the relationship between exposure and adverse health outcome. The magnitude of the RR is an indication of the potential for a causal relationship between exposure to an agent and a disease while the AR is useful as a measure of the impact of a potential preventive programme once causality has been established.

One version of the cohort design which is often used in occupational settings is the historical cohort in which information on the study subjects is collected from historical records and the assumption is made that this information has not changed by the date of data collection.

Cohort studies often provide a complete understanding of experience after exposure occurs and have the advantage that both impacts and risk of exposure can be evaluated for a range of health outcomes. However, given the large numbers of people potentially exposed to many environmental pollutants and the likelihood that for many pollutants the excess risk of disease at the level of the individual is small, in order to detect any excess risk, many thousands, hundreds of thousands or even millions of people may need to be studied over a prolonged period for a cohort approach to be applied. This is especially true for rare diseases such as congenital anomalies, and childhood and many adult cancers that may be of particular interest to restrictions and authorisation under REACH. In addition, there may be follow-up problems (i.e. incomplete datasets for a proportion of the study population) and other changes over time that also impact on the health outcomes of interest.

3.2.4 Case-control Studies

In case-control studies, individuals with a given disease (the cases) are compared with a group of individuals without the disease (the controls). Information on past exposure to possible risk factors is then obtained for both cases and controls and compared, giving the *odds ratio* of disease associated with a particular exposure (Rothman and Greenland 1998). In a case control study, the relative risk cannot be calculated because the total numbers of exposed and non-exposed in the target population are unknown; the groups are selected because they either had or did not have the disease of interest at a particular point in time and are not a sample from populations of all those with high or low levels of the exposure under investigation. However, if the numbers developing the disease are small compared with those who do not develop the disease in the target population then the odds ratio (OR) is a good approximation to the relative risk.

The case-control approach is much more efficient in terms of time and cost than the cohort study as only cases and a relatively small number of controls need to be assembled and studied. However, because of the unavoidably retrospective nature of the exposure assessment and possible selection effects, such studies are prone to bias that can seriously distort risk estimates.

3.3 Ecological Studies

Where individual-level follow-up studies are infeasible and case-control studies are considered too expensive or impracticable, group-level (or ecological) studies are often undertaken. Ecological studies are generally thought to be of weaker design than individual-level studies because inferences made at the group level may not pertain at the individual level, the so-called *ecological fallacy* (Piantadosi et al, 1988). However, ecological studies have played a major role in the investigation of aetiological associations of public health importance, such as the relationship between type and amount of dietary fat and heart disease (Keys, 1970).

In the context of environmental epidemiology, two ecological designs are commonly employed, those that group people in time and those that group in space. Temporal studies are exemplified by studies on the health effects of outdoor air pollutants. In these studies, time-varying data on concentrations of air pollutants are available from one or a small number of monitoring stations at city level (Katsouyanni et al, 1998). It is assumed that exposure to a range of outdoor pollutants of whole city populations can be characterised by such data and patterns of daily mortality or morbidity (such as hospital admissions for asthma) are then compared for the city in relation to daily fluctuations in air pollution. This is a powerful study design for public health purposes since the daily mortality/morbidity and exposure to environmental pollutants for many thousands or millions of people can readily be captured using existing data sources, and problems of confounding by individual characteristics such as smoking can be minimised, as these can be assumed to stay constant over the time of the study.

The second type of ecological study involves using location as a proxy for exposure. Often, proximity (to a factory or polluting industry) is used as the marker of exposure; examples include the incidence of certain cancers near municipal solid waste incinerators (Elliott et al, 1996) and the occurrence of congenital anomalies and other birth effects near landfill sites in Great Britain (Elliott et al, 2001). In other instances, some kind of exposure modelling may be done to define areas considered to have high levels of exposure (Nyberg et al, 2000).

Semi-ecologic designs offer an attractive means of reducing the possible biases that may affect ecological studies (Prentice and Sheppard, 1995). In these studies, data on the exposure of interest (such as air pollution) is measured at the ecological level, but other data, including major confounders (see below), are collected at individual level, e.g., for a representative sample of individuals in the study regions (Dockery et al, 1993).

3.3.1 Confounding and Interaction

An important issue in the interpretation of results of an observational study is whether they might be explained by a factor or factors other than that under investigation. This is not usually a problem in an experimental setting (such as a randomised controlled clinical trial or in animal experimental studies) since the process of randomisation - provided that the sample size is sufficient - should ensure that the groups under study are similar with respect to other potentially causative factors. In

epidemiological studies, the term *confounding* is used to describe the situation where an association between the factor of interest and the disease outcome is explained by the association of both these factors with another variable, the *confounder*, which itself is either a cause or closely related to a cause of the disease. Age and social class, for example, are commonly regarded as confounders as they are strongly related to disease occurrence and are also related to a wide range of environmental exposures.

The effects of confounding variables can be at least partially removed, either by *matching* (in a case-control setting) or by statistical *adjustment* in the analysis. In studying the effects of low-level environmental pollutants, risks are likely to be much lower, so that unmeasured or inadequately controlled (*residual*) confounding in the observational data needs consideration.

Another important issue to consider is whether the effect on disease outcome of one factor is modified by levels of another factor, so-called *effect modification* or *interaction*. An example is the effect of cigarette smoking on risk of cardiovascular disease which is strongly modified by age. Interaction effects are increasingly thought to be important and may lead to new ideas about aetiology and mechanisms of disease. However, they are difficult to investigate as much larger sample sizes are required than studies examining only "main" effects. In particular, recent interest has focused on potential *gene-environment interactions* in determining the combined genetic and environmental influences on disease risk.

3.3.2 The Role of Systematic Review and Meta-analysis

Systematic review and meta-analysis methods involve the collation of the literature on a particular area of interest, assessment of the extent and quality of the studies found, and provision of a compilation of the results, often including quantitative estimation of risk estimates from the combined studies. These methods facilitate transparency and reproducibility of the methodology and results and ease of updating. They can be useful to identify the extent of, and gaps in, the knowledge base and areas for future research. Quantitative meta-analyses can give greater statistical power than single studies and provide a framework for investigation of possible sources of heterogeneity between studies (Blettner et al, 1999). In spite of controversy over the opportunity for bias and other sources of heterogeneity compared with clinical trials, these techniques are being increasingly used in epidemiological research and a number of guidelines have been produced recently on the topic (Egger et al, 1998, Sutton et al, 2000, Stroup et al, 2000).

There has also been a growing interest in cross-design synthesis, i.e. the quantitative combination of results from different study designs and across disciplines (Piegorsch and Cox, 1996). In particular the potential for the use of meta-analysis techniques to combine data from animal studies with that of human studies is beginning to be explored. Once wider understood and appreciated, this will have an important impact on the development of risk assessments and the setting of environmental standards (Peters et al, 2005; Jones et al, 2009).

3.3.3 Addressing Uncertainty and Bias

Uncertainty and variability affect all aspects of assessment of risks from environmental pollutants. Epidemiological designs have inherent biases in them as described above. A lack of adequate exposure data has been reported to be the major limiting factor in preventing the identification of causal associations (Checkoway, 1991). Critical issues include:

- exposure assessment method: personal monitoring, biomarkers, exposure modelling, the use of monitoring and time-activity data;
- characteristic patterns of exposure over time: frequency, duration, intensity, continuous or intermittent, critical time windows relevant to the health effect of interest;
- appropriate exposure metric: cumulative exposure, intermittent exposures; and
- inclusion of all sources of exposure (routes and media).

Quantification of uncertainty and variation can be addressed using statistical inference procedures and the use of probabilistic modelling. The latter allows incorporation of sensitivity analyses to examine the robustness of models to input assumptions and to identify those parameters to which the output is most sensitive (Barnett and O'Hagan, 1997). In addition, Bayesian modelling has been successfully used to analyse risks when available data have been inadequate for adoption of classical statistical approaches to risk assessment and where there is the desire to incorporate the opinions of experts. However, the use of modelling approaches to the assessment of risk has been viewed with some scepticism by some governments, particularly in Europe. Adequate testing of the robustness of results from modelling is required and care is needed in the interpretation and communication of these results, particularly to non-specialists.

3.4 Human Experimental Studies

3.4.1 General Considerations

Human experimental studies play an important role alongside epidemiologic and non-human toxicological studies in the identification and description of health effects. Like animal and laboratory studies, they are designed with the aim of reducing variation by extraneous factors as much as possible. They include:

- clinical trials where patients are the subjects studied, although these are rarely appropriate for environmental pollutants;
- field trials where interventions are assigned to individual members of a community, for example testing the effectiveness of large doses of vitamin C in preventing the common cold, or testing polio vaccine on school children;
- community intervention trials where interventions are assigned to whole communities, for example, water fluoridisation. These can in some situations be relevant for the evaluation of environmental risk factors; and

- volunteer studies such as food challenge studies and chamber studies for study of air pollutants.

3.4.2 Controlled Human Exposure Studies

These potentially offer the opportunity to provide convincing evidence of a relationship between exposure to a risk agent and an adverse health effect. For this reason, they are often carried out once an exposure of interest has been identified. For example, air pollution chamber studies have been carried out for a number of individual pollutants (e.g. ozone and sulphur dioxide) to characterize exposure-response, assess individual variability in response in 'normal' subjects and potentially sensitive or susceptible subjects such as those with asthma, and by development of appropriate biomarkers of both exposure and health effect, to quantify retained dose and give insight into the mechanisms of action that may operate in humans (McDonnell, 1993). Volunteer studies also potentially allow research on the effect of mixtures, although assessing the nature of such interactions requires knowledge of the dose-response characteristics of each of the individual pollutants (Greenland, 1993).

3.4.3 Advantages and Limitations of Controlled Human Exposure Studies

Because these studies usually take place in a laboratory, the investigator can control the levels and conditions of exposure and, as highlighted above, exposures to single agents or more complex mixtures can be used. The advantages of these over observational studies is that they can determine direct cause-effect relationships by comparing exposed groups with a control (unexposed) group; their design also allows the reduction of bias by controlling for potential confounders. A major strength of clinical trials is the random assignment of subjects to treatment groups, which reduces both confounding and selection bias. Blinding of researchers to the treatment of trial subjects also reduces observer bias. With care random assignment and blinding can also be applied to many volunteer studies.

Volunteer studies enable components of exposure, such as concentration, frequency and duration to be measured more precisely than in epidemiological studies. This reduction in measurement error of both exposure and effect reduces the misclassification bias experienced in epidemiologic studies. Another obvious advantage is that the temporal order in which exposure and effects occur can be ensured.

While volunteer studies are powerful in the assessment of many effects of interest, they are generally limited for obvious ethical reasons to studies of mild and reversible health effects and short durations and, usually, low levels of exposure. A study in which permanent effects may be induced in subjects cannot be undertaken, thus limiting investigation of chronic diseases. The study of reversible effects that require prolonged exposure of subjects may also not be practical, e.g. the effect of a long exposure to ozone and acid aerosols on bronchoalveolar inflammation. This limits the degree to which the outputs of such studies may be relevant to the main health risk drivers for restrictions or authorisation. However, they may remain important for

assessing the additional acute or chronic effects such as respiratory sensitisation that may occur alongside the key risks of concern.

There may also be cost and practical considerations, for example due to the need for multiple exposures, the amount of time required for measurement of outcomes and for maintenance and auditing of equipment. Many of these studies therefore commonly involve only small numbers of subjects who are generally healthy, frequently male, and with a limited range of characteristics related to age, lifestyle and socioeconomic status. This poses problems of statistical power so that it may be difficult to study exposures that produce small or imprecisely measured effects and generalisation of the results may be limited. Volunteer studies may be inefficient for the direct study of rare events although this can be overcome if biomarkers exist. For example occurrence of an asthma attack from an air pollutant would be rare but an increase in airway hyper-reactivity could be measured.

It should also be noted that there may be differences in chemical and physical composition of chemicals generated for laboratory studies from those that occur naturally. For example, commercial produced laboratory samples of silica containing rocks may differ from samples collected at workplaces in terms of percentage quartz.

3.5 Toxicity Studies

3.5.1 Mammalian Toxicokinetic and Toxicity Studies

In order to fully establish the nature of the potential hazard posed by a particular chemical (its hazard profile), it is necessary to investigate many aspects including:

- the extent to which a chemical is absorbed into an organism and the manner of its transport around the body, the metabolic reactions that occur within various tissues and organs and the manner in which it is eliminated from the body, all of which may be influenced by route and level of exposure and, potentially, by frequency of exposure. These aspects are addressed by toxicokinetic studies; and

- the range of potential responses of the organism to exposure will be reflected by, for example, the development of metabolic or other homeostatic responses that do not in themselves constitute ‘damage’. Alternatively the organism may suffer various adverse effects ranging from impairment of growth, elicitation of abnormal behaviour, through to tissue and organ damage and death. The range of possible adverse effects is extremely wide and the outcome of any given exposure will be influenced by not only level of exposure (dose) but route and frequency of exposure, stage of development of the organism and its sex, etc.

Historically, within the science of toxicology, a wide range of test model designs using a number of animal species have been developed to enable the systematic study of the effects arising from exposure to a particular chemical. Although in recent years considerable progress has been made at least for some endpoints that enable the consequences of exposure to be inferred from computer model systems or in vitro test

systems (discussed below), in practice many crucial potential effects can still only be adequately established using study designs that involve the use of intact animals (in vivo studies).

A number of generic types of in vivo study design can be defined (Hodgson & Levi, 1987; OECD Guidelines for Testing of Chemicals) and these are discussed in broad terms below. However, the individual design adopted for a particular study will depend, for example, on the specific regulatory requirements it is being conducted to support. Thus, for example, the precise test requirements for a substance under the REACH and CLP regulations can be expected to differ from those that are specified for other regulatory purposes or by other jurisdictions. In addition, particular test protocols may be subject to modification to enable them to better answer a particular question(s) or because of the physicochemical nature of the substance being tested. Furthermore, while many studies conducted to support chemical regulation adopt reasonably standard designs, studies that are intended to elucidate the underlying mechanistic basis of a toxic change will tend to demand use of a more focused, individualised approach.

Toxicokinetic Studies

Toxicokinetic studies are intended to provide information on the manner and rate at which a chemical is absorbed, distributed within the body, metabolised and ultimately excreted (i.e. ADME) in order to assist in the interpretation and evaluation of findings from studies on its toxicity. It may, for example, be important to establish if there are changes in the importance of particular metabolic pathways as dosage increases (e.g. a detoxification pathway may become overloaded as dose increases resulting in an alternative pathway becoming more important that may possibly lead to the generation of a toxic metabolite). In some instances, radio-labelled forms of the chemical may be used with the label being attached to particular parts of the molecule to facilitate tracking through the body and to establish the metabolic fate of parts of the molecule for chemicals that undergo chemical reactions in the body to generate a number of metabolites. In addition, radio-labelling offers one approach to the quantification of the importance of various routes of elimination (e.g. via urine, faeces, exhaled air, etc).

Characterising the ADME of a chemical generally requires a range of studies (possibly including both in vivo and in vitro testing), with each focusing on particular aspects, and therefore there are no generally applicable 'standard' designs (although the OECD have published guidance on a generic approach). Rather each package of studies is designed specifically to suite the particular chemical in question. Even to answer quite basic questions may require several studies if multiple routes of exposure have to be considered. However, the basic questions are often addressed through inclusion of additional animals as sub-groups within a more standard toxicological study design to provide samples or tissues for detailed analyses.

For many 'general/consumer' chemicals (as opposed to, for example, pharmaceuticals where a detailed characterisation is required), the extent of information on toxicokinetic behaviour may be sparse and, where present, may be limited to just one

route of exposure. In some instances it may be possible to infer the outcome of giving by one route using data for another route. Extrapolations of this type are however only valid for systemic, as opposed to local (site of exposure) response and there is a need to use expert judgement to interpret such predictions as a number of factors (such as first-pass metabolism by the liver following oral intake) may confound interpretation. There are a number of established approaches to route-to-route extrapolation; these have been discussed in detail by a number of authoritative bodies including IGHRC (2006), and are therefore not discussed further here.

Toxicity Studies

In general, the route of exposure (e.g. oral by stomach gavage, in feed (i.e. diet) or in drinking water, and inhalation or dermal) employed in a toxicity study is selected to best mimic that expected to be experienced by the target species of concern (i.e. humans). For some types of chemical, other routes may be more appropriate, e.g intravenous or intraperitoneal may be appropriate for some pharmaceuticals. The species (and strain) selected for use in testing is based on an understanding of the similarities and differences in which it will respond to a chemical compared with humans, and on the historic data available. A further consideration is its practicality in terms of cost of provision, maintenance and also time taken for an effect to be seen.

The more standard test designs routinely encountered in relation to the regulation of general and consumer chemicals have been defined by various Competent Authorities such as the EU[25] and internationally-agreed design guidelines are also published by the OECD[26].

The most common types of in vivo tests used to investigate the various aspects of toxicity and their outputs are discussed in generic terms below.

- **Acute Toxicity**: These studies focus on defining the amount of chemical necessary to cause the death of an animal (most often a rodent) within a set time period following a single administration of the chemical; usually this is expressed in terms of the dose or exposure concentration that is expected to result in death of 50% of the exposed population (i.e. LD_{50} or LC_{50} respectively). Deaths per group are mathematically analysed to derive a LD_{50} or LC_{50} value, usually in units such as mg/kg or mg/m^3. Depending on the regulations for which the study is being conducted, various species may require testing. This type of study may also provide information on the specific target organ toxicity following a single exposure, and the output is often used to inform the classification of a chemical in terms of its acute toxic hazard. Increasingly, many countries are adopting classification systems based on the United Nations Globally Harmonised System (GHS), for example, the recently introduced CLP Regulation ((EC) No 1272/2008) in the EU. However, some care may be necessary when comparing classification information drawn from multiple sources since, even when the

[25] See Internet site http://ecb.jrc.ec.europa.eu/testing-methods/

[26] See Internet site http://www.oecd.org/department/0,3355,en_2649_34377_1_1_1_1_1,00.html

classification was based on GHS, it may have been implemented in subtly different ways in various jurisdictions.

- **Irritation and corrosive potential:** Tests here focus on the effects of a single direct application of a chemical to sensitive tissues such as the skin and eye or, more rarely, on the effects of inhalation exposure on the respiratory system. There are, however, increasing efforts to develop test models that do not rely on the use of live animals, with a number of in vitro designs having recently completed validation by the OECD.

- **Sensitization potential:** There are no robust animal test models yet available to assess respiratory sensitization but three in vivo methods have been widely used to assess sensitization in the skin; the Magnusson Kligman Guinea Pig Maximisation Test, the Buehler test (again in Guinea pigs) and, increasingly, the Mouse Local Lymph Node Assay (SCCP, 2006). Each design involves the application at intervals of several doses of test substance (sensitization or induction phase) followed in the case of the first two designs by a subsequent dose (challenge phase) to assess the extent of dermal response. In the case of the Local Lymph Node Assay, the allergic response is assessed in terms of the extent of lymphocyte proliferation in lymph nodes draining the site of dosing.

- **Repeat dose toxicity**: This type of study is aimed at characterising the nature of the toxic effects (type of effect and organ/tissue affected) that can be elicited when a chemical is given on multiple occasions (ranging from 1-2 weeks to several years depending on the purpose of the study) by a particular route, and its dose-response characteristics (i.e. the degree of severity associated with a particular dose). Within a regulatory setting, a particular concern is to determine the dose levels that are tolerated (i.e. at which no adverse effects occur – the no adverse effect level, NOAEL) and to define the dose at which adverse effects start to occur (i.e. the lowest adverse effect level, LOAEL) . Common routes of exposure include oral gavage, inclusion in diet or drinking water, application to the skin (dermal) and inhalation exposure.

- **Genotoxicity:** This endpoint is normally addressed through the use of a battery of tests addressing the various potential mechanisms by which genetic damage may occur in a cell, with the overall assessment as to a chemical's genotoxicity being based upon a 'weight of evidence' approach through use of expert judgement. It should be noted that both in vitro and in vivo test designs are widely used to investigate this type of toxicity. The objective of these tests are to identify two principal types of genotoxic effect. Mutagenicity is where a chemical causes a permanent change in the genome, or may in some circumstances arise indirectly by interference with DNA-repair mechanisms; such changes may occur in either somatic or germ cells The other main form of genotoxicity that a chemical may show is termed clastogenicity. Here there is an alternation in the gross structure of the chromosomes or in their number (anueploidy and polyploidy). Damage to DNA that does not constitute a mutation may also be detected by some test methods, e.g. in the form of unscheduled DNA synthesis (UDS). Under the REACH and CLP regulations, the default assumption for chemicals showing

genotoxicity is that there will be a non-threshold, linear dose-response relationship[27]. However, it is increasingly recognised that in some instances both direct and indirect mechanisms may demonstrate a threshold. Where adequate mechanistic data are available, it may therefore be that the default assumption may be considered inappropriate.

- **Carcinogenicity:** This is normally assessed using tests in which rodent species are exposed via a particular route to a chemical for a substantial proportion of their normal life span, and examined to detect the development of tumours. The extent of a chemical's carcinogenic potential is determined by the nature of changes in the numbers (incidence and multiplicity per animal) and types of tumours forming in animals (benign or malignant – including consideration of rarity) and the times at which the tumours develop (latency). However, it may be difficult to fully distinguishing the underlying mechanism by which tumours are cause, i.e. whether it is due to a genotoxic or non-genotoxic (e.g. promotional) processes. For substances showing carcinogenic responses that also exhibit non-threshold genotoxic activity, it is not possible to derive a DNEL under REACH, rather a DMEL may be determined where there is sufficient information. However, in other circumstances, where the dataset is inadequate, only a qualitative risk characterisation may be possible (ECHA, 2009). A further complication when seeking to establish an understanding of the dose-response of a substance (or to compare potencies of different substances) relates to adjusting for differences in routes of exposure and for physiological differences across species. Various approaches have been developed to aid data extrapolation and comparison; for example, the Carcinogenic Potency Database (CPDB)[28] an extensive dataset on many experimental cancer bioassays that may assist in such comparisons.

- **Reproductive Toxicity**: The objective of these tests is to characterise – for reproductive endpoints (including fertility) and developmental parameters (offspring growth, rate of development, presence of abnormalities, etc.) separately – the nature and dose-response of the effect. Various test designs are available that may focus separately on reproductive and developmental endpoints or may consider offspring and parental effects together. Furthermore, valuable information on effects on reproductive organs may also be obtained from the repeat dose (and rarely acute) toxicity studies. A particular concern in relation to developmental endpoints is the identification of chemicals that may cause teratogenic changes in the offspring of treated animals, particularly where such effects occur in the absence of obvious parental toxicity (N.B. at high doses that are causing marked toxicity to parental animals, developmental changes may occur through non-chemical specific mechanisms). Where teratogenicity is detected, attention would be given to considering the its significance in the light of the evidence regarding the genotoxic potential of the chemical, to determine if this

[27] ECHA Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific guidance. Available at Internet site http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7a_en.pdf

[28] See Internet site http://potency.berkeley.edu/

may reflect a non-threshold mechanism (such as DNA mutation). In such cases, under REACH, it would be considered inappropriate to derive a DNEL although derivation of a DMEL may be possible depending on the extent of the dataset.

- **Other Types of Toxicity:** A number of other, more specialised, study designs may occasionally be employed by toxicologists to address specific toxic endpoints. These include studies to inform on subtle differences in neurological or neurobehavioural responses or of immune function (e.g. response to challenge by a pathogenic organism following exposure to a chemical) or that investigate the possibility of phototoxicity. The metrics arising from such investigations may be varied but will generally include an attempt to define the dose-response in terms of changes in number of animals affected or severity of effect against dose.

Gaps in Coverage

For some aspects of toxicology, the availability of suitable test models is limited, for example:

- the characterisation of the sensitizing potential of chemicals to humans where, although the recent introduction of the LLNA has somewhat improved the situation, our ability to predict sensitization potential is limited (particular in relation to respiratory sensitizers); and

- identifying and characterising chemicals with endocrine disrupting potential. Recent published guidelines from the OECD have improved the situation to some extent although the currently available designs may only be suitable as screening tools to detect oestrogenic, androgenic and, to a limited effect, thyroid-mediated effects.

A further issue that may complicate regulatory decision making is the situation where there is a need to compare findings from non-standard (often academically-focused) studies conducted to investigate, for example, subtle changes in neurobehaviour and neurodevelopment which may detect inter-group differences that are not detectable (or relate to endpoints that are not normally addressed) using the standard designs. In such instances, expert judgement based on the weight of evidence is generally essential.

3.5.2 In Vitro Studies on Toxicity and Toxicokinetics

Types of Study

The term 'in vitro test' refers to a model system that utilises whole organs, tissues or cells taken directly from animals (primary cells) or that have been developed into standardised cell lines, as well as non-cell based tests systems such as the use of tissue homogenates or of isolated cellular structures such as hormone receptors.

The range of toxicological endpoints to which these systems may be applied is extensive including: assessment (outside of a regulatory context) of acute cell

toxicity; irritancy; immunological effects (that may suggest a sensitizing potential); mechanistic elucidation of target organ responses; and assessment of some aspects of fetotoxicity, neurotoxicity and endocrine disruption. Toxicokinetic aspects are also frequently investigated using in vitro model systems with, in recent years, predictive models being developed to inform on absorption potential. Some of these aspects are briefly highlighted below.

Perhaps the largest contribution – and the sector where the largest number of regulatory accepted studies have been established to date - is for assessing mutagenic and clastogenic activity. As regards interpretation of the outputs of in vitro genotoxic assays, while a positive response in a series of such studies strongly suggests that a chemical will possess an intrinsic genotoxic potential, in vivo data will generally be necessary to definitively establish the biological significance. Also, while it is generally recognised that it is not possible to identify a no-effect-level (i.e. a threshold) for a chemical that acts via a mutagenic mechanism, there are some indirect mechanisms of genotoxicity for which it may be possible to determine a 'practical' threshold of effect (ICH, 2008; COM, 2010).

A number of in vitro assays have been developed as screening tools or putative replacements for in vivo studies on developmental toxicity and teratogenicity. These generally involve the culture of whole (e.g. Woehrmann et al, 2006) or parts (such as the mouse limb bud, central nervous system (CNS) or other cells; Wise et al, 2005; Steeley and Faustman, 1995) of an embryo or fetus in a solution containing the test chemical for a short period before assessing the impact of exposure on development in terms of visual appearance or metric such as rates of DNA synthesis. A number of these have undergone comparative validation by ECVAM (Genschow et al, 2002) and have shown in some cases encouraging predictivity when compared with in vivo studies. However, assays of this type are inherently limited since they do not include all the levels of complexity present within the in vivo situation. As such, these assays may be of particular value as pre-screens for previously untested compounds (Daston, 1998) or to investigate particular responses or the underlying mechanisms of effect.

Limitations of In Vitro Test Models

The assessment and validation of in vitro test systems in Europe falls to ECVAM, and their website[29] and Worth and Balls (2002) can be consulted for details of prospects for, and current progress in, the development and implementation of these types of test systems.

In summary, however, in vitro tests (e.g. for genotoxicity) are particularly useful in elucidating the potential hazard potential of a chemical, as well as playing a valuable role as pre-screening tools to prioritise chemicals for more detailed investigations or detailed mechanistic study. However, there are a number of intrinsic limitations in relation to the ability of in vitro test systems models to address the influences of toxicokinetic processes on the chemicals toxicity and the range of complexities and interactions that may occur within the intact organism, that limit their ability to

[29] See Internet site http://ecvam.jrc.ec.europa.eu/index.htm.

provide definitive clarification for a number of important toxic endpoints (particularly those relating to repeat dose and reproductive/developmental endpoints).

In addition, while of particular value in classification of hazard, it is not possible to accurately extrapolate dose-response information from the in vitro system to the intact organism and ultimately to humans, thereby limiting their value for risk characterisation and comparison purposes. Detailed discussions on the availability and application of non-animal test systems have been published by CSTEE (2004 and 2005) and, more recently, by EFSA (2009b) and SCCS (2009).

3.5.3 Computation Models on Toxicity and Toxicokinetics

Increasing attention is now given to the development of hazard assessment methods that do not rely on the testing of chemicals on animals or even cell systems but rather use computational methods to predict the activity of a given chemical drawing on the existing knowledge base for other chemicals and basic physiochemical knowledge of the behaviour of chemicals. These tend to be classified into two categories, described below.

Qualitative and Quantitative Structure-Activity Relationships Models

Structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) models are theoretical models that predict the physicochemical, biological and environmental fate properties of molecules on the basis of the chemicals structure. SARS are based on a qualitative relationship between a (sub)structure to the presence or absence of a property or activity of interest. The substructure may consist of adjacently bonded atoms or an arrangement of non-bonded atoms that are collectively associated with the property or activity.

QSARs are mathematical models (often based on statistical correlation) that relate one or more quantitative parameters derived from chemical structure to a property or activity of interest. For example, properties that may be used included calculated properties (e.g. log P), structural descriptors (2- or 3-dimensional topography; Tetko et al, 2008). These yield continuous or categorical results. Models are generally developed using so called 'training sets' of chemicals for which the properties to be predicted by the model are already established. Such approaches may find particular application in the investigation of aspects such as irritancy/corrosivity, toxicokinetic behaviour, and in receptor-interaction studies. Some models also attempt to predict a range of toxic outcomes, including estimates of dose-response (e.g. commercial models, such as TOPKAT). While the predictive power of a model may be quite high for substances which posses key properties similar to those of the training sets, establishing the accuracy and relevance of a prediction may be quite difficult where the substance's structure is somewhat different from those used to establish the model (Tetko et al, 2008).

A number of SAR and QSAR models have recently been made freely available by the CEFIC Long-Range Research Initiative as part of their Toolbox[30]. These include the Algebraic Manipulation by Identity Translation (AMBIT) model which comprises a database of more than 450.000 chemical structures and attribute descriptors (including test findings) that can be interrogated to define potential concerns, and a Fertility and Developmental Toxicity in Experimental Animals (FeDTex) database which uses data on 100 chemicals to identify the potential for reproductive and developmental effects. Other Cefic models include the IndusChemFate model which is a generic PBPK screening tool to derive human biomonitoring equivalent guidance values (BEGV) for data-poor chemicals, and the Model Equation Generator (MEGen) which facilitates route-to-route extrapolation of regulatory toxicity data.

Chemical Categories and Read-across Models

As an alternative, or an adjunct, to experimental and computational approaches, the REACH legislation allows for development of understanding of the hazard profile of a substance based upon 'read-across' from data and information that may be available on other substance(s) or groups of substances with which it shares similarities in either chemical structure and/or physicochemical properties; this may be achieved through the use of various grouping approaches[31].

A chemical category is a group of chemicals whose properties are likely to be similar or show predictable trends across members of the group, usually as a result of structural similarity. Application of the chemical category approach provides a potential means of filling data gaps, thereby avoiding the need to test all members of a category for all properties/endpoints.

Such approaches include the **RepDose** relational database (recently included by Cefic LRI in their toolbox) which uses experimental NOEL/LOEL values for repeat dose toxicity endpoints to evaluate categories of chemicals and inform on thresholds of concern (TTC). The US EPA has also made their Aggregated Computational Toxicology Resource (ACToR) publically available[32]. This is a collection of databases on over 500,000 environmental chemicals (including high and medium production volume chemicals, pesticides water contaminants) that are searchable by name, other identifiers and structure. It holds information on chemical structure, physicochemical values and in vitro and in vivo toxicology data, and links to screening tools such as ToxCast and the Toxicity Reference Database (ToxRefDB) to provide insights into a chemicals toxicity profile or comparative information on the toxicity profile (including dose-response) of other chemicals.

[30] See Internet site http://www.cefic-lri.org/lri-toolbox.

[31] For detailed discussion refer to the REACH Guidance on information requirements and chemical safety assessment – Chapter R.6: QSARs and grouping of chemicals, available at Internet site http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08

[32] See Internet site http://actor.epa.gov/actor/actor_help_20080903.htm

3.5.4 Limitations of Computation Methods

The use of validated computational methods for the classification of chemicals and risk assessment is permitted under REACH, particularly in relation to facilitating read-across of information within a related group of chemicals. However, it is essential when applying such models to fully appreciate (and document) their limitations, for example in relation to their ability to predict effects in chemicals with structures dissimilar to those used in the models reference or training datasets and their fundamental inability to inform on previously undetected forms or mechanisms of toxicity.

3.5.5 Dose-Response Characterisation from Toxicity Studies

In all toxicity study designs, a key intention is to define the nature of effects caused by exposure to a chemical and, importantly, the dose-response shown. In practice, epidemiological studies cannot distinguish mechanism of action per se, this instead must be given by a focused toxicity or ecotoxicity study. However, once the mechanism of action is known this becomes important in the interpretation of the epidemiological studies for risk characterisation.

As part of the interpretation of study findings, it is also essential to appreciate that other factors may profoundly influence study outcome including: route of exposure to the chemical; the species tested (and in some case, the strain); genetic susceptibility; physiological state; and sex and age of the exposed organisms.

Concepts of Threshold and Non-threshold Mechanisms

A central tenant of toxicology is that, in general, the types of toxic effect seen, the severity and the numbers of individuals affected will increase as exposure level (as defined in terms of dose, duration and/or frequency) rises, i.e. that effects will show a dose-response relationship. However, an important concept in toxicological research, and one which has important consequences for the development of a risk assessment under REACH and the subsequent regulatory consequences for a chemical, is that of threshold and non-threshold mechanisms of action.

In the case of effects that are mediated via a threshold mechanism, there is postulated to be a level of exposure below which no (observable) adverse changes will occur. Thus at these low level exposures a harmful chemical is tolerated by the organism, for example, through the operation of endogenous detoxification mechanisms, by compensation through normal physiological homeostatic mechanisms or by cellular adaptation or repair. At higher exposures, however, the ability of the organism to adequately compensate may become increasingly overwhelmed, leading to a toxic outcome such as impaired function or development of disease state (Health Canada, 2008).

In contrast, for a non-threshold effect it is assumed that any level of exposure will associate with some adverse impact on an organism (Health Canada, 2008). Indeed, under many chemical regulations, including REACH, this mechanistic basis forms the

'default' assumption for chemical which show mutagenic, genotoxic or carcinogenic activity, particularly where such activity is apparent in an in vivo model.

It has however been conjectured that even in the case of some DNA-mediated effects there may exist a 'practical' threshold representing a balance point between the damage caused to the genome by the genotoxic agent and the endogenous cellular DNA-repair mechanisms while it has also been suggested that non-DNA-reactive genotoxins, such a those operating via inhibition of topoisomerase or inhibition of the spindle apparatus, may also have a 'practical threshold' (Foth et al, 2005; Lynch et al, 2003). Nonetheless, unless such a plausible threshold-based mechanism (supported by convincing experimental data) can be firmly established on a case-by-case basis for a chemical, then most regulatory authorities will treat a chemical showing genotoxicity- and carcinogenic activity as being non-threshold.

Where a threshold mechanism can be demonstrated, then some regulatory authorities will permit the establishment of a NOAEL (see below) to which appropriate factors (termed assessment factors in REACH) can be derive the basis for risk characterisation (COM, 2001; Health Canada, 2008).

Definition of No or Low Effect Levels

The data derived from toxicity studies may be reported as quantal, ordinal or continuous data. The traditional approach in a toxicological experiment has been to compare the responses shown by groups of animals receiving a step-wise series of dosages with that of a group of untreated animals, the (negative) controls, so as to establish at which levels there are no effects (or no adverse effects) – the highest such dose in a study is then defined as the no-observed-effect level (NOEL) or no-observed-adverse-effect level (NOAEL). Also of importance is establishing the lowest dose at which effects are seen (i.e. LOEL or LOAEL). Generally, the dose selection is designed to allow identification of a NOEL or NOAEL which is then used as the basis for risk extrapolation. If this is not possible, then – depending on the endpoint under consideration - the lowest dose at which any effect is seen (i.e. LOEL, LOAEL) may be used to extrapolate to a dosage or exposure concentration at which the level of risk to the target species of concern (e.g. human) is considered acceptable. The derivation of such an acceptable level is achieved by dividing the established no (or low) effect level by a suitable series of factors (termed assessment factors under REACH but elsewhere termed uncertainty or safety), the size of which will depend on the underlying degree of uncertainty; in all cases a higher factor would be used for a LOAEL than for a NOAEL because of the greater degree of uncertainty surrounding the basis for the extrapolation.

Benchmark Dose Approach

An alternative to the traditional approach of establishing a NOAEL-type metric is to apply a statistical approach, termed benchmark dose (BMD) analysis. This statistical technique was first proposed by Crump (1984) and is finding increasing application as a risk assessment tool to analyse experimental and, as undertaken by EFSA (2009a), human data. Proponents of the BMD approach note that while the traditional

NOEL/LOEL approach focuses only on the data points of the 'apparent' NOEL and LOEL group, BMD analysis draws upon the full dataset. There is therefore suggested to be a lower chance of a significant difference in outcome than if NOEL's for the same endpoint are compared in two apparently very similar studies. It is also suggested that a NOAEL/LOAEL metric is more open to influence by sample size and associates with a greater degree of uncertainty and a higher probability of false negatives than a BMD-based measure (Cal EPA, 2004; Slob, 2002).

In the BMD approach, a mathematical method is used to derive a POD (i.e. that point in the dose-response curve at which the response rises above zero effect) based upon the entire dataset (including both treated and control group data and potentially drawing on data from several studies and multiple species). This is achieved by fitting the data to a modelled dose-response equation with the aim of estimating a dose at which a pre-defined level of response is anticipated to occur. Although any response value could theoretically be defined as the POD, by convention in BMD analysis rates of either 5% (for continuous data) or 10% (for incidence data) are generally used to define the POD (Slob, 2002).

Theoretically the BMD approach provides greater consistency in establishing the threshold dose across studies and chemicals (i.e. effect levels derived show a closer relationship for a defined response of a given endpoint) and the degree of uncertainty is reduced. It has been noted that, compared with NOAELs, BMD-based estimates produce lower numerical values of the POD for data of poor quality but that values are often similar to NOAELs where such a comparison is possible with, for example, BMDs associated with 5% additional risk producing dose estimates similar to NOAELs (Kortenkamp et al, 2009). It has also been suggested that this metric is preferable for the study of dose (concentration) addition mixture effects (Kortenkamp et al, 2009).

A number of issues have, however, restricted wider adoption of this approach:

- although there are now a number of models, in particular the U.S. EPA's BMDS[33] and RIVM's Proast[34], which are publicly available and represent reasonably robust software, no one model has yet been fully developed or universally accepted;

- the EPA and Proast models each have particular strengths and weaknesses. For example, Proast provides more options and greater flexibility than the BMDS software (e.g. inclusion of covariates in the analysis, modifiable plotting options and ease of inter- and intra-species extrapolations using probabilistic assessment factors) but is much less easy to set-up/use, with users ideally requiring some knowledge of S-plus or R computer languages[35];

[33] For details see Internet site http://www.epa.gov/ncea/bmds/bmds_training/software/overp.htm

[34] For details see Internet site http://www.rivm.nl/en/foodnutritionandwater/foodsafety/proast.jsp

[35] A graphical user interface (GUI) is currently in development for Proast (personal communication W. Slob 6TH Oct, 2010) which should facilitate ease of use of Proast; the initial release of which is anticipated in mid-2011. However,. since this requires the underlying code to be totally revised, a full validation of the software will then be necessary

- the choice of software - and indeed selection of particular model for a particular dataset during fitting – can significantly influence the output values;

- the use of the BMD method requires significant co-operation between scientists and statisticians during data analysis and interpretation (US EPA, 1995);

- there is a danger with BMD software that it can be deceptively simple and the output may be uncritically accepted. Importantly, this type of analysis should not replace expert judgment in risk assessment. An example might be in determining the biological significance of the occurrence of a very rare (but important) fetal abnormality that may not be recognised as of importance solely on the basis of statistical analysis;

- in a 'real world' situation, the key dataset relating to a suspected critical effect may be found to be unsuitable for detailed BMD modelling, and it may be unethical to require additional testing involving the use of vertebrate animals; and

- the existing regulatory toxicity test designs (typically comprising three treated groups and one control group) were developed with the intention of identification of a NOAEL or LOAEL. As such, they are not ideally suited for use in BMD modelling, for which a larger number of dose groups (each possibly comprising a smaller number of animals) would be preferable (US EPA, 1995).

The NOAEL involves a number of decision points for which slight changes in data can have a sizable effect on the outcome. Determinations of a LOAEL and a NOAEL are based, at least in part, on the degree of statistical significance. Thus, changes in response of only a few animals (or in even a single animal) can change a significant response to non-significant and vice versa. Further, according to the definition of a NOAEL, effects that are not statistically significant can be determined to be biologically significant. The calculation of BMD, on the other hand, does not require judgments about whether an effect is present in individual dose groups. The BMD also appears to be less sensitive than the NOAEL to small changes in the data (US EPA, 1995).

Finally, the extent to which the traditional default uncertainty factors (i.e. assessment factors in REACH) used in risk assessment are directly applicable to the outputs from BMD can be questioned. While the traditional uncertainty factors have been criticized as arbitrary, it may be more appropriate to consider them imprecise (Dorne and Renwick, 2005). In the case of BMDs it is necessary to consider the appropriateness of the uncertainty factors for within-human and animal-to-human variability (as per the traditional designs) but also the severity of the modelled effect and slope of the dose-response curve. While a BMD_5 has been shown to be similar to a NOAEL in some studies, others have found that a BMD_{10} may frequently be similar to the corresponding LOAEL (US EPA, 1995) raising questions as to what factors are most appropriate in various circumstances.

It has been suggested that while use of NOAEL-type approaches does have limitations, in practice the theoretical advantages of BMD modelling may be outweighed by its disadvantages related to the potential complexity of its application within a regulatory context. Thus, it is likely that the two methods will develop to have complementary roles with NOAEL used as a routine summary of effect and BMD analyses providing additional insight where higher tier assessment is appropriate (Travis et al, 2005).

Threshold of Concern (TTC) Concept

The Threshold of Concern (TTC) concept was initially envisaged as a means of defining a threshold for regulatory concern by the U.S. Food and Drug Administration in respect of indirect food additives, having evolved from earlier work by Munro on a Threshold of Regulation in relation to food contact chemicals. However, it has been suggested that the TTC principle may be of wider applicability in risk assessment than just the field of food-related chemicals (Kroes et al, 2005).

The basis of the TTC principle is that, in the absence of a full toxicity database, a *de minimus* value may be identified for many chemicals based on their chemical structures and the known toxicity of chemicals which share similar structural characteristics that would avoid the expenditure of resources on unnecessary toxicity testing and safety evaluations under scenarios where estimates of human intake suggested that exposure would fall below this threshold value (Kroes et al, 2004).

In its basic form, estimates of oral intake are compared with a TTC value derived from chronic oral toxicity data for structurally-related compounds. In non-food related applications such as in relation to cosmetic ingredients and impurities, there is however a need to consider whether route-dependent differences in first-pass metabolism that could affect the applicability of TTC values derived from oral data to another route, since the physicochemical characteristics and use pattern will influence the average internal dose value which TTC values reflect. However, it has been suggested that it is possible to extrapolate oral-based TTC values to at least dermal exposure scenarios provided that conservative default adjustment factors are incorporated.

It must be appreciated though that the TTC approach can only inform on the degree of safety with regard to systemic endpoints, and will not be predictive of possible local effects at non-oral sites of exposure (Kroes et al, 2007). The use of a decision tree has been proposed in which the first step is the identification and evaluation of possible genotoxic and/or high potency carcinogenic activity. Non-genotoxic chemical are then evaluated stepwise in relation to the concerns associated with increasing intakes since the distribution of NOELs for a wide range of endpoints have been found to be not dissimilar to that of NOELs for general toxicity endpoints. However, to date the approach has been shown to be unsuitable for a number of classes of chemical (e.g. proteins, heavy metals and polyhalogenated dibenzodioxins) and the limitations of this approach have yet to be fully defined. As a result, it should only at this time be regarded as a preliminary risk characterization tool where it may be useful in

preventing the need for extensive and expensive evaluation procedures (Kroes et al, 2005).

While the underlying principle of the TTC approach has recently be accepted by a number of EC scientific committees (SCCP, SCHER & SCENIHR, 2008), its suitability for use in the safety evaluation of chemicals was noted to highly dependent on the robustness of the underlying toxicity datasets and the need for a reliable exposure estimate was considered crucial. For many product categories such exposure data would be limited or absent. Overall, it was therefore suggested that further methodological development was required.

Toxic Equivalency Factor and Total Equivalent Quantity

The toxic equivalency factor (TEF) concept is based on an assumption that a group of (structurally-related) chemicals each exerts its toxicity via a similar mechanism of action and possesses a parallel concentration (or dose) response curve. Under these conditions, the total toxicity of a mixture of such chemicals can be expressed in terms of the toxicity that would be shown by an equivalent concentration of an index compound. The total equivalent quantity TEQ is estimated by the summation of the individual concentrations (or doses) of the chemical components in the mixture components, with the level of each multiplied by its respective TEF to correct for potency differences. A variant, the PODI method, is based not on reference dose but on POD (using NOAELs or BMD metrics). Extrapolation (e.g. animal to human) for risk assessment is then achieved by applying an overall uncertainty factor applicable to that group of chemicals (Kortenkamp et al, 2009).

Under the auspices of the WHO and the International Programme on Chemical Safety (IPCS), the TEF) concept has found application in the assessment of mixtures of chemicals sharing common mechanisms and behaviours, particularly in relation to dioxins, furans and dioxin-like PCBs. This component-based approach has also found limited application in the study of a few other compound groups, such as phenols, PAHs and oestrogens (Kortenkamp et al, 2009). As the underlying requirements for use of these techniques are only met for a small number of chemical groups, it is unlikely to find frequent application in the context of risk assessments relating to SEA requirements.

3.6 From Hazard Data to Health Impacts

3.6.1 Introduction

The aim of the various methods described above is to provide information on the intrinsic properties of chemicals with regard to human health. They are also aimed at providing data on how much of a chemical is necessary to produce a toxic response in a animal (toxicity studies) or human (epidemiology or human experimental studies) so that a "safe" level of exposure can be defined. Within a REACH specific context, the objective – through application of appropriate assessment factors to the data – is to develop a Derived-No-Effect-Level (DNEL) or, if necessary for non-threshold effects,

a Derived-Minimal-Effect-Level (DMEL) that can be compared with exposure estimates to characterise the nature of risk posed by use of the chemical (ECHA, 2010b). Default values are available for the assessment factors in the ECHA guidance; these address the issue of interspecies differences in sensitivity between experimental animals and humans in addition to differences in route or duration of exposure between the experimental scenario and the risk scenario under consideration (ECHA, 2008b). In situations in which there are adequate data available regarding the comparative toxicokinetic or toxicodynamic behaviour of the substance in animals and humans, it is possible to modify the assessment factors required for inter-species variability (Dorne and Renwick, 2005). Inter-species differences will obviously not need to be considered when human data are used as the starting point although appropriate adjustment would still be needed in the risk assessment to allow for intra-species variability (e.g. in relation to life-stage or genetic susceptibility differences) and the extent of uncertainty relating to the available datasets (ECHA, 2008b). Within REACH, this combination step is carried out as part of the exposure assessment.

This comparison of hazard information with exposure estimates allows, within health impact assessment (HIA), the development of an understanding of the likelihood of toxic effects occurring for a given exposure scenarios, thereby paving the way to derive estimates of types and numbers of cases of disease or adverse health outcomes that may associate with a particular exposure scenario for a given population.

3.6.2 Human Study Data and Toxicity Study Data

As indicated above, the outputs of toxicity studies can take a range of different forms, with the most common metric used in EU risk assessments to denote the POD being a NOAEL which can then be used to generate a DNEL for risk characterisation. An alternative metric for POD is given by the BMD approach (i.e. the BMD_5 or BMD_{10}). In either case, application of an appropriate assessment factor will be required to reflect the extent of uncertainty surrounding the available data.

Traditionally, the approach adopted in chemical risk assessments has been to calculate a risk characterization ratio in the form of either:

- the ratio of expected exposures to the DNEL, where a RCR>1 indicates a risk of concern; or
- the ratio of DNEL to expected exposures, to determine the Margin of Safety (MOS) associated with a given use of a chemical.

Within the context of REACH, it is not possible to derive a NOAEL, and thus a DNEL for non-threshold effects (e.g. non-threshold mutagens and carcinogens). As noted above, however, depending on data availability, it may be possible to develop a DMEL which constitutes a reference level that is considered of very low concern. In such cases, RCRs may then be developed in a manner synonymous to the use of DNELs; this is termed a 'semi-quantitative' risk characterisation. Where derivation

of a DMEL is not possible then, under REACH, the expectation is that a qualitative risk assessment would be undertaken instead[36].

While the resultant RCRs are essential for the chemical risk assessment process, the extent to which they provide information with which to inform an SEA is limited, as they provide no information on the severity or extent of effects that might be anticipated to occur in an exposed population.

Thus, within the context of SEA, it may be beneficial to utilise more sophisticated approaches that allow quantitative measures of risk to be generated which, in turn, can be used to derive estimates of the nature and scale of predicted human impact following a given exposure. Examples of such approaches are those which draw on mathematical models that use dose-response data from experimental studies in animals or epidemiological studies to determine a concentration of the chemical which, if humans were to be exposed to, would equate to a certain level of risk. For example, it may be possible to derive data on the level of exposure that is estimated to associate with a 'negligible' level of risk (e.g. a lifetime risk of 1 in 10^6); under some regulatory systems such information may, indeed, be used as the basis for exposure standard setting.

However, it must be appreciated that the criteria applied by different regulatory agencies may vary considerably. For example, the level at which a low-dose cancer risk may be considered as "essentially negligible" may vary between agencies, e.g. between 1 in 10^5 and 1 in 10^6 for exposure of the general public (Health Canada, 1996). In the evaluation of new chemicals, a value of estimated cancer risk falling within or below this range is not considered to represent a significant risk of carcinogenicity in the general public. In some circumstances a higher level of risk (e.g. 1 in 10^4 or 1 in 10^3) may be accepted, for example in occupational settings or, to take a very different scenario, to decide if use of a particular medicine to treat a disease which otherwise has a high fatality rate was acceptable.

Thus, outputs from the risk characterisations based on hazard and exposure assessment available for subsequent SEA may take the form of either a RCR or fuller dose-response functions. Examples of the latter are given by the work of SCOEL in setting occupational exposure limits for workplace exposure to carcinogens; for example, a dose-response function has been established for exposures to chromates which provides an indication of the number of workers per 100,000 predicted as contracting a case of lung cancer with exposure to chromates at different concentrations (SCOEL, 2004).

Where such dose-response functions are readily available or can be derived, it should be possible to move towards a quantitative SEA.

[36] See ECHA Guidance on information requirements and chemical safety assessment. Part E: Risk Characterisation, available at Internet site http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_e_en.pdf?vers=20_08_08

Key Issues in the Context of REACH

Calculation of the DNEL using NOAEL or a BMD-based value will incorporate a range of assessment factors, which are used to reflect uncertainty and to ensure that the resulting figure is a conservative estimate (i.e. provides a high level of protection with regard to risk). Within the context of human risk assessment, REACH also allows, where necessary, for the derivation of a derived minimal effect level (DMEL) in situations where a threshold of effect is not believed to exist or can't be established (e.g. for non-threshold mutagens or carcinogens). Under some risk assessment systems, in the absence of a NOAEL, it may be considered acceptable to use the available data on the LOAEL and to apply appropriate assessment factors (to reflect the extent of uncertainty) to derive a value that can be used as the basis for risk assessment.

In addition, as indicated above, it is not generally possible to move from in vitro study data to the derivation of in vivo dose-response information with any degree of confidence. This limits the degree to which hazard characterisation data from in vitro studies can be used to establish a NOAEL, and hence DNEL, estimate.

For impact assessment purposes within REACH, it should be noted that the use of assessment factors mean that the derived DNEL values do not in reality reflect a true estimate of the actual level at which a population would suffer 'no effect'. Rather it represents some level below this that is considered to provide an adequate allowance for the uncertainties implicit in the extrapolations undertaken (i.e. the derived value will rightly represents a conservative, protectionary estimate).

In order to quantify the scale of potential impacts within the context of a SEA, it is necessary to consider not only the established NOAELs but also the LOAELs (or BMD values) established within the hazard characterisation process, and to also collate data on effect levels above this where data are available, so that the nature of the dose-response curve for relevant endpoints can be fully characterised. If only data on the N(L)OAEL or BMD value are available, then the impact assessment may be constrained to consideration of only 'existing exposure' and 'no exposure' scenarios, rather than considering the changes in impact associated with a range of exposure levels. Depending on whether other possible risk reduction measures are available, this may or may not assist in comparing the costs and benefits of risk reduction in the context of a restriction proposal versus other measures. In the context of authorisation, however, it may be adequate as the assessment will focus on the use versus no use scenario.

In any event, uncertainties surrounding any N(L)OAEL or BMD indicative effect level should be made clear and quantified where possible; this is important as an impact assessment should not only consider the 'worst case' assumptions necessary for the risk assessment and characterisation process, but also consider 'average/median' and 'best value' estimates. Quantification of uncertainty in terms of upper and lower bounds around the N(L)OAEL or BMD would be particularly helpful in this regard.

Finally, as noted above, there are likely to be some cases where the risk characterisation is qualitative in nature. This has been the case for some carcinogens (e.g. those operating via a genotoxic mechanism) and for certain irritants and sensitizers. Where this is the case, it is not generally possible to carry out a quantitative impact assessment. In these, some type of benchmarking process may be more appropriate, setting out generic descriptions of hazards against the types of risk management actions that might be appropriate based on a consideration of both the consequences of the health effect and the likely numbers exposed.

3.6.3 Use of Epidemiological Data

The outputs of epidemiological are essentially an estimate of the likelihood and the severity of an effect (e.g. 1 case per 100,000 exposed). The studies can potentially generate a range of summary measures that can then be utilised in risk assessment and worker health and consumer and general population health impact assessment. For example, epidemiology data has been used to generate a set of response functions to characterise the impact of chemicals, in this case air pollutants) in relation to a entire population rather than for particular sub-groups (Hurley et al , 2005).

Other measures of the burden of disease, such as attributable fractions and numbers and measures of quality of life, can be generated from epidemiological and human studies and these data are also widely used in socioeconomic assessments. These measures are based on the use of risk ratios (and a variant of this the standardised mortality ratios, SMRs) and odds ratios.

The summary measures resulting from such studies can be categorised into those relating to the adverse health outcome (risk estimates such as the odds ratio and relative risk) and those relating to the exposure of concern (levels of exposure, sector of population exposed, numbers or proportions exposed). If data are sufficient, then the relationship between the adverse health effect and measures can be presented as a dose-response relationship. These measures and relationships have wide use for standard setting, for example in the derivation of NOAELs and LOAELs, benchmark doses values and directly from quantitative exposure response models.

Key Issues in the Context of REACH

Human-derived information is, in principle, the most relevant source of information on the toxicity of a substance to humans since the mode of action of any effects detected is of obvious relevance and because no inter-species safety or assessment factors will need to be incorporated into the assessment. However, although the risk ratios derived from epidemiological studies may be relatively reliable, the associated data on exposures may be poor or based at too high a level to provide reliable predictions particularly in relation to environmental (as opposed to occupational) exposure scenarios. The data are also often historic and some analysis may be required to adapt information to reflect current exposure levels (for example, due to a reduction of permitted occupational exposure levels or measures that reduce exposure via the environment).

Given these reservations, in practice, when human data are available for a substance, they are considered alongside experimental data as part of the overall human hazard assessment process under REACH. Indeed, as discussed in a recent draft guidance document by ECHA (2010b), a wide range of human study types (including epidemiological studies, medical case reports and volunteer studies) may be used as the bases for deriving DNEL or DMEL values.

Perhaps more of an issue is the fact that the coverage (i.e. availability) of these studies may be too limited to provide the data needed for the types of chemicals likely to be subject to restriction or authorisation in the future. For example, while risk ratios have recently been developed for carcinogenic agents and occupations classified by IARC as a Group 1 (established) or 2A (probable) carcinogen that, for occupational exposures, had either 'strong' or 'suggestive' evidence of carcinogenicity in humans for the specific cancer site (Rushton et al, 2007 and 2010), such information may not be readily available for compounds assigned by IARC to other Groups or for other (non-cancer) endpoints.

4. METHODS OF IDENTIFYING ENVIRONMENTAL RISKS

4.1 Introduction

The strengths and weaknesses of ecotoxicology methods have been reviewed previously by various EU bodies in relation, for example, to the interpretation of effects in the assessment of risk to the aquatic (EC, 2002) and terrestrial (CSTEE, 2000) environments, and have been extensively discussed with regard to the REACH Regulation in the ECHA Guidance. More recently, the basic limitations of the ecological sciences and ecotoxicology to inform on the extent to which a ecosystem may be damaged by an environmental stressor (e.g. a chemical) was again highlighted (WCA, 2010).

Environmental risk assessment of chemicals share many methodological aspects with human health risk assessment. However, environmental risk assessment covers millions of species (rather than the one in human health) and the overarching goal is to protect populations and ecosystems as a whole rather than individual organisms. Environmental risk assessment relies on ecotoxicology, a multi-disciplinary approach involving:

- chemistry: primarily to determine the inherent chemical properties of the substance and their likely fate and behaviour in the environment (the interaction between the substance and environmental systems);

- toxicology: primarily to assess interactions between substances and species (modes of action and effects); and

- ecology: primarily to assess and predict the effects, interactions and recovery at the population level and between species.

The contribution of each of these areas is discussed below with regard to the implications for the environmental risk assessment (ERA) of chemicals and how the outcome of these traditional EU risk assessment approaches might be adapted or interpreted for the purpose of SEAs. A particular issue with regard to the relevance to SEA is that the Risk Characterisation Ratios (RCRs) that are the ultimate output of the risk assessment process do not in themselves provide adequate data with which to characterise, quantify or cost the impacts to the environment. RCR-based approaches are essentially intended to identify a concentration level at which there will be no appreciable risk of any adverse effect. However, for the purpose of SEAs, there is a need to establish what effects may occur at given environmental concentrations.

As a result, it is therefore important for this study to also look at what approaches to ERA are available and the extent to which these may provide additional information of value to SEAs. These include the use of species sensitivity distribution (SSDs) curves or multispecies (system) tests which aim to estimate what proportion of species will be affected at particular concentration levels. In addition, within the scope of

SEA, there is a need to develop suitable approaches to address not only the quantification and costing of toxicity impacts but also to define approaches that can address issues such as persistence and bioaccumulation.

4.2 Chemical Properties and Fate and Behaviour

4.2.1 Introduction

The environment can be divided into four distinct compartments (or media): water, air, soil and living organisms. However, in many assessments the environmental compartments are further distinguished according to, for example, their different properties. Movement and transformation of a substance in and between the compartments are dependent on physicochemical properties inherent to that substance, on the properties of the media and on the influence of biotic factors such as food webs. The chemicals' physicochemical properties are used in environmental risk assessment in order to determine the likely behaviour and fate of chemicals that are released into the environment. The commonly used physicochemical measures are:

- **water solubility:** the polarity o f molecules affects their solubility in water. Some substances (such as lipids and hydrocarbons) are hydro-phobic, i.e. they do not mix with water. These so-called lipophilic substances are more likely to move through biological membranes (and thus reach different organisms and their organs/parts) and therefore are more likely to have a toxicological impact;

- **partition coefficients:** like oil and water, octanol (a non polar liquid) and water (a polar liquid) will separate if mixed together. If a chemical is dissolved in this mix, it will partition or split between the two liquids, however, the ratio of the chemical that equilibrates to the water or octanol parts varies from substance to substance. This so-called partition coefficient is the measure of the ratio of the solute (chemical) in the two forms of liquid, i.e. K_{ow} (the partition coefficient between *n*-octanol and water) = concentration in octanol / concentration in water. This provides an index of a substance's hydrophobicity, which affects its behaviour in the environment, for instance whether it is more likely to remain dissolved in river water or to adsorb onto the sediments in the river, and is also an important indicator of a substance's bioaccumulative potential (see Section 4.6);

- **vapour pressure:** is a measure of the tendency for a liquid or solid to volatilize, and is defined as the pressure exerted by the vapour of a substance at equilibrium. It can be expressed as a fraction of normal atmospheric pressure, which is 760 torr. Since substances volatilize faster at higher temperatures (like the steam that comes off a pot of water as it is heated up), vapour pressure increases with rising temperature (i.e. more vapour is created); and

- **persistence (chemical stability):** chemicals may be broken down by chemical and/or biochemical processes such as hydrolysis, oxidation, photodegradation or enzyme systems. The rate at which the degradation takes place is influenced by

environmental factors such as temperature, light and pH; however, different chemicals will have different degradation times under the same environmental conditions. The ability of a chemical to persist in the environment partly determines its potential for transport: chemicals that break down fast are unlikely to be transported far away from where they were emitted before they are broken down whereas the most persistent chemicals may end up in remote, pristine areas such as the arctic.

Table 4.1 below shows the information on physicochemical properties that may be required for REACH registration (depending on tonnage).

Table 4.1: Physicochemical Properties Required for REACH Registration
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

These properties in combination affect the way a chemical will behave in the environment, i.e. whether it is adsorbed onto solid surfaces or absorbed into the solid, more likely to impact on aquatic or terrestrial species and its rate of transport. This information is therefore used to the construction of models for environmental fate and behaviour.

4.2.2 Transport in Different Environmental Compartments

The transport of chemical pollutants between environmental compartments is a major factor impacting upon its potential to cause damage, as it affects the exposure rate of different ecosystems.

Transport in Water

Pollutants may be present in water as suspended particles or droplets (e.g. oil) or in solution, and this impacts upon how far the chemicals are transported in a water body. Liquid droplets may float to the surface or become adsorbed onto the surface of sediments suspended in the water body. Particulates are likely to remain suspended if they are light enough to be carried by the turbidity of the water, and then fall to the

bottom in less turbid waters (e.g. at estuaries where a river enters the sea). Bigger particles therefore have shorter transport ranges than smaller particles or liquids, whereas stable chemicals which are dissolved in fast flowing rivers have the potential to be carried furthest away. Other factors influencing the transport in water are sea currents and temperature (which affects the density of sea water). The movement and precipitation patterns of pollutants in water mean that their distribution is not uniform. This is further impacted if the pollutants enter the food web.

Transport in Air

Pollutants may be present in air in the gaseous state, as droplets or particles or in association with droplets or particles (for instance adsorbed onto rain drops or dust particles). Their transport is dependent of physical processes such as diffusion as well as the global circulation patterns of air. Pollutants released higher up above the Earth's surface (e.g. emissions from aviation) are more liable for longer range transportation. Pollutants in the air may be deposited back onto the Earth's surface by means of wet deposition (i.e. washed out by rainfall) or dry deposition (i.e. adsorbed onto surfaces such as the surface of a lake).

Transport in Soil

The fate and behaviour of chemicals in the soil compartment depends largely on their partitioning between the soil particles and the water in the soil pores. Substances are more likely to adhere onto the soil particles in clay rich soils, whereas in sand they are more likely to be found in the pore-water. Substances in the soil pore-water are more likely to enter the food web as they are taken up by earthworms which are then assimilated by predators.

Transport in Living Organisms

Substances can move between living organisms via the food web. The bioconcentration factor is a measure of to what extent an inorganic pollutant is *assimilated* by an organism. The bioconcentration factor (BCF) can be expressed by concentration of the chemical in the organism / concentration in the environment. The bioaccumulation rate of the chemical depends on the rate at which the substance is excreted or metabolised by the organism.

4.3 Assessing Ecotoxicity

The first (and often only) step in support of meeting the requirements for in vivo studies for environmental risk assessments is normally single species studies, where the impact of a chemical is assessed on one species at a time. However, this is generally repeated for a number of different species across a range of taxonomic groups as they will show varying sensitivities to different chemicals.

With 1.5 million species classified, it would be impossible to test a representative sample of species (van Leeuven et al, 2003). A limited number of species are therefore selected for testing the choice of which is, in part, based on the relevance of particular species in terms of their ecological function, their morphological structure and their route of exposure. There are nonetheless a range of practical factors that also strongly influence the choice of test species; these include, for example, the availability of organisms for testing throughout the year, their cost, suitability for maintenance under laboratory conditions, and their convenience for testing (e.g. see OECD, 1992). The underlying intention in the selection of a range of species for use in a testing strategy is to generate as much relevant information as possible within a practically achievable test program.

Often the available dataset will comprise only short duration studies that address a restricted set of endpoints and are generally performed in only a small number of test species, often involving only a part of their life cycle. The nature of the hazards and risks to the environment, in terms of individual organism and population consequences, are then 'inferred' from this dataset. Importantly, only a few substances have been subject to investigation using higher tier methods such as microcosm and mesocosm studies.

As a consequence, most existing risk assessments are subject to some significant weaknesses (WCA, 2010):

- Toxicity tests generally focus on the most sensitive life stage for the individual organism but this be unrepresentative of the stage of greatest significance to the long-term viability of a population;
- Simplistic acute endpoints do not inform on demographic responses of populations to exposure;
- Residual or delayed onset effects after cessation of exposure are infrequently considered;
- Interpretation of population consequences of simplistic dose-response functions (such as for lethality) is uncertain; and
- Particular uncertainty exists when attempting to infer temporal or spatial impacts using simplistic ecotoxicity models.

While these difficulties exist when attempting to infer effects at a population level, even greater challenges may exist when attempting to extrapolate to the wider ecosystem. For example, the impact of an acute (lethal) event could have long-term consequences at the community level depending on the life cycle of the particular species affected and the extent of any resultant change in inter-species interactions or there might be either direct or indirect (e.g. through loss of the principle prey species) loss of a keystone or dominant species which would result in a step change in ecosystem structure. It might even be that prolonged exposure to a low level thought to be of limited impact on the basis of the available toxicity tests would result in a sufficient loss in vitality at the population level to influence long term sustainability (WCA, 2010).

Thus, there are significant challenges when undertaking environmental risk assessments on substances that can only be addressed by adopting a precautionary approach when deriving a metric for use in risk characterisation. Against this background, the challenge for SEA can be seen to be significant since here the focus is to determine what the nature of any environmental impacts might be under a particular exposure scenario and, furthermore, to develop a suitable qualitative or quantitative description of the impact to inform the decisions of policy makers. The various approaches that are currently available to risk assessors are discussed further below, starting with the currently most commonly used method, derivation of a PNEC.

4.3.1 Single Species Tests

The ecotoxicological information which may be required for REACH registration (depending on tonnage) is summarised in Table 4.2.

Table 4.22: Ecotoxicological Information Required for Registration under REACH

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

The different types of test (computational models, in vivo and in vitro studies) and, in generic, terms their particular strengths and weaknesses have already been discussed extensively in relation to human health. Rather than repeat these aspects here, the focus in the following discussion is only the specific issues that arise when attempting to extrapolate the findings from experimental tests to assess the risks that may associate with environmental exposure, in particular the problem of interpreting the potential impacts at the level of population, community and ecosystem on the basis of experimental data on a limited number of laboratory species. However, it must be appreciated that an additional complication in cross species extrapolation in the field of ecotoxicity is the extent to which the environment to which a test species is native may influence its sensitivity to a substance. For example, Kwok et al (2007) showed that tropical species tend to show greater sensitivity than their temperate counterparts to ammonia, phenol and some pesticides but are less sensitive to most metals. Also, the range of endpoints investigated by ecotoxicity tests tend to be somewhat more limited than those applied in respect of human health assessment and generally focus on endpoints such as survival/mortality, growth and reproduction; it must be re-emphasised that while a substances may cause a particular effect in one test system or species, it may elicit a different (or no effect) in another test model at the same exposure.

The range of endpoints that may require consideration has in recent years widened as the significance of a wider range of toxic mechanisms has been appreciated. For example, it is now recognised that endocrine disrupting chemicals may cause changes to the hormone systems of organisms directly by mimicking or blocking natural hormones or as a result of secondary mechanisms. Since hormone systems control the reproduction and development of most if not all species, endocrine disruption may result in a wide range of effects across various species. The potential for a chemical to exert endocrine disruptive activity can be determined by in vitro studies (based on cell lines or receptors, often derived from mammalian tissues) or in vivo (e.g. looking for changes in reproduction or sexual development of two-generation full life-cycle tests to look at effects on second generations). Ecotoxicity in vivo tests for endocrine disruption are often carried out in fish species. However, since different genera may have markedly different endocrine systems – potentially with structural similar or identical hormones exerting different physiological effects - and may not therefore react in the same way to a chemical, tests on a wider range of animal species have recently been, or are in the process of being, validated by the OECD (van Leuuven et al, 2003*;* OECD, 2010).

4.3.2 Approaches to Risk Characterisation in REACH

During a risk assessment, the ecotoxic potential of a substance is often defined in terms of its Predicted No Effect Concentration (PNEC), i.e. the concentration below which exposure to the substance is not expected to cause any appreciable adverse effect. PNECs are generally derived separately for each of the environmental compartments routinely considered and this generally includes consideration of aquatic and benthic organisms (generally in freshwater but also, where relevant, marine sspecies), terrestrial organisms, higher predators and also microorganisms (in

relation to risk to STWs). A PNEC value for a particular substance is then generally derived from the most sensitive endpoint from amongst the available single species tests (see above) for the particular compartment under consideration.

The available dataset may be limited to the results of short duration tests (or the output from computer models, (Q)SARs) addressing endpoints such as lethality, growth inhibition or, possibly, reproduction (i.e. based on metrics such as LDx, LDx, EDx or ECx). The metric selected - which effectively acts as the POD – is then divided by an appropriate assessment factor (generic values are defined in the TGB; ECHA, 2008d) so as to establish a PNEC for the relevant environmental compartment that can be compared with estimated (or measured) environmental exposure levels to derive a risk characterisation ratio (RCR). The types of effect-concentration measure generally used in this approach to deriving a PNEC are listed in Table 4.3. It is possible that the increasing focus (driven by ethical considerations) on the preferential use of non whole animal test methods, may restrict the nature of future datasets available for establishing the ecotoxicity profile. For example, some of the current 'alternative' methods do not provide specific NOEC values or dose-response relationships that are needed to inform a robust PNEC.

Table 4.3: Effect Measures

Effect Measures	Definition	Unit	Variations
LC_{50} (Lethal concentration 50 or median lethal concentration)	The concentration of a chemical that is lethal to one-half (50%) of the experimental animals exposed to it Similarly, LC10 is the concentration lethal to 10% of the test subjects	Concentration of the chemical in the test environment, such as ml/l in water	
LD_{50} (Lethal dose 50 or median lethal dose)	The amount (measured as a dose) of a chemical that is lethal to one-half (50%) of the experimental animals exposed to it	Weight of the chemical per unit of body weight (mg/kg)	The substance may be fed (oral LD_{50}), applied to the skin (dermal LD_{50}), or administered in the form of vapour or aerosols (inhalation LD_{50})

Table 4.3: Effect Measures			
Effect Measures	**Definition**	**Unit**	**Variations**
EC_{50} (Effective concentration 50)	The amount of a chemical that causes a given effect to one-half (50%) of the experimental animals exposed to it This is similar to LC_{50}, however, the endpoint is not death but another adverse effect such as reproductive failure or non-lethal toxicity Similarly, EC_{10} is the concentration that causes the effect in 10% of the animals exposed to it	Weight of the chemical per unit of body weight (mg/kg)	The substance may be fed (oral EC_{50}), applied to the skin (dermal EC_{50}), or administered in the form of vapours or aerosol (inhalation EC_{50}) EC_{10} is the concentration causing the effect to 10% of the test subjects
ED_{50} (Effective Dose 50)	The concentration of a chemical that has a given effect on one-half (50%) of the experimental animals exposed to it	Concentration of the chemical in the test environment, such as ml/l in water	
NOEC (No Observed Effect Concentration)	The concentration at which no effects were observed This is only meaningful if the concentration at which effects start to occur is also known (e.g. LOEC)		
LOEC (Lowest Observed Effect Concentration)	This is the lowest concentration at which any effect was observed		

According to the OECD there are three main approaches possible when deriving a PNEC depending on the extent of information available (van Leeuven et al, 2003):

- **preliminary effect assessment:** this first stage applies if only QSAR estimates (i.e. computational models rather than laboratory testing of the chemicals) or a few short term (acute toxicity) laboratory studies to determine the toxicological impact (such as LC_{50} or EC_{50} values, i.e. the concentration that is lethal or has an effect on 50% of the population being tested) are available;

- **refined or intermediate effects assessment:** the next assessment level requires a a few chronic (i.e. longer-term) test results that enable establishment of chronic No Observed Effect Concentrations (NOECs)); or

- **comprehensive effects assessment:** the highest level can only be used where field studies, multi-species toxicity studies (or many chronic results in a wide range of species) are available.

The use of PNECs is of course based upon the acceptance of a number of implicit assumptions (Leeuven *et al*):

- the species selected for testing are representative of all species found in the ecosystem;
- the chronic toxicity threshold determined for the most sensitive species is also the relevant chronic toxicity threshold for ecosystems; and
- species and species level properties of ecosystems are the most sensitive to ecosystems.

However, the degree to which these assumptions actually apply to any given case will vary. Thus, for example, not all species demonstrate the same degree of sensitivity to different substances, nor are they subject to the same mode of action (e.g. a substance may cause death or reproductive failure in one species but not in another). In order to account for the known differences in sensitivity among species and to provide reassurance regarding the conservative and protective nature of the output, as noted above, assessment factors are used in REACH to reflect the extent and nature of the data. The assessment factors recommended by ECHA have thus been designed to address the degree of uncertainty that surrounds data in terms of intra- and inter-laboratory variability, intra- and inter-species biological variance, difference between relevance of short- and long-term toxicity data, and uncertainties in extrapolation of laboratory-derived data to field situations.

The aim in using single species data in a SEA is to adopt an established dose-response function for a particular species to make predictions against. The dose-response is characterised by the relationship between dose (i.e. amount) of toxicant and the response (generally incidence); the response may be a lethal effect or a sub-lethal change (e.g. altered development, growth, reproduction, behaviour or physiology). To establish the dose-response, test animals are generally given a substance at one of a series of controlled doses via an appropriate route of administration. Often within ecotoxicology, test organisms are kept in an environment maintained at known concentrations to establish the concentration-response relationship (e.g. fish kept in water containing specific concentrations of the toxicants). By comparing the effect seen at different doses or concentrations, a dose (or concentration) response curve can be derived (Figure 4.1))[37]:

[37] http://www.emcom.ca/science/dose.shtml

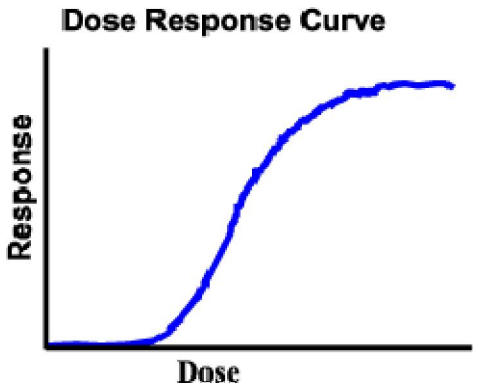

Figure 4.1: Example of a Dose-Response Curve

Generally, increasing the dose or concentration of a harmful agent will result in a proportional increase in the incidence (and possibly severity) of an adverse effect. This assumes that:

1) response will increase as dose increases;

2) there is a threshold dose below which no effect can be detected; and

3) there will be a maximum dose above which no further increase in response is seen (i.e. the effect (response) is maximal).

This simple model approach is useful to develop basic dose-response relationships. However, more complex relationships may occur with some toxic mechanisms (e.g. in the case of receptor-mediated endocrine disruption where there may be an unexpected fluctuation in the dose-response, for example, at very low exposures, termed a non-monotonic dose response). Usually, dose-response findings are summarised using metrics such as the median lethal or effective dose (i.e. the dose which kills or has an effect on 50% of the individuals tested, LD_{50}, LC_{50}, ED_{50} or EC_{50}). However, since the precise nature of the dose-response curve is likely to vary greatly between species, a dose-response relationship should not be automatically assumed to be directly applicable to another species, even if closely related. Approaches such as Species Sensitivity Distributions (SSDs) have therefore been developed to attempt to address this limitation (see discussion below).

A number of recent research programmes have focused on novel approaches to the use of single species experimental test data to infer effects at the population level; many of these have focused on the study of the potential effect of endocrine disrupting substances on the demography of fish populations. For example, in the EDCAT project sponsored by the UK's Environment Agency and Defra, evidence suggested that it might be possible to link the extent of intersex seen in fish to population level consequences (Brunnel University et al, 2009) while Grist (2003) studied approaches to extrapolation from N(L)OECs for endpoints such as gonad histology to generate estimates of intrinsic rate of population growth (r = ln (l)), a

parameter of demographic importance using as a model the effects of ethinyl oestradiol on fish. Studies in Switzerland on the brown trout (*Salmo trutta*) by Burkhardt-Holm (2008) have also investigated the linkage between experimental results from the YES assay and plasma vitellogenin (VTG) measurement in fish, to the effects of oestrogens on sexual development and reproductive parameters in the species. Importantly, this study established that factors (e.g. habitat quality) other than oestrogen exposure exerted a stronger influence on population structure than oestrogen exposure but suggested that populations might be more sensitive to changes in survival rate in the first winter and beyond than to changes in early life stage survival or reproductive parameters. Gleason et al (2001) also reported on linkages between markers of endocrine effects to indicators of population level effect using basic population models on the fathead minnow (*Pimephales promelas*).

There is also a growing interest in the possible application of novel markers of effect or exposure through use of '-omic' technologies (such as genomics and proteomics) as an alternative to the traditional toxicity endpoints in order to determine the response to a substance at the level of the individual (see review by Ankley et al, 2006). While this possibility has yet to be fully elucidated, efforts are also being made to seek methods for establishing linkages between gene expression level changes and population level responses. For example, Fedorenkova et al (2010) have studied this question mechanistically (through a conceptual framework) and correlatively (using SSD approaches – see below) in respect of the effect of cadmium on aquatic species. Gene level responses (lowest observed effect concentrations) and individual level responses (median lethal concentrations, LC_{50}, and no observed effect concentrations, NOEC) were compared and it was noted that gene expression could be detected on average 4-times above the NOEC and 11-times below the LC_{50} values. It was concluded though that, for a mechanistic gene-population link to be established for risk management, research was required to establish at least one meaningful end point at each level of organization. However, a recent review by Schrimer et al (2010) considered the implications of developments in omic-technologies and the possible implications with regard to ecosystem risk assessment. These include use of toxicant-specific gene expression profiles to identify effects attributable to particular chemicals (quoting examples for copper, cadmium and zinc). Studies on the freshwater cladoceran invertebrate *Daphnia magna* using toxins such as cadmium, ibuprofen and in the nematode *Caenorhabditis elegans* using silver nanoparticles, were reported to have shown that measured gene responses may be linked to impacts on somatic growth, development and, importantly, population growth.

Thus, in the longer term it may be that implementation of such methods will increase the extent to which population level effects can be inferred from experimental tests. However even within the context of current scientific understanding, where a particularly valuable species is anticipated to be affected by a substance, use of an assessment based upon single-species dose-response functions may be of particular value to a SEA.

For example, if a toxicant is known to affect the survival rate of trout, a dose-response curve for this endpoint could be used to assess the proportion within a given

population that would be likely to be affected at various exposures. This could then be compared with environmental concentrations predicted for the different risk management scenarios considered in the SEA and, hence, estimates derived of the likely scale of fish losses. Such estimates might then form the basis for estimates of economic cost in terms of impact on fisheries, etc.

A possible limitation with regard to the interpretation of single species dose-response function is that much of the test data available for many species may relate to only 4 day exposure periods (as the current working consensus is that lethality occurs within the first 100 hr of exposure). However, this is not necessarily true for all toxicants. For example, one study found that, of 375 cases examined, 42 (11%) showed the most sensitive lethal threshold only after greater than 4 days exposure (Sprague, 1969, as quoted by Newman and Clemens, 2008). Care is therefore needed when attempting to infer outcome in a natural environment where exposure is not controlled and may well not be time-limited.

Furthermore, although the single species method may be highly informative if data are available on the species of interest (or can be shown to be likely to be predictive of the species of concern), other approaches may still be required to address possible wider environmental impacts. Also, the use of species-specific dose-response functions of sufficient predictive ability are unlikely to be available for some species (e.g. top predators or key species such as polar bears).

Multiple Species Approaches

Although PNECs are frequently based on the findings from one study on a single species that is considered to show the greatest sensitive, a more refined risk assessment approach is also considered acceptable under REACH. This attempts to better characterise the nature of a substance's impact across a range of species such as might be present within the environment (ECHA, 2008e). This approach, known as a Species Sensitivity Distribution (SSD), uses statistical extrapolation techniques and is based the following assumptions:

- distribution of species sensitivities follows one of a series of theoretical distribution functions; and

- the group of species for which test data represents a random sample of the overall species sensitivity distributions.

SSDs have however been subject to some criticism on the basis of: concerns regarding lack of transparency of methodology; the extent to which test species used are representative; the extent to which it is possible to compare endpoints combined within the analysis; and the arbitrary nature of choosing a particular percentile of response to form the basis for establishing a PNEC.

Such concerns are addressed at least in part in the ECHA guidelines by requiring a robust dataset to be applied if this approach is adopted. Specifically, the guidance suggests that data should be drawn from at least 10 species covering 8 taxonomies:

1. Class Osteichthyes (e.g. salmonids, minnows, bluegill sunfish, channel catfish etc.);
2. A second family in the phylum Chordata (in the class Osteichthyes or an amphibian etc.);
3. A crustacean (e.g. cladoceran, copepod, ostracod, isopod, amphipod, crayfish etc.);
4. An insect (e.g. mayfly, dragonfly, damselfly, stonefly, caddisfly, mosquito, midge etc.);
5. A family in a phylum other than Arthropoda or Chordata (e.g. Rotifera, Annelida, Mollusca, etc.);
6. A family in any order of insect or any phylum not already represented;
7. Algae; and
8. Higher plants.

The detailed methodology for developing a SSD estimate is presented in the Guidance document (ECHA, 2008a) and will not be repeated here. In brief, normally the NOECs obtained from a series of single species tests spanning several taxanomic groups are subject to log normal transformation (although other transformations may be considered where these are mathematically preferable) before being plotted. A best fit curve is established using one of the available standard statistical techniques (see example in Figure 4.2).

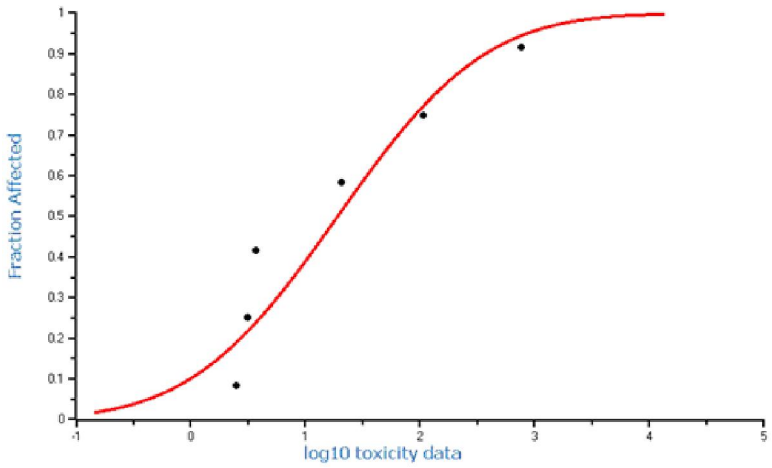

Figure 4.2: Example of a Species Sensitivity Distribution Curve

The SSD curve thus developed can be used for:

- calculating the risk (expressed as the potentially affected fraction, PAF) at a certain concentration – i.e. what percentage of all species are predicted to be affected at a specified environmental concentration of the substance?; or

- calculating the environmental quality criterion (EQC) for a certain cut-off value, such as the 5^{th} percentile (HC_5 - the hazardous concentration for 5% of the species within an ecosystem) (van Leeuwen, 2003) – i.e. what concentration of the substance could be allow in the environment if we are willing to accept an impact on an arbitrary percentage of the species (such as 5%)?

In REACH assessments, the fifth percentile is generally adopted although this is a pragmatic rather than a scientifically justified choice. Importantly, the sensitivity of the data is also considered by generating at least the 50% confidence interval. The value thus derived is then used to derive the PNEC. This is achieved in the risk assessment by dividing by an assessment factor which, although tending to be somewhat smaller than those applied for PNECs based on single species data, may have implications with regard to the use of such data directly within an SEA assessment. It has, however, been suggested that it may be appropriate to consider the need for assessment factors when extrapolating between SSD curves, depending on whether they are based on tropical or temperate species (Kwok et al, 2008).

The adoption of an SSD approach has been recommended recently even in situations where the datasets are significantly less than that constituting the ECHA standard dataset requirement; this is provided that the greater degree of uncertainty of the output is adequately recognised. For example, the value of the SSD in case studies on only six NOECs drawn from 3 trophic levels or 4 species from 2 trophic levels, were used to demonstrate the potential benefits of the SSD approach (WCA, 2010).

SSD curves may however be of wider value than their use to generate a PNEC. In respect of SEAs, they offer a mechanism by which the potential implications of environmental exposures could be explored with regard to the extent of the environment that might suffer varying levels of adverse impact under a particular exposure scenario. For example, by overlaying a SSD curve with one showing the concentration distribution for a substance in an environmental compartment under study (e.g. drawing on actual monitoring data or estimates from modelling), the probability that a percentage of the rivers (or whichever other environmental compartment is analysed) may be at risk of exceeding the NOEC for a given percentage of species, can be easily determined (see Figure 4.3).

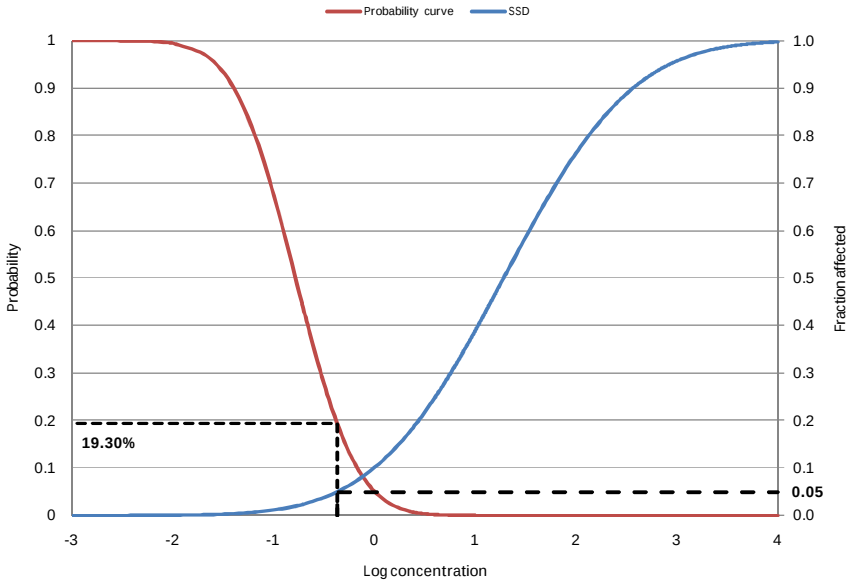

Figure 4.3: SSD Curve Overlaid with Environmental Concentration Probability Curve

In the example given in Figure 4.3, the dashed lines show that, for an arbitrary effect level of 5% of species, 19.3% of all rivers will have concentration levels predicted to exceed the concentration causing this magnitude of effect.

Both the SSD and PNEC approaches are based on a number of common key assumptions. For example, that the types of test species for which data are available are predictive of the range of species present in the ecosystem, that the response is seen at the level of each species, and that species' level responses are the most sensitive indicator of ecosystems effects. In the case of the SSD approach, there is further an assumption that the sensitivity of the individual species is predicted by a simple distribution curve, and that drawing on a number of such distributions provides adequately describes the range of sensitivities that would be present in the entire ecosystem under consideration. Such implicit assumptions bring with them a number of limitations as to the predictive ability of the approach; for example, it cannot be discounted that there may be more sensitive species (or life stages) present in a particular ecosystem. Within the risk assessment process, these concerns are addressed through application of an assessment factor during the derivation of a environmental quality criterion (EQC) based upon a nominal concern 'cut-off' limit, such as the HC_5.

4.3.3 Systems Level Tests

There are some investigative approaches that attempt to address the limitations of environmental risk assessments based on either a single study derived PNEC or use of the SSD approach to combine data from a series of studies each on a single species, which have currently found the widest application in relation to pesticide risk assessment (WCA, 2010). These designs attempt to study the impacts of chemicals at the ecosystem level, and comprise:

- **natural field studies:** here both stressors (in this case chemical pollutant) and the test system are naturally derived (i.e. these are studies on 'real world' scenarios). An example would be study of the effects of the effluent from an industrial site on a river system by comparing sites up- and down-stream of the point of contamination. Field studies are the most extensive system level test available. However, these studies are hard to interpret and are open to confounding factors; as a result, it may be hard to distinguish between chemically induced effects and natural background variation. Also, the results from one test cannot be readily extrapolated to another scenario since there are so many differences between different ecosystems and these are little understood or characterised; and

- **simulated field systems:** these are less complex systems level tests where the test system is either:
  - a man-made physical model (for instance fabricated tanks large enough (typically 2,000 to 20,000 L) to be representative of benthic ecosystems, such as ponds); these are termed microcosm studies; or
  - an isolated subsection of a natural environment (a mesocosm).

In the case of the simulated field system type of study it is necessary to manually apply the substance under study to achieve a predetermined release rate or achieve a target concentration (an activity that would be considered of questionable ethics except in exceptional circumstances were the release to the open environment). These simulated studies – while offering an opportunity to study a relatively complex ecosystem system – allow a greater measure of experimental control, are much more cost efficient and efficient, and are also of greater ethical acceptability than natural field studies.

Thus, system level studies go a significant way towards overcoming the limitations implicit in risk assessments based on single species laboratory studies since they provide a realistic assessment of a chemical's impact on an ecosystem under known conditions (e.g. can readily inform on bioavailability of the chemical and its fate and behaviour within the system under study). They have also found application in the study of ecosystems following exposure to a known chemical. Field studies in particular offer a potential means of validating the findings from risk assessments, confirming the fate and behaviour of specific chemicals but have also played a key role in basic research into the influence of stressors on the structure and function of ecosystems (Graney, 1993).

Nonetheless, there remains a number of limitations to use of these approaches (WCA, 2010; van Leeuwen, 2003):

- they are much harder to interpret than single species tests due to difficulties in controlling test conditions (e.g. it is much harder to achieve target environmental concentrations of the substance);
- for non-field studies, there are ethical constraints to choice of species to be included (e.g. use of vertebrates);

- there are also practical constraints (e.g. inclusion of species with seasonal lifecycles);
- there remains uncertainties as to how best to extrapolate from the study community to natural ecosystems; and
- such studies can be extremely expensive and time consuming.

Hence, these types of study are unlikely to be used within routine REACH assessments but may find application as detailed investigations to resolve outstanding issues the normal risk assessment steps have been exhausted, e.g. where the risk assessment has indicated a low margin of safety but there are high economic consequences at stake.

4.3.4 Computation Models of Ecotoxicity

Reflecting the situation with regard to methods for assessing hazards to human health, an increasing focus of research is the development of computation methods that can inform on the ecotoxicological properties of a chemical without the need to undertake experimental testing.

In particular, the OECD has developed a QSAR-based toolkit for estimating the aquatic ecotoxicity of substances[38]. More recently, further models were included in the Cefic LRI toolbox, such as the Bio-Concentration Factor database (BCF) which was designed to identify non-bioaccumulative substances for fish by linkage of this database with a AMBIT QSAR-based model, a Bayesian Uncertainty System (Busy) model which allows calculation of 'Expected (Ecological) Risk' and uncertainty using univariate exposure distribution and Species Sensitivity Distribution (SSD) estimates; and the Biotransformation Susceptibility (BiotS) software which uses a substances molecular structures to identify potential fragments which may be susceptible to biotransformation to toxicologically active forms.

The US EPA has also developed the Ecological Structure Activity Relationships (ECOSAR) program[39] which is a computerized predictive system that was designed to estimate the aquatic toxicity (acute and chronic in fish, aquatic invertebrates and aquatic plants) of industrial chemicals by use of a Structure Activity Relationship (SAR) approach. In addition, the US EPA also publishes extensive databases of information on ecotoxicity, for example the ECOTOX[40] system available since 2000 which integrates the AQUIRE, PHYTOTOX and TERRETOX databases to provide data, mainly from the peer-reviewed literature, of the toxicity of substances to aquatic, terrestrial plants and wildlife species. It currently contains test data from the 1970s to the present and is updated quarterly including information on endpoints that are

[38] See Internet site http://www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html#what_does_the_toolbox_do

[39] See Internet site http://www.epa.gov/opptintr/newchems/tools/21ecosar.htm

[40] See Intenet site http://cfpub.epa.gov/ecotox/

concentration based (e.g. LC_{50} and NOEC), time based (e.g. LT_{50}) as well as a bioaccumulation/bioconcentration factor (e.g. BCF), and covers many widely used chemicals. Information on the supporting reference sources are also provided so a user can assess the quality of the supporting data. Similar databases are also available that are dedicated to the ecotoxicity and fate and behaviour of pesticides[41].

4.4 Models for Determining the Environmental Distribution of Chemicals

Once one has established an estimate of the ecotoxicity profile of a chemical, this has to be compared with the concentrations of the chemical anticipated to be present in the environment as a whole and in the particular compartment (or medium) of concern. For this, one can draw on either monitoring or modelled data.

Monitoring data are clearly 'real world' in nature and hence would be anticipated to be a more accurate/realistic indication of environmental exposure but such data are often not available for all (or possibly any) the geographic areas or environmental compartments of interest. Also, monitoring data can only provide information about historic (where available) or present concentrations. For the purpose of developing a SEA it would be useful to be able to predict how concentrations would change under different use scenarios (such as if there were to be continued use of the substance as at present and compare this with the consequences of a total or partial restriction or the authorisation of certain uses only). In particular, it would be useful to know how such actions would impact upon different regions (e.g. the habitat of a particularly sensitive species or areas of greater emissions or risk), environmental compartments, with if necessary consideration of any temporal changes (e.g. if there were concerns regarding a gradual increase in levels due to increased use or build up due to persistence over time).

Various models have been developed to try to predict the distribution of chemicals that are released into the environment, and hence the potential for exposure. Different types of model can be used to assess chemicals in their final equilibrium state or predict changes over time, or in a steady state environment or in a more natural situation where the pollutant is constantly being added (for instance from industrial use) and removed (e.g. by degradation).

Fugacity models are based on physicochemical properties (such as partition coefficients) which determine distribution, and environmental variables (such as temperature, pH, light) and water and air movements. The environmental variables are complex and therefore these models are of limited success for predictive purposes. However, they may be useful in providing some rank order among a group of chemicals with regards to their tendency to move within and between the different environmental compartments.

[41] See Internet site http://www.epa.gov/oppefed1/general/databasesdescription.htm#ecotoxicity

Examples of such models include a series developed by the Cefic LRI. These include: the Atmospheric DEPosition and Transport model (ADEPT) developed by Cefic LRI to inform on atmospheric deposition and long-range transport; a GIS-based Geography-referenced Regional Exposure Assessment Tool for European Rivers (GREAT-ER) to assess environmental risks in river basins; and a Generic Estuary Model for COntaminants (GEMCO) which addresses risk in estuarine environments. The principles underlying such models and their useS to calculate predicted environmental concentrations (PECs) are discussed in detail in Section 5, which also provided examples of models that are currently used in regulatory regimes.

4.5 Summary of the Environmental Risk Assessment Process

In order to understand the potential impacts of chemicals on the environment, ecotoxicological data have to be interpreted and the predicted effect-concentration relationships combined with estimates of environmental concentrations, so as to allow predictions to be made of the consequences of the anticipated levels of exposure on the ecosystem at the level of the individual organisms, populations or communities.

As described above, in the REACH risk assessment process, a PNEC that is based upon the most sensitive endpoint for each compartment is generally used. For instance, where the PNEC is based on a single test species approach, if the most sensitive endpoint for freshwater was hatching success to rainbow trout, then the NOEL from the critical study would be used and an assessment factor applied to derive a PNEC. Comparison of this with the predicted environmental concentration (PEC) then allows the Risk Characterisation Ratio (RCR) to be calculated:

$$RCR = PEC/PNEC$$

As part of this process, the contributions to exposure from various sources will be included (e.g. emissions from each stage in the life cycle of the substance including production, formulation, use, service life and waste treatment (including recovery/recycling)).

Where the RCR is greater than one, a potential risk is assumed to exist (as the environmental concentration is likely to be higher than the level at which effects are anticipated to occur). However, this finding (i.e. the RCR value) which is the principle outcome of the risk assessment process, does not of itself provide any information on either the precise nature nor of the extent of the anticipated environmental consequences. For instance, knowing that the RCR is greater than one for a given exposure scenario will not identify or quantify the potential impact in terms of damage to the ecosystem overall or even inform (except in general terms) on the part of the ecosystem that may be at risk (e.g. knowing that the RCR is 1.45 for the freshwater compartment does not automatically tell us what impact(s) are likely to take place, the extent to which these impacts may occur, nor the overall consequences to the sustainability of that ecosystem).

Furthermore, in situations where the differences in the risks between a substance and its possible alternatives are being considered, as is the case in an authorisation based SEA, it is not particularly helpful to just to seek to compare the magnitude of the RCRs that are greater than 'one' for each substance. The RCRs could well be derived on the basis of markedly different effects in different species from different trophic levels; for example, comparison of RCR values of 1.45, 23 and 27 for the substance and two alternatives does not provide any insight into the nature or consequences of the impacts that could arise for each substance. Hence, a simplistic reliance on the magnitude of the RCR as an indicator of importance could lead to quite disparate impacts on the environment and that may associate with very different economic costs.

Even if we know the specific endpoint used to derive the PNEC underlying the RCR (for example, hatching success in a test species such as rainbow trout), this only tells us that this effect (reduced hatching success) is predicted to occur in this particular species at the predicted exposure level. It does not tells what the nature or extent of impact may be in other species (indeed, since the effect was identified in a test using laboratory animals, it is possible that wild fish might respond quite differently (because of different environmental conditions (e.g. water pH or temperature), nutritional status, etc). Also, the PNEC provides no insight into the extent of the impact that might be anticipated under other exposures conditions or in other species with different physiologies.

The absence of an implicit linkage in the risk assessment to actual ecosystem impacts creates significant problems with regard to developing an assessment of environmental impacts, which requires a measure (qualitative or quantitative) of the potential changes that would occur under different use/exposure scenarios.

The challenge for the SEA process is thus to translate the data derived for and the output from, the risk assessment into some other more meaningful measure of impact. This would then enable questions to be addressed such as 'if we continue with the current emission, how would this affect the ecosystem?' or 'would fish die and what is the economic value associated with this?'.

If it were to possible to determine or infer the impact on different species, for example, by predicting a river water concentration of x µg/l of a certain substance would cause a loss of y % of the trout or general fish populations, then it might be possible to apply established values (in this case the re-stocking costs of the river) to estimate the economic value of the impacts. However, this approach would have to be repeatable for each of the major effects identified, not just that relating to the most sensitive endpoint used as the basis for the PNEC, in order to allow estimation of the overall economic damages associated with a particular level of exposure.

It is also important to bear in mind that a substance has to be bioavailable in order to elicit toxic effects. Some forms of a chemical that may be present in the environment may be unavailable for uptake by an organism – for instance, methylated mercury will

be more readily taken up than un-methylated mercury (Wolfe et al, 1998). Environmental factors may also significantly influence the extent to which a chemical is bioavailable; for example, pH while largely determine how much of a metal is dissolved in waters.

Finally, it must be remembered that chemicals are normally tested, and the risks they pose assessed, in isolation (i.e. one by one). However, in the actual environment, chemicals are present as complex mixtures, and it is well established in toxicology that organisms may respond to exposures to chemicals in mixtures by showing effects which differ from what would be predicted based on consideration of the responses seen with single chemical exposures. For example, depending on the particular chemicals, mixtures can show additive effects (where the effect of substance A and substance B are added together, e.g. 1+1=2), synergism (where the effect of substances A and B are greater than their sums, e.g. 1+1=3) or there may be antagonisms (where the effects of the substances cancel each other out to some extent, e.g. 2-1=1).

Developing suitable methodologies to assess the risk of environmental mixtures is a focus of ongoing research (for example with regard to chemicals showing endocrine disrupting potential), but as yet no generic methods have been adopted that can be readily applied to a disparate mixtures of chemicals. There are, however, approaches that exist that can inform on the likely overall effects that would be elicited by mixtures of some groups of chemicals that possess similar structures or that elicit their toxicity by a common mechanism of action.

4.6 Assessment of PBT and vPvB substances

REACH requires determination of whether a substance is PBT (Persistent, Bioaccumulative and Toxic) or vPvB (very Persistent and very Bioaccumulative) as defined in Annex XIII of the Regulation. The ability to persist and bioaccumulate in the environment means that substances with such properties are considered to pose a particular concern as their long-term effects are unpredictable and any effects would be difficult to reverse as simply stopping emissions of the chemical into the environment would not solve the problem. As discussed earlier with regard to environmental fate, these properties also mean that such substances are more likely to be transported over long ranges, possibly on a global scale.

Although vPvB substances may also pose toxic effects, these will be at levels below those which would trigger classification as defined in the Regulation. REACH recognises though that there may exist as yet unidentified mechanisms of toxicity that are not routinely tested for by existing testing strategies. The case of endocrine disruption, a mechanism of toxicity that is now considered to be of 'equivalent concern' under REACH, provides a historical illustration of the development of new scientific understanding. This mechanism of toxic action - and its potential consequences for humans and the environment - only became appreciated during the

1990s. Prior to that time, the mechanism was not appreciated and no chemicals were tested for possible endocrine disputing activity (Colborn, 1996).

Part of the rationale for the focus in authorisation on PBT and, particularly, vPvB substances, is that if novel mechanisms of toxic effect are found in the future for a substance that is highly persistent or bioaccumulative, it would be difficult to reverse any environmental consequences; indeed, the substance's persistence or bioaccumulative properties could mean that even after the removal of such a substance from use, it would take potentially a very long time for it to be removed from an ecosystem (see Hansson, 2001).

Substances that fulfil the PBT/vPvB criteria therefore need to be subject to a risk assessment process that addresses issues such as biodegradation, bioaccumulation and that includes long-term toxicity tests for aquatic organisms and consideration of potential human health hazards (van Leeuwen et al, 2003). However, within the context of SEA, a further challenge is to define a mechanism whereby a value can be placed on the presence (or potential presence) of a substance in the environment and biota, since the assessment of environmental impacts relies on establishing a link between the presence of a chemical in the environment at a certain concentration and established toxic effects.

4.7 Implications for SEA

The main implications of the issues discussed in this section with regards to the development of SEAs are:

- the use of PNECs and comparing these to environmental concentration (to derive the risk characterisation ratio) appears simple, straightforward and is ideally suited to chemical risk assessment;

- in contrast, for the purpose of developing an SEA, there is a need to draw on underlying detailed hazard and exposure assessment data from the risk assessment, rather than just the RCR values;

- there are many underlying assumptions, such as different endpoints, acute vs, chronic effects, safety margins and species sensitivities that need to be considered and care must be taken to ensure that all relevant effects are considered and that the various wider uncertainties, not just the assessment factors used to derive PNECs, are explicitly stated (to avoid inappropriate comparisons of 'worst case' with 'most realistic' scenarios, for instance);

- use of either single and multi-species studies may help in predicting the impacts on ecosystems but there are issues in using each of these approaches and ensuring that the underlying assumptions are valid and that the uncertainties are adequately established;

- field studies and simulated field studies potentially provide a better basis for understanding ecosystem effects but are unlikely to be available for most of the chemicals to go through restrictions or authorisation; and

- the main concern with PBT and vPvB is not their toxic properties per se, so it is impossible to quantify direct environmental toxic impacts. Extreme care must therefore be taken when such substances are compared, for instance, to substances with well established and quantified toxic properties.

A number of important recommendations on possible changes to the reporting requirements for data in REACH dossiers have been made recently (WCA, 2010); these are intended to improve access to key toxicity and exposure data, and thereby would act to assist in the generation of a transparent SEA.

5. EXPOSURE ASSESSMENT METHODS

5.1 Introduction

Sections 3 and 4 set out the approaches and metrics used to identify potential hazards for human health and the environment respectively. The next step in a risk assessment process would be for these hazard data to be combined with information on exposure to provide risk characterisation ratios. The development of these ratios has been discussed already in Sections 3 and 4.

The aim of this section is to examine the approaches that have been used to develop exposure data for risk characterisation and impact estimation, and to consider their applicability to SEA.

The literature review has highlighted that the approaches that are used to determine exposures, and hence develop risk estimates, rely either on the use of standardised models or on stepped approaches involving a range of statistics and assumptions, with the latter being based on available information and the analyst's (expert) judgement. A number of approaches falling under these two categories are reviewed below, with general approaches to evaluating health impacts being considered separately from those that assess effects on the environment.

5.2 Approaches to Assessing Human Exposure

5.2.1 Use of Exposure Assessments in Health Impacts in support of SEA

The data derived from hazard assessments described in Section 3 provide the starting point for a health impact assessment (HIA). However, preparing a HIA also requires information on:

- the number of people exposed at particular level(s);
- the number of people affected by a particular effect or disease related to the chemical exposure; and
- the degree to which a given effect will reduce an individual's quality of life and the extent to which effects may be reversible.

Below we review approaches that have been used to model exposure from the occupational, consumer and environmental pathways (for public health effects; i.e termed 'man via the environment' under REACH). While these are reviewed here separately in order to highlight differences between approaches applicable to the different settings, it is clear that there are considerable similarities and overlaps across these scenarios. An example of similarities includes the approaches used to assess occupational and public health exposure while an example of overlap is offered by the

WHO (2000) which notes that risks from the different exposure routes are not simply additive and therefore interactions between occupational and environmental exposure should be considered within a joint (over-arching) assessment framework.

5.2.2 Worker Health

From the literature, three basic types of approach can be identified to undertaking an exposure and impact assessment in relation to workers' health. The first is based around the use of dose-response functions, the second around calculation of attributable fractions and the third relies on the use of prevalence and incidence data. Each of these is described in detail below.

Dose-Response Based Approaches

As discussed in Section 3, human studies can be used directly to generate dose-response functions, while the outputs of toxicity studies can be used in models to extrapolate across to human-equivalent dose-response estimates.

Within the context of REACH restrictions and authorisations, the best examples of where use of such functions may be of benefit is carcinogens, and includes the considerations of DG Employments' Scientific Committee on Occupational Exposure Limits (SCOEL) on the excess rates of cancer due to different worker exposure levels to some substances.

Table 5.1 below presents quantitative risk estimates for lung cancer associated with occupational exposure to Cr (VI) compounds (SCOEL/SUM/86 final document). SCOEL concluded that lung cancer was the critical effect upon which any occupational exposure limit should be based. The values in the table are based on an analysis of 10 epidemiological studies and were derived using a linear no-threshold model. SCOEL considered that such a linear extrapolation approach was appropriate given that the Cr (VI) compounds are comprehensively genotoxic. However, SCOEL also notes toxicological reasons why the model could lead to an overestimation of lung cancer risk at low levels of exposure (HSE, 2007).

Table 5.1: Risk Assessment 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 estimated reasonable worst case inhalation exposure estimates based on actual monitoring data, to predict the excess relative lung cancer risk per 1,000 workers (over a 45 year working life). For example, if it is assumed that each year's exposure for 1,000 workers to 1 mg/m^3 is equivalent to *one*

unit of exposure, then the associated cancer risk per unit exposure can be derived – as illustrated in Table 5.2. These figures can be combined with data on the number of workers exposed to estimate the annual excess cancer risk for the low and high excess cancer risk scenarios.

Table 5.2: Excess Lifetime Risks for Lung Cancer

Exposure Level (lifetime working)	Units of Exposure* (over 45 years)	Excess Cancers per 1000 workers	Cancer Risk per Unit Exposure*	
			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*				

Louekari (2009) also provides the example of the use of job exposure matrices (JELs) in order to model occupational exposure in a health impact assessment. JELs graphically associate a job and/or position with a certain level of exposure expressed as a percentage of the relevant occupational exposure limit and can be combined with other data to feed into a health impact assessment. Louekari (2009) offers an example of JELs developed by the Finnish authorities where data from industrial hygiene measurements, interview-based surveys and from the workforce survey were used to assess the overall extent of occupational exposure. It was further noted that the Finnish Occupational Health Institute was planning to update the Finnish job exposure matrices on a regular basis (every three years).

Attributable Fractions

The term attributable fraction (AF) was defined in Section 3. A study conducted by the WHO (2004) provides a methodology for the estimation of health impacts from occupational exposure to carcinogens based on the use of relative risk ratios and calculation of an AF. The methodology applied in this study involves the following steps:

- estimation of national level exposure using workforce data and data on exposure to carcinogens in different industries;
- estimation of the relative risk of cancer for each carcinogen (based on literature review);
- use of the above data to derive a population attributable fraction of deaths and disability caused by exposure to carcinogens in the workplace; and
- use of the attributable fraction to derive the absolute number of deaths and change in DALYs.

There are a number of approaches that have been used to calculate the attributable disease burden. These include:

1) derivation of the AF (the proportion of the disease caused by a certain risk factor) by combining a risk estimate from epidemiological studies with an estimate of the proportion of the population exposed;

2) use of absolute risk measures for disease outcomes for which the AF associated with an exposure is thought to be 100%, for example mesothelioma, uniquely caused by exposure to asbestos;

3) use of registry data to estimate odds ratios for different risk factors, e.g. occupations, for example, using a case-referent method with the disease of interest as cases and all other diseases as controls, and job history as recorded by the registry;

4) linkage analysis of census and registry data can be used if national databases permit. For example a population based (often a national census) cohort can be established with cancer registration or death certificate follow-up;

5) the 'Delphic principle' which uses panels of experts to estimate AF; and

6) descriptive analysis of incident cases, for example, estimation of the proportion of newly diagnosed cancers occurring over a set period of time that were linked to a particular occupation or by taking these as a percentage of all the cancer cases in the study.

Estimation of the AF using the first method listed above has been fairly widely used in both occupational settings and for the general population by national governments as well as the WHO. A recently developed methodology for occupational cancer in the Britain (Rushton et al, 2007 and 2010) has calculated AFs using risk estimates, adjusted for important confounders where possible, derived from industry based studies together with estimates from national databases of proportions of workers exposed over a 'risk exposure period' (REP), i.e. the period in which relevant exposure occurred taking into account the latency of the cancer. Estimation was carried out by broad industry sectors and the proportions exposed over the REP were adjusted for turnover and trends in employment. The study has derived attributable fractions for all IARC Group 1 and 2A carcinogens, together with numbers of attributable cancer deaths in 2005 and numbers of attributable cancer registrations in 2004. For short survival cancers, such as lung cancer, the numbers of deaths and cancer registrations are similar. However, attributable numbers (AN) of cancer registrations are more useful for longer survival cancers.

The use of attributable numbers of disease cases to assess burden with regard to carcinogens assumes that all cancers are equally life damaging, whereas the impacts for example of mesothelioma (always quickly fatal although usually has long latency so develops later in life) and leukaemia (life-threatening and generally appearing at younger ages) and non-melanoma skin cancer (for which the prognosis is usually very good), are clearly not equal. In order to get a better estimate of the relative costs to the individual and society of the impact of disease from an exposure, AFs can be used

to derive measures such as lost years of life and lost quality of life (see also Section 6).

An extension of the methods used to derive current burden of occupational cancer in Great Britain (AF, AN, DALY – see also Section 6) has been developed to predict and monitor future burden under different scenarios of change. For this, the risk exposure periods are projected forward in time with, in the UK study, forecasts are made at 10 yearly intervals. A range of scenarios can be introduced, for example, using data on change in exposure levels to predict future patterns, introduction of an exposure limit at a specific time, reducing the proportion exposed gradually over time, banning the substance etc.

Such scenarios can be developed and applied to all those potentially exposed or to different defined groups, for example in the occupational setting by size or type of industry sector. The forecasts can include past exposure and future predicted exposure depending on the latency of the disease of concern. The results for different scenarios can be compared (these can include attributable fractions, numbers and quality of life indicators) to a no action scenario to identify appropriate risk reduction strategies.

Prevalence or Incidence Based Approaches

The study carried out by the University of Sheffield (Pickvance et al, 2005) for the ETUI on the potential benefits of REACH in reducing certain morbidity effects (dermatitis and respiratory effects) illustrates an approach based on the use of incidence data.

In this study, the burden of occupational disease was calculated using the following approach:

1. incidence rates (per million) were obtained for each of the diseases using different methods:

    a) obtain incidence rate of new cases of each occupational disease using incidence data when available;
    b) calculate incidence rates using proportion attributable to work where the diagnosis is generic;
    c) calculate incidence rates from prevalence rates for occupational or generic disease using an estimated mean duration.

2. estimate the proportion of cases attributable to exposure to substances affected by REACH.

3. apply proportion from Step 2 to Step 1.

4. use incidence rate of REACH-affected disease to calculate preventable disease for the EU-25 workforce (200 million).

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 risk ratios or odds ratios for different occupations or the use of dose-response functions.

5.2.3 Consumer Health

Moving to consumer health, the approach to impact assessment will need to vary. In this case, 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 products in which a chemical is used;
- market data on sales of the products;
- information on usage of the product and whether consumers are likely to follow manufacturer's instructions regarding safe use (e.g. wear gloves, masks, etc.);
- frequency of use by the consumer, i.e. every day, once a month, once a year; and
- duration of use, i.e. whether for a few minutes, a few hours, etc.

Louerkani (2009) highlights the centrality of information on the product type in which the substance is used. While some types of products (textiles, paints, furniture and building materials) are likely to lead to exposure of the majority of the general population, speciality chemicals with a limited number of application typically lead to lower levels of exposure.

Within the context of chemical exposures relevant to REACH, few studies have been identified that have tried quantify consumer exposures within a health impact assessment type of framework. The most significant of these is the recent study undertaken by RIVM and TNO on health impact assessment of chemicals in non-food consumer products (Schuur et al, 2008a). This draws on the use of a range of different approaches to predicting exposure, including the use of prevalence and incidence data and relative risk ratios.

RIVM and TNO Study on Non-food Consumer Products

This involved the conduct of nine case studies on chemicals or groups of chemicals that together address a wide (but not comprehensive) range of toxic endpoints such as acute toxicity, carcinogenicity, mutagenicity, reproductive toxicity and sensitizing potential. The chemicals (and uses in non-food consumer products) selected comprised: acrylamide (in cosmetics); azo-dyes (in textiles and tattoos); dichloromethane (in DIY-products); formaldehyde (in chipboard, textiles and cosmetics); lamp oil (prevention of intoxication); nickel (in alloys in contact with skin); nitrosamines (in teats and soothers, cosmetics and balloons); volatile organic compounds (VOCs, in paints and varnishes); and toluene (adhesives and paint spraying).

The approach adopted in the assessments is stated by the authors to have drawn on that proposed by Crettza et al (2002) and Pennington et al (2002) in which Life Cycle Assessment (LCA) techniques are used to enable quantitative assessment of the impacts of both cancer and non-cancer endpoints.

The report indicates that a key step should be the derivation of an estimate of the exposure that is anticipated as equating to a 10% response over background (an ED_{10}). This is synonymous with the derivation of a BMD_{10} value in the bench mark dose technique discussed in Section 3, which increasingly used to interpret toxicology studies. It is proposed that the ED_{10} value is used as a 'POD' for subsequent linear extrapolation to lower doses. A further step would be, for non-cancer effects, to score the endpoint using a three level categorisation system to weight the effect in terms of severity so that 'weighted' disability adjusted life years (DALYs) can then be generated to feed into a LCA. The LCA can then be used to estimate health impacts in terms of weighted DALYs based on the mass of the chemical released into the environment.

Examination of the individual detailed case studies, however, does not fully illustrate application of such an approach. Instead, the case studies illustrate some of the difficulties that can arise in trying to quantify consumer exposures for use in an impact assessment context. They also highlight the wide range of data sources that may need to be called upon, and the number of assumptions that may have to be made in order to develop exposure estimates. For example:

- **Dichloromethane**: Dichloromethane (DCM) is an organic solvent widely used in a wide range of products such as paints, glues and oils which are associated in do-it-yourself (DIY)-activities which can result in very high acute exposures. It is also a known human central nervous system (CNS) toxicant. In this case, the exposure scenario considered that 25% of the adult population (approx. 3 million) undertook DIY-activities for 1-4 hours per week (based on published data). However, the proportion of the individuals who may use products containing DCM was noted to be uncertain. Various options were explored to address this but, in the absence of a reliable estimate, a nominal value of 5% was adopted resulting in a target population of 150,0000. The ConsExpo model was then run for both acute and chronic exposure and based on a number of assumptions regarding the area treated with DCM, duration of the paint stripping activities, size of the room, ventilation rates, breathing rates for adults, and dermal exposure.

  The acute health impact considered was CNS toxicity, and exposure estimates were compared with human exposure guideline values for various effects published by NAC/AEGL (2005) rather than by extrapolating from animal data. The authors noted that this was a crude approach since it did not allow direct risk characterisation. Attempts were made to estimate the severity of symptoms that might occur at differing exposures and the proportions of those exposed who would show effects, by comparing predicted exposure distribution with guideline values. The various acute health effects – from dizziness to life-threatening- were then assigned disability weightings to determine DALYs. Despite the detailed

calculation of chronic exposure estimates, no estimates of health impact were made for this since the principle chronic toxic endpoint identified was found to be a non-human relevant cancer.

- **Nitrosamines:** In this case study, the specific exposure scenarios considered comprised: rubber teats/soothers in infants; other rubber products (i.e. balloons) mouthed by children; and, for the general population, cosmetic use. Estimation was also made of the impact of background sources such as household gloves and exposure from tobacco smoke and food. The change in health impacts arising from reductions in exposure were estimated from an animal-derived unit risk factor of 1.5×10^{-3} $(\mu g/kg/d)^{-1}$ for the well characterised nitrosamine NDMA. As such, since NDMA is one of the most potent of the nitrosamines, the use of this value will tend to result in overestimation of effects. No adjustment was made for age at exposure or for the impact of acute peak exposure level. The total estimated saving was 1.8 cases per year, equating to 14 DALYs per year. An alternative approach, based on epidemiological risk data on certain gastrointestinal tract cancers, suggested a much greater health impact may have been achieved of between 1,068-9,250 cases prevented. The authors however note, irrespective of the approach used to estimate the health impact, there are concerns as to the robustness of exposure estimates pre- and post-introduction of the measures suggesting that considerable caution is needed when attempting to interpret findings.

- **Formaldehyde**: It is unclear why some of the cases considered in the RIVM/TNO study were progressed – particularly formaldehyde – since it would be expected that only a brief comparison of the exposure levels prior to introduction of legislative measures with the effect threshold for carcinogenicity and checking on availability of suitable exposure data for consideration with respect to the contact dermatitis endpoint, would have been sufficient to demonstrate that there has a justifiable basis for attempting to estimate the associated health impacts.

- **VOCs:** In this case study, acute CNS effects together with skin and eye irritation and/or sensitisation effects on consumer users of solvent based paints were examined. The assessment focused on the percentage of the population that undertake DIY activities, at approximately 25% for 1 – 4 hours per week; it was then further assumed that this would include the use of paints at least once per year. Estimates of exposure were based on both measured data and the results of modelling using the ConsExpo system. These two approaches provided very different results with the measured exposures suggested that the average value for a solvent based product would be 660 mg/m^3 while the modelled worst case was 5880 mg/m^3, with these values then used to create a distribution for exposure levels and hence different levels of health impairment.

- **Toluene:** This case study was focused on adhesives and spray paints and examined a range of (generally minor) neurological symptoms associated with acute exposure events and, based on occupational studies, a range of subtle

changes in neurological and neuromuscular functions that associate with chronic exposures to relatively low levels. Data from the EU Risk Assessment on toluene were used to examine use of glue in scale modelling, spray painting by hobbyists and filling of vehicles with petrol at self-service stations. Exposure estimates for each scenario were derived using standard physiological assumptions and assumed a 100% dermal and inhalation absorption (as per EU RAR). The only scenario examined in detail was that of spray painting, with this requiring a range of assumptions regarding the number of people involved in hobby spray painting a year, the size of room in which the activities were undertaken and the appropriate disability weight (in this case linked to visual impairment) for quantifying impacts.

Despite the recommendations in the report for the use of an exposure estimate based upon the anticipated 10% response over background (ED_{10}) as a POD, it is apparent from the case studies that a range of approaches to estimating the extent of both exposure and of effects on the Dutch population had to be applied, and with varying success. The case of formaldehyde and some others highlights the need to adopt a logical, step-wise approach when attempting to determine consumer health impacts. It suggests an approach that starts with a screening exercise to:

- identify endpoints of concern;
- ascertain exposure ranges over which they may operate;
- establish availability of relevant exposure data/estimates before/after legislative measure of concern; and then
- if adequate data appears to be available, briefly compare exposure information prior to the measure with dose-response data for endpoints to confirm that there is a reasonable basis to assume that there was a risk of health impacts occurring prior to introduction of legislation.

A possible further criticism of the approaches followed here is the lack of consistency with regard to the derivation of exposure estimates, with these in several instances being based on a mixture of average and 'worst case' assumptions or data. As illustrated by the VOC case study, the choice of estimate could have a significant impact on the results of the assessment. Although in some instances probabilistic approaches were included within aspects of the methodology, they were not generally extended to allow an exploration of the degree of uncertainty surrounding the estimates of the health impacts where these were estimated. Inclusion of such approaches would have been of value as they would have provided information on the likelihood of end estimates and better support comparisons between a substance/use and its alternatives, as will be required within SEAs intended to support Restriction or Authorisation decisions.

A major gap in the scope of this project was that it did not attempt to address effects on reproductive endpoints. However, the report does draw attention to the issues of parameters other than DALYs which may be of potential value in informing policy decisions; these were noted to include:

- estimation of decreases in exposure (based on the assumption that any reduction in exposure must be a positive step when considering the likelihood of adverse effects at a population rather than a individual level); and
- extent to which a fall in exposure will influence risk perception in the population.

The report also suggests that 'in real life', the level of serious health consequences in the Netherlands that may be attributable to exposure to 'dangerous' chemicals in consumer products is probably low, since the largest contributors to adverse effects have probably already been subject to prohibition, or that significant human exposures have already been prevented by existing measures.

Of particular note is the principal conclusion of this report that HIAs should only be used in support of policy decisions under two situations:

- where a single measure is found to associate with an estimated (very) high impact; or
- as a tool to compare between several potential measures as part of a prioritization exercise.

5.2.4 Public Health

A particular concern with regard to the risks associated with chemicals that enter the general environment is the extent to which these might pose a risk to the health of the general population (or potentially to specific sub-populations who may be particularly susceptible to the effects). Such concerns fall within the discipline of the public health sciences, and are best exemplified within the REACH requirements by the considerations given to the possible risks associated with indirect exposure of 'man via the environment'. The routes of principle concern are:

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

According to Louekari (2009), human exposure is to a 'large extent' determined by the following factors: the volume of releases; the regional/geographical distribution of emissions; and environmental fate of the substance in question.

In relation to the scale of exposure, Louekari (2009) notes that often the whole population is exposed, in particular in cases of substances which are persistent and bioaccumulative (examples given include methyl mercury, DDT, cadmium, brominated flame retardant, several pesticides). However, regional distribution of emissions may mean that a smaller group (sub-population) is exposed or that different groups may be exposed to varying degrees while – depending on the nature of the dietary route of exposure – it may be that subgroups with particular dietary habits may be at elevated risk.

According to the WHO (2000), there are two main approaches for estimating health impacts from environmental risk factors:

- exposure-based approach: this approach necessitates the use of a dose-response model together with an estimation of the exposure distribution or other type of exposure data; and

- outcome-based approach: this involves the identification of a health outcome and definition of share of the outcome attributable to the relevant risk factor.

The above two approaches resemble the approaches discussed earlier in this chapter in relation to occupational exposure, with the exposure-based approach mirroring dose-response approaches discussed under worker exposure and the outcome-based approach resembling AF based approaches. In the context of the approach discussed in WHO (2000), it appears that the AF/outcome-based approach may be less data intensive, as input data can rely to a larger extent on expert opinion rather than empirical data.

In addition to the above, several other approaches are discussed by WHO (2000) including the use of multiple scenarios: where relationships between causes and outcomes are too difficult to model for the exposed population at large, it is proposed that a number of more narrowly defined exposure scenarios are developed.

According to WHO (2000), likely exposure may be estimated on the basis of data on emissions, data on concentration of the substance in the environment gathered through environmental monitoring, and data on concentration in human blood or breast milk. However, there are factors which may confound the situation and interfere with the estimation of expected exposure, such as human behaviour. According to Louekari (2009), the main sources of data on indirect exposure via the environment would be dietary surveys and environmental monitoring data. Unfortunately, this represents an idealised scenario with regard to the types of chemical that are considered under REACH and in practise most substances will have little or no monitoring data available; rather exposure via these routes will need to be estimated using various models.

A number of case studies were developed in WHO (2000) to estimate the disease burden from different environmental risk factors. These include the assessments of impacts from indoor air pollution and from exposure to lead. These two case studies – which are somewhat unrepresentative of the situation with regard to most industrial or consumer chemicals that will be considered under REACH - are discussed in more detail below to illustrate the types of approaches that are available and their limitations.

The case study on **indoor air pollution** in WHO (2000) compares four major approaches to estimating the global burden of disease from indoor pollution (however, little detail on the methods underpinning some of these approaches is provided). The four methods are:

- pollutant-based (exposure-response extrapolation);
- child survival (survival analysis);
- cross-national (regression); and
- exposure-based (disease by disease summation, includes estimation of exposure and risk leading to estimates of morbidity and mortality and calculation of population attributable risk; the weaknesses of this approach include the absence of exposure-response curve).

The authors of the case study on indoor air pollution note that all of the above approaches (with the exception of the exposure-based approach) are likely to lead to an overestimate while the exposure-based approach is likely to underestimate the impacts.

The second case study focuses on the global **burden of disease from environmental exposure to lead** and uses primary data from a database of studies measuring blood levels in population samples to derive a probability density function estimating the health burden (this is done separately for children) and is used subsequently to calculate the associated DALYs. The shortcomings of this method as given by the author appear to relate to the quality of the primary data and include the following issues:

- human lead level data concentrate on high-risk groups, such as occupationally exposed adults or children residing in the vicinity of a lead smelter;
- blood lead samples may not be a reliable measure of exposure and reflects recent rather than long-term exposure;
- no information on quality control measures in relation to some of the samples is available (e.g. use of lead free sampling kit); and
- some of the studies in the database may have been conducted in countries which subsequently implemented lead reduction programmes.

Wismar et al (2007) note that where the necessary exposure and dose response data are not available or not sufficiently understood by science, it is possible to conduct a sociological HIA based on drawing information on the likely outcomes from people who are likely to be affected thus taking account of their "fears, perceptions and experience of living in a community which is likely to be affected".

WHO (2008) analysed the specifics of the impacts of road traffic on children. The following risk factors were taken into account: road noise, transport-related air pollution, road safety and insufficient physical activity due to road transport hindering cycling and walking. It is noted that health impacts of road traffic differ between the adults and children as children have a specific physiology, they spend amounts of time in some environments that are different from amounts of time spent there by adults and they have different behavioural patterns. Although the context of this study is very different from REACH, it highlights that, where underlying data are available, it may be appropriate to analyse exposure separately for different population groups where they exhibit different physiological or behavioural features, such as for children and adults.

5.3 Approaches to Assessing Environmental Exposure

Under REACH, Exposure Scenarios (ESs) are required to demonstrate that a substance can be used safely. An ES sets out for a given use how the substance can be used in a way that risks are adequately controlled, by describing the conditions for use (including process descriptions, operational conditions and risk management measures). ESs therefore form an integral part of the chemical safety assessment (CSA) and the chemical safety report (CSR). The development of the ESs follows six main steps (van Leeuwen, 2003):

- identification of use and processes;
- description of manufacturing or use processes;
- development of a "tentative" ES;
- exposure estimation and risk characterisation;
- defining the "final" ES; and
- developing the annex to the SDS.

The information from the ES can then be fed into a risk estimation tool along with characteristics of the substance and the local environment. The resulting exposure levels can then be compared to the available effect levels to determine whether the risks are adequately controlled.

An exposure assessment for the environment requires consideration of:

- how a substance is used and associated quantities;
- emissions over the life cycle of the substances production, use and disposal (including recovery and recycling); and
- transport, fate and behaviour in the environment and across the different environmental compartments - air, water (fresh and marine), soils and living organisms.

These assessments are usually carried out using the models that have been developed for these purposes. In particular, the EUSES risk assessment model which was developed initially to support the Technical Guidance Document for risk assessments under Directive 93/67/EEC (New Substances Directive), Regulation (EC) No 1488/94 (Existing Substances Regulation) and Directive 98/8/EC (Biocidal Products Directive). Non-modelling based approaches to the exposure and risk assessment would appear to be rarely used in relation to the environment, as compared to human health. Environmental exposure measurement is only likely to have been conducted in those situations where the available models (and the assumptions on which they are based) do not apply, for example for metals.

Since the introduction of REACH, the TGD has been superseded for the risk assessment of new and existing substances by the guidance set out in the Annexes to REACH, supported by "Guidance on Information Requirements and Chemical Safety Assessment" produced by ECHA. The REACH guidance draws heavily on the earlier TGD. As with risk assessments using the TGD, risk assessments under REACH are

most likely to use models such as EUSES, ECETOC TRA or Chesar (now available in beta-version[42]), with limited manual calculation needed.

However, it is important to highlight that a range of factors may be important as inputs to or as part of the interpretation of the outputs from a modelled exposure assessment:

- use of a substance may be concentrated in particular locations or regions;
- the transport and behaviour of a substance in the environment may vary widely depending on their the physicochemical properties, and thus affect their final geographical distribution; and
- exposure intensity (continuous or non-continuous) may vary across environmental compartments, and these variations may be important to interpreting predicted environmental concentrations; frequency will also be relevant in this regard, for example, concentrations of a chemical in agricultural soil will be determined by the frequency of sewage sludge applications.

It has been suggested in various fora that if the location of users were known it would be possible to map emission points using GIS based systems, with this then providing an indication of areas/regions where exposures may be concentrated (with this type of approach being embedded within the Life Cycle Impact Assessment Models described below). By the nature of substances and uses that are likely to be subject to restrictions, for example, the use of these models may not be feasible due to the large number of dispersive releases, the location of which may not be known. It is only likely to be feasible and useful to map the spatial distribution of emissions when they are associated with a limited number of well-defined sources.

However, monitoring data on environmental concentrations may be available and these may be relevant to understand the geographic dispersion of chemicals. For example, data from river or estuarine monitoring sites in EU member states can help inform on both the distribution of the chemical in the environment and on associated concentrations. This may help identify the number of sites where there is likely to be a risk concern.

For example, in a study for UBA being carried out by Oekopol and RPA (forthcoming), data from the nonylphenols (NPs) risk reduction strategy was examined to try and gain a better idea of environmental exposures. Data were collated from the ESR risk assessment for nonylphenols to develop an illustrative dose-response function and information on environmental concentrations. Monitoring data are collated from the risk assessment for 20 rivers across the EU and used to develop a cumulative density function for environmental concentrations. These data are fed into a Monte Carlo analysis to develop a representative function for EU rivers based on a lognormal distribution.

[42] See:: http://chesar.echa.europa.eu/

In the ESR Risk Assessment Report on NP/Es, information on LC_{50}s is available for several types of living organisms, with this case study focusing only on freshwater fish and invertebrates. Data given in the risk assessment are complemented by other data provided in the IUCLID report. The various LC_{50} data were summarised and sorted by exposure period. The most common exposure period was 96 hours and these therefore formed the basis for developing an acute toxicity dose-response function (insufficient data of a consistent exposure type were reported in the risk assessment report to create a chronic toxicity dose-response function which would be the more appropriate indicator of damages). Again these were fed into a Monte Carlo simulation, with a log normal distribution fitted to the toxicity data for fish and invertebrates.

The probability that the concentration of NPs is higher than the LC_{50} can be derived by combining the above distributions for the percentage of rivers with different predicted concentrations and the frequency that concentrations exceed different LC_{50} values. The resulting probability is illustrated in Figure 5.1 and is equal to the area of the overlapping zone between the concentration and LC_{50} distributions. This area can be broken down into two parts which both provide a measure of damages:

- Area 1 ranges from 0 to the concentration at the intersection between the two distributions. This corresponds to the area under the LC_{50} distribution;
- and Area 2, where damages are limited by the predicted frequency of rivers having NP concentrations above 55 µg/L (with the possible maximum concentration assumed to be 300 µg/L).

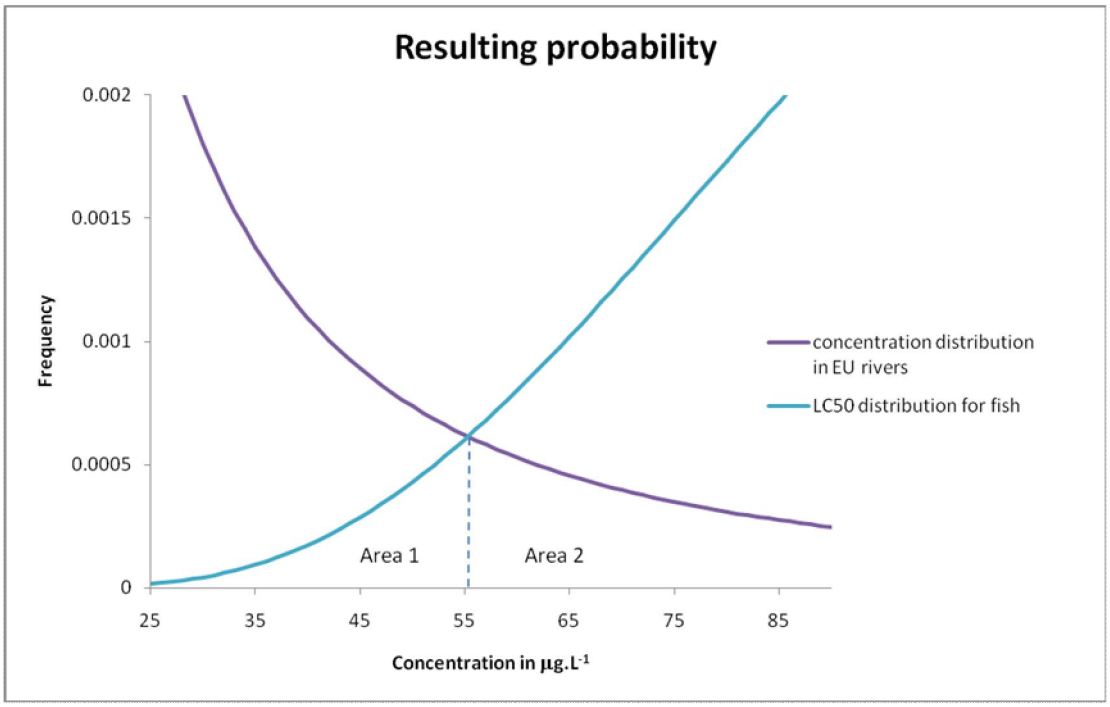

Figure 5.1: Combined Probability of River concentrations and Acute Toxicity Effects

If data were available, an approach based on a Species Sensitivity Distribution (SSD) could be applied in this situation. Due to the concentration in sediments, bottom feeding organisms would be at a higher risk of exposure than others and therefore so would those organisms that feed on these bottom feeders (i.e. food web effects would be anticipated). The impact on a range of species would therefore need to be considered if a SSD approach was used.

However, the use of this type of approach has been rare, particularly within the EU. More typically risk assessment has relied on the outputs of a modelled exposure assessment in the form of a risk characterization ratio (RCR), as discussed below. However, in the context of a SEA, it should be recognised that output from a SSD model may provide a valuable surrogate indicator of the scale of potential impacts in cases where full quantification of effects on the environment is not feasible.

5.4 Standardised Models for Undertaking Exposure Assessments

5.4.1 Overview of the Main Models

Two distinct types of modelling tools are being examined for this study, those that have been typically used in chemical risk management to undertake exposure and risk assessments and those such as the life cycle impact assessment (LCIA) models that are used in a number of relevant fields but that have not been widely used to date in chemical risk management.

Many models of each type have been developed to date and the following examples have been considered in detail to illustrate their theoretical basis, strengths and limitations, with particular regard to the extent to which they may serve to provide information for a REACH SEA:

- **Chemical Risk Assessment Tools including Exposure Assessments**:
  - EUSES 2.1 (European Union System for the Evaluation of Substances); and
  - ECETOC TRA (European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment Tool); and
  - CHESAR (CHEmical Safety Assessment and Reporting tool) is provided by ECHA as a plug-in to the IUCLID 5 software needed to prepare and submit registration dossiers. CHESAR uses the EUSES 2.1 and ECETOC TRA tools as described above.

- **Life Cycle Impact Assessment Tools**:
  - USEtox;
  - IMPACT 2002; and
  - Pangea.

- **Health Impact Assessment:**
  - *EcoSenseWeb*

- *ConsExpo*
- *RiskPoll*

5.4.2 Exposure Assessment Tools

The Estimation Programs Interface (EPI) Suite is a screening-level tool to be used where acceptable measured values are not available. EPI Suite provides estimates of physicochemical and chemical fate properties to allow potentially hazardous substances to be identified for further risk assessment within the context of chemicals legislation in the USA.

Both the European Union System for the Evaluation of Substances version 2.1 (EUSES 2.1) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Targeted Risk Assessment (TRA) Tool(s) version 2 are designed to facilitate precautionary risk assessment of substances in the context of chemicals legislation in the EU.

EUSES 2.1 is designed to facilitate both screening risk assessments (known as Tier 1 assessments under REACH) and more refined (higher tier) risk assessments. The model applies the EU Technical Guidance Documents (TGD) on Risk Assessment for New Notified Substances, Existing Substances and Biocides. ECETOC TRA enables exposure and risks to be estimated for defined uses. The tools address exposure to consumers, workers and the environment and are similar in scope to the EUSES model. However, ECETOC TRA has been designed to apply the requirements, use descriptors and risk assessment methodology developed for REACH registration.

As noted previously, ECHA's Chemical Safety Assessment and Reporting Tool (Chesar) has now been released. This software was developed by ECHA to support substance registration under REACH. Chesar works as a plug-in to IUCLID 5.2, the software tool which all registrants must use to record their registration details. This current version (v 1.1.1) is designed to:

- import substance data, including hazard data, from IUCLID 5.2 (hazard data may only be amended in IUCLID 5.2);
- document uses for use reporting, including tonnages used for different stages of a substance's life-cycle (these may be exported back to IUCLID 5.2);
- undertake risk assessment (primarily Tier 1 but can be adapted for higher tier assessments);
- develop exposure scenarios;
- generate a Chemical Safety Report (CSR); and
- partially generate exposure scenarios for the extended Safety Data Sheet (eSDS).

Importantly, a further upgrade is planned for Autumn 2010 which will complete this functionality.

The Tier 1 risk assessment uses the ECETOC TRA tool for human health (consumer and worker) assessments and EUSES 2.1 for environment assessments where release estimations are linked to the Environmental Release Categories (ERCs) identified by the registrant for each life-cycle use. Chesar also allows the use of exposure/release estimates generated by other models, as well as inclusion of actual measurement data (which can be entered manually to generate higher tier assessments).

5.4.3 LCIA Modelling

Essentially, within LCIA two types of methods have been established, one is the problem-oriented (mid-point) approach and the other being a damage-oriented (end point) approach (see Figure 5.2):

- In problem-oriented methods, the mass or energy flows are split into the environmental themes to which they contribute (e.g. human and aquatic toxicity). The intention is to thereby simplify the complexity of various flows into a few environmental areas of interest.

- Alternatively, damage-oriented methods start with a classification of mass or energy flows into various environmental themes but the damage from each theme to human health, ecosystem health or resources is modelled separately. From this, the aim is to establish the relevance of each environmental theme.

USEtox enables the comparative assessment of substances released to air, water and soil and of their toxic effects on the human population and ecosystems. The outputs of USEtox are designed to be applied to LCIA and comparative risk assessment (CRA) of the global environment. IMPACT 2002 is a Life Cycle Impact Assessment (LCIA) toxicity model for the estimation of cumulative chronic toxicological risks and the potential impacts associated with substance emissions. The outputs of IMPACT 2002 are designed to be applied to life cycle impact assessment.

Pangea is a model for the analysis of impact pathways of organic and inorganic substances at different spatial scales. Pangea allows the comparison of impacts from a range of polluting substances that may lead to widespread exposure population via many pathways. EcoSenseWeb is an integrated atmospheric dispersion and exposure assessment model designed for the analysis of single point sources (electricity and heat production) in Europe but it can also be used for analysis of multi emission sources in certain regions.

As far as possible LCIA methods are based on internationally- and scientifically-accepted approaches and a consensus of opinion although issues about some categories (e.g. human toxicity) remain challenging with respect to the appropriate modelling procedure. In addition, an important outstanding issue is the best way to

communicate the results correctly since LCIA outputs involve the use of concepts such as DALYs to weight the damages identified.

Importantly, from a life cycle perspective the fact that certain emissions are associated in the model with one or more particular impact categories does not imply that the investigated chemical, product or process will actually cause such an effect. Rather, it means that during the different stages of a life cycle, as modelled, certain emissions are generated "that contribute to a pool of similar emissions known to be associated with [...] environmental themes or impact categories" (Zoller, 2004, p. 206). Models from LCIA are therefore useful tools to assist in the determination of the extent to which the emissions of a particular substance may associate with a particular impact category. This offers an approach by which a direct comparison can be made between chemicals with different impact types and for various spatial scales.

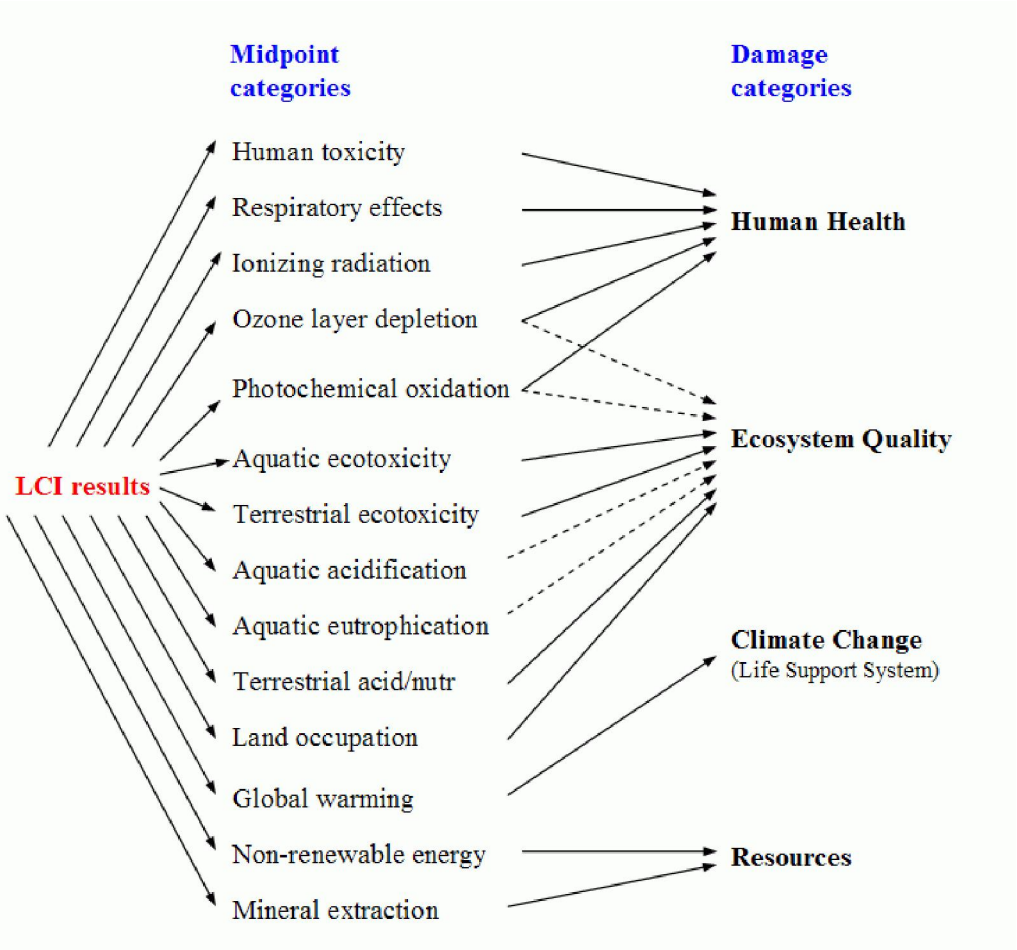

Figure 5.2: Overall scheme of the IMPACT 2002+ framework, linking Life Cycle Impact results via the midpoint categories to damage categories (Jolliet et al, 2003)

Specifically, for the calculation of the environmental fate and behaviour of chemicals, since different media (e.g. air, fresh- and marine water, agricultural and natural soil and biota) may play a significant role for the different impact categories and exposure

pathways (e.g. air for human toxicity via inhalation), most of the LCIA models available include all of the important environmental media (i.e. compartments; see Figure 5.3) that are routinely considered within the REACH risk assessment process,

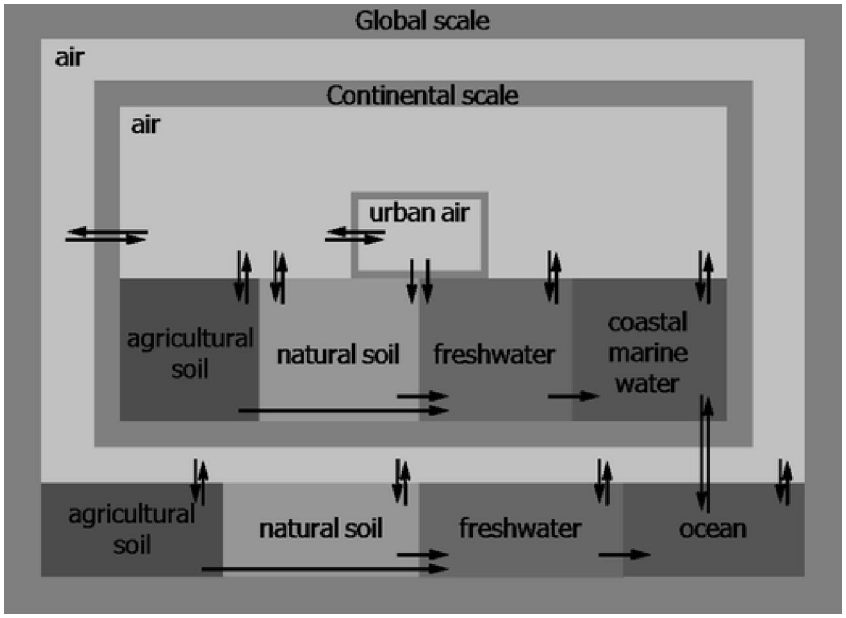

Figure 5.3: Compartment setup of the consensus model USEtox for calculations of the environmental fate of chemicals at various spatial scales (Rosenbaum et al, 2008)

During modelling, human toxicological effect and damage factors are given as output for each chemical considered, and these contain information related to the exposure route and disease type (i.e. cancer and non-cancer). Most LCIA methodologies apply a route-to-route extrapolation factor between inhalation exposure to ingestion (and vice versa) whenever there is an absence of data available for one of the intake routes. The exception to this is where a chemical is known to elicit only local effects. In such instances no extrapolation is made (van Zelm et al, 2009) as it would be inappropriate. The human damage factors are referred to as the change in damage to the total human population and are expressed as DALYs. These comprise disease-specific slope factors (as calculated by Huijbregts et al, 2005a) and a chemical-specific toxic potency factor. The basis on which the human effect factors are established differ between models. For example in the USEtox model, effect indicators for human toxicity are based on best estimates of effect concentrations (ED_{50} or ED_{10}, possibly extrapolated from NOAEL) not on a reference dose that incorporates safety (assessment) factors. Use of unadjusted best estimates of effect as the basis for estimation imply that the optimal basis for a comparative assessment is not the use of 'worst-case' values since these implicitly include various 'safety' (i.e. uncertainty or assessment factors).

If the basis for the human toxicity effect assessment in an LCIA was changed, for example to use worst case estimates, a user would need to be aware that this would have important implications when it came to the interpretation of the results of the

analysis. Thus, if values incorporating 'assessment[43]' factors were introduced into the effect assessment element of the model, the LCIA outputs would of necessity become precautionary in nature rather than informing on comparative impacts of the various agents (e.g. substances or products) considered in the analyses.

Due to the complexity of the modelling approaches embodied within LCIA, it is important to address the uncertainty that may exist in each model. Most LCIA models address uncertainty by giving an indication of the recommendation status of each output. For instance, in the USEtox model the authors give an overview of the precision of each characterisation factor, based on comparisons among the different models that have been reviewed as basis for the USEtox model implementation. Furthermore, the authors state that the uncertainty range in this model's results is "due to variation between the models and does not include parameter uncertainties attached to the input data" (Rosenbaum et al, 2008, p. 543) that have been used for the calculation of the characterisation factors as the underlying input data were kept the same. Based on that, a distinction was introduced between "interim" and "recommended" characterisation factors so as to reflect the level of reliability of the calculations in a qualitative way. In addition, in order to provide a user with an estimate of the model uncertainty (excluding parameter uncertainty), the square of the geometric standard deviation is given for each characterisation factor based on an assumption that they are log-normally distributed.

5.4.4 Scope

The models reviewed were produced to fulfil very different purposes and so it is only to be expected that they will have equally divergent scopes, as summarised and compared in Table 5.3.

[43] In other words, uncertainty or safety factors, depending on terminology preferred

Table 5.3: Summary Comparison of the Scope of Models

Model	Substance Types Covered	Substance Types Explicitly Not Covered	Spatial Resolution	Receptors and Target Media Included		
				Human Health		Environment
				Workers	Consumers[44]	
EPI Suite	Most organic chemicals including organophosphorus compounds	Metals, inorganic substances generally and organometalics	N/A	N/A	N/A	Estimates of physicochemical properties and environmental fate to air, water, sediment, soil and sludge but not exposure. Also dermal fate. Some toxicity estimates for aquatic receptors (fish, daphnia and algae)
ECETOC TRA version 2	Most substances	Dissociated substances (low log Kow and ionisable substances e.g. metal salts and some metal containing substances)	Local, regional and EU wide	Dermal, inhalation and via environment (including recovery but not waste phase)	Dermal, oral, inhalation and via environment (including for adult vs. child)	Air, water, sediment and soil
EUSES 2.1	Most substances	Dissociated substances (low log Kow and ionisable substances e.g. metal salts and some metal containing substances)	Local, regional, EU wide and limited EU plus	Dermal, oral, inhalation and via environment (including recovery but not waste phase)	Dermal, oral, inhalation and via environment (including for Male/female, children, toddlers, babies, elderly and/or vulnerable groups e.g. pregnant women)	Air, water (including sub-compartments), sediment, soil (including sub-compartments) and sludge. Species resolution for fish, daphnia, other aquatic receptors, terrestrial plants, earthworms, microorganisms, birds, mammals and other terrestrial receptors
Impact 2002	Most substances including heavy metals, persistent organic pollutants and particulate matter	None identified	Site specific, local, regional, EU wide and EU plus (13 continental zones, 8 oceanic zones, 21 atmospheric	None	Oral and inhalation via the environment (including for male/female, children, toddlers, babies, elderly and/or vulnerable groups e.g. pregnant women)	Air, water (including sub-compartments), sediment and soil. Species resolution for fish, terrestrial plants and other terrestrial receptors

[44] Models from LCA/impact assessment do not distinguish between consumers of a particular product (and its related emissions into the environment) and the rest of the population. Hence, in these models the average of the population (or sub-groups, if defined) is referred to as the target receptor.

Table 5.3: Summary Comparison of the Scope of Models						
Model	**Substance Types Covered**	**Substance Types Explicitly Not Covered**	**Spatial Resolution**	**Receptors and Target Media Included**		
				Human Health		**Environment**
				Workers	**Consumers**[44]	
			zones)			
Pangea	Most substances including heavy metals and persistent organic pollutants	None identified	Site specific, local, regional, EU wide and EU plus, global (spatially flexible grid that may vary between scenarios)	None	Inhalation via the environment (including for male/female, children, toddlers, babies, elderly and/or vulnerable groups e.g. pregnant women)	Air, water (including sub-compartments), sediment, soil (including sub-compartments) and sludge (as option). Species resolution for fish, terrestrial plants, and other terrestrial receptors
USEtox	Most substances including heavy metals and persistent organic pollutants	None identified	EU wide and EU plus	None	Oral and inhalation via the environment (including for male/female, children, toddlers, babies, elderly and/or vulnerable groups e.g. pregnant women)	Air, water, sediment and soil (including sub-compartments). Species resolution for fish and terrestrial plants
EcoSenseWeb	Air pollutants (sulphur dioxide, nitrogen oxides, primary particles, ammonia, non-methane volatile organic compounds, secondary particles and ozone), heavy metals (arsenic, cadmium, hexavalent chromium, lead, mercury, nickel) and persistent organic pollutants (polycyclic	Substances not included in previous column	Site specific, local, regional, EU wide, EU plus (China, Brazil and Russia) and hemispheric	None	Inhalation via the environment (including for male/female, children, toddlers, babies, elderly and/or vulnerable groups e.g. pregnant women)	Air including for impacts to terrestrial plants, agricultural crops and building materials

Table 5.3: Summary Comparison of the Scope of Models						
Model	**Substance Types Covered**	**Substance Types Explicitly Not Covered**	**Spatial Resolution**	**Receptors and Target Media Included**		
				Human Health		**Environment**
				Workers	**Consumers**[44]	
	aromatic hydrocarbons, polychlorinated biphenyls, dioxins/furans, benzene, benzo-[a]-pyrene 1,3-butadiene, ethene, formaldehyde					

5.4.5 Outputs

EPI Suite produces a wide range of estimates of physicochemical and chemical fate generated by (Q)SAR type models. The Annexes VI to XI to REACH provide for the use of non-test derived values based on (Q)SAR estimations. Data generated by the EPI Suite tools may therefore be included in the information submitted for registration and may form part of the evidence used in SEA.

EUSES 2.1 and ECETOC TRA v.2 both produce precautionary exposure estimates and risk characterisation ratios (RCRs) for a range of environmental compartments and sub-compartments as well as for human health receptors. In both cases outputs are for single substances only and do not take into account the cumulative effects of several substances.

IMPACT 2002 produces midpoint rather than precautionary characterisation factors for approximately one thousand substances in terms of toxicity and ecotoxicity (aquatic and terrestrial). USEtox produces characterisation factors for carcinogenic impacts, non-carcinogenic impacts, and total impacts for chemical emissions to urban air, rural air, freshwater and/or agricultural soil and, in a comparison of several LCIA models, has been shown to generate characterisation factors within a factor of 100-1000 for human health and 10-100 for ecotoxicity of those from other models and has been suggested as providing the largest coverage of substances amongst models yet developed (Rosenbaum et al, 2008).

Pangea produces risk and/or impact assessments in the form of effect and/or characterisation factors (Efs/CFs) and/or concentration/exposure-response relationships. All Pangea outputs can be provided as either monthly or annual averages or averages based on time-archetypes, e.g. seasons. EcoSenseWeb produces outputs in terms of concentration levels (primary and secondary particles and ozone), receptor exposure (population, crops, building material), physical impacts resulting from exposure to airborne pollutants and damage costs for impacts to human health, crops, building materials, ecosystems and due to climate change.

The outputs from the various models are summarised and compared in Table 5.4. It should be noted that the risk assessment models such as EUSES 2.1 and ECETOC TRA will produce precautionary values for exposure and risk which will not be analogous to the estimates intended to match actual conditions produced by models such as EcoSenseWeb.

5.5 Inputs

The information requirements of the different models vary as greatly as their different scopes and outputs. Furthermore, the different models have different facilities for accepting additional data. Table 5.5 sets out a comparison between the information requirements for registration under REACH and the required and optional information for most of the models. EPI Suite requires only the substance identity in order to provide estimates and thus it has not been included in Table 5.5.

Table 5.4: Summary Comparison of the Model Outputs						
Model	**Data Type**	**Release Estimates**	**Exposure Estimates**	**Risk Estimates**	**Other Outputs**	**Life Cycle Stages Covered**
EPI Suite	(Q)SAR estimations of physicochemical and fate properties	None	None	None	None	None
ECETOC TRA v. 2	Precautionary estimates based on Margin of Safety (MOS) factors	Yes (see scope for more details)	Yes (see scope for more details)	Yes as precautionary risk characterisation ratios (RCRs) (see scope for more details)	CMR impacts, RCRs for predator species	Import, manufacture, downstream industrial, professional and consumer
EUSES 2.1	Precautionary estimates based on Margin of Safety (MOS) factors	Yes (see scope for more details)	Yes (see scope for more details)	Yes as precautionary risk characterisation ratios (RCRs)	CMR impacts, RCRs for predator species and biocides	Import, manufacture, downstream industrial, professional and consumer
Impact 2002	Best estimates of impacts appropriate for LCIA (assessment of precautionary estimates based on ED_{10} values for predicting risks and DALYs)	Yes (see scope for more details)	Yes (see scope for more details)	Precautionary cumulative risk for human health and aquatic ecotoxicological effects	Potential impact per kg emission for human health and aquatic ecotoxicological effects. Assessments for CMRs, POPs and plant protection products	Import, manufacture, downstream industrial, professional, consumer and waste phase
Pangea	Estimates of monthly or annual or time-archetype average concentration response relationships. Estimates may seek to match actual impacts (from epidemiological data) or may be precautionary (from toxicological data)	Yes (see scope for more details)	Yes (see scope for more details)	Precautionary and "real life" estimates including for human health, agricultural crops and ecosystems (see scope for more details)	Impact and cost assessments of risk assessment outputs. Assessments for CMRs, POPs, plant protection products	None

Table 5.4: Summary Comparison of the Model Outputs						
Model	**Data Type**	**Release Estimates**	**Exposure Estimates**	**Risk Estimates**	**Other Outputs**	**Life Cycle Stages Covered**
USEtox	Estimates of impacts appropriate for LCIA intended to match actual impacts (assessment of precautionary estimates based on ED_{50} values for predicting risks and DALYs)	Yes (see scope for more details)	Yes (see scope for more details)	Precautionary cumulative risk estimates for human health and aquatic ecotoxicological effects	Potential impact per kg emission for human health and aquatic ecotoxicological effects. Assessments for CMRs, POPs and plant protection products	Import, manufacture, downstream industrial, professional, consumer and waste phase
EcoSenseWeb	Estimates of annual average concentration response relationships which seek to match actual impacts (from epidemiological data)	Yes (see scope for more details)	Yes (see scope for more details)	"Real life" risk estimates including for human health via the environment, agricultural crops and building materials (see scope for more details)	Impact and cost assessments of risk assessment outputs. Assessments for CMRs, POPs, greenhouse gas emissions and climate change	None

Table 5.5: REACH Registration Information Requirements Compared to those of Models[1]													
Properties	**REACH Tonnage Threshold**[2]	**ECETOC TRA v. 2 (2010)**		**EUSES 2.1**		**Impact 2002**		**Pangea**		**USEtox**		**EcoSenseWeb**	
		Required by Model	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**
Physicochemical Properties[3]													
Molecular weight	1	Yes	No	No	No	No	No	No	No	No	No	No	No
Physical state of substance	1	No	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Melting/freezing point	1	No	Yes	No	Yes	No	No	No	Yes	No	No	No	No
Boiling point	1	No	Yes	No	Yes	No	No	No	Yes	No	No	No	No
Relative density	1	No	No	No	No	No	No	Yes	No	No	No	No	No
Vapour pressure	1	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	No
Surface tension	1	No	No	No	No	No	No	No	Yes	No	No	No	No
Water solubility	1	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	No
Partition coefficients	1	Yes – Octanol/ Water	Yes - any	Yes – Octanol/ Water	Yes - any	No	No	Yes	No	Yes	No	No	No
Flash-point	1	No	No	No	No	No	No	No	No	No	No	No	No
Flammability	1	No	No	No	No	No	No	No	No	No	No	No	No
Explosive properties	1	No	No	No	No	No	No	No	No	No	No	No	No
Self-ignition temperature	1	No	No	No	No	No	No	No	No	No	No	No	No
Oxidising properties	1	No	No	No	No	No	No	No	No	No	No	No	No
Granulometry (solids only)	1	No	No	No	No	No	No	No	No	No	No	No	No

Table 5.5: REACH Registration Information Requirements Compared to those of Models[1]													
Properties	**REACH Tonnage Threshold**[2]	**ECETOC TRA v. 2 (2010)**		**EUSES 2.1**		**Impact 2002**		**Pangea**		**USEtox**		**EcoSenseWeb**	
		Required by Model	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**	**Required by Model**	**Optional to Model**
Stability in organic solvents and identity of relevant degradation products	100	No	No	No	No	No	No	No	No	No	No	No	No
Dissociation constant	100	No	No	No	No	No	No	No	Yes	No	No	No	No
Viscosity	100	No	No	No	No	No	No	No	No	No	No	No	No
Toxicological Information[4]													
Skin irritation or skin corrosion	1 & 10	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Eye irritation	2 & 10	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Skin sensitisation	1	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Mutagenicity	1 & 1,000	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Acute toxicity	1 & 10	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Repeated dose toxicity	10, 100 & 1,000	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Reproductive toxicity	10, 100 & 1,000	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Toxicokinetics	10	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Carcinogenicity study	1,000	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Ecotoxicological Information[2]													
Aquatic toxicity	1, 10 & 100	No	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No

Table 5.5: REACH Registration Information Requirements Compared to those of Models[1]

Properties	REACH Tonnage Threshold[2]	ECETOC TRA v. 2 (2010)		EUSES 2.1		Impact 2002		Pangea		USEtox		EcoSenseWeb	
		Required by Model	Optional to Model	Required by Model	Optional to Model	Required by Model	Optional to Model	Required by Model	Optional to Model	Required by Model	Optional to Model	Required by Model	Optional to Model
Degradation	1, 10, 100 & 1,000	Yes	Yes (more detailed data)	No	Yes	No[3]	No	Yes	No	Yes	No	No[3]	No
Fate and behaviour in the environment	10, 100 & 1,000	No	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No[3]	Yes
Effects on terrestrial organisms	100 & 1000	No	Yes	No	Yes	No	No	No	No	No	No	No	No
Long-term toxicity to sediment organisms	1,000	No	Yes	No	Yes	No	No	No	No	No	No	No	No
Long-term or reproductive toxicity to birds	1,000	No	Yes	No	Yes	No	No	No	No	No	No	No	No

Notes:
1. EPI Suite requires substance identity data only and so has not been included here.
2. Where more than one tonnage band/annex is shown, the information requirements increase with each tonnage band as detailed in the respective annex.
3. The EcoSense model is a modular system, which may be connected to an environmental fate model. Depending on that underlying fate model, the required/optional physicochemical properties may vary.
4. Some toxicological and some ecotoxicological data are required for risk assessment but not for exposure assessment. Additional data refines any risk assessment.

5.6 Additional Risk Assessment Models

There are known to be a great many computational models that may be used in support of risk assessment that could be applied in the context of an SEA. Therefore, REACH guidance documents published by ECHA and the experience of the study team were used to identify a further twenty-eight risk assessment models to be reviewed.

A summary of the key features of these models, as well as a comparison with the models already reviewed, is set out in Table 5.6.

5.7 Review of Additional Life Cycle Assessment Models

The assessment of LCIA models to date has focused on those models used by members of the study team. However, there are a number of other models that are also well known and respected within the field and, while not all address the direct effects of substances on humans or ecosystems, they all could potentially be used to provide data to address some of the issues which might occur within a SEA; these models are summarised below.

5.7.1 USES-LCA

Toxic Equivalency Factors (TEF) are standard values used in Life Cycle Assessment (LCA) and Comparative Risk Assessment (CRA) to facilitate comparison of toxic impacts between substances. Environment fate, human exposure and toxic effects are generally included in the calculations of TEFs. The multi-media fate, exposure and effects model USES-LCA is based on the Uniform System for the Evaluation of Substances 2.0 (USES 2.0). An update of the fate and exposure part of USES-LCA is now available. The new fate and exposure module of USES-LCA was applied to calculate human population intake fractions and fate factors of the freshwater, marine and terrestrial environment for 3393 substances, including neutral organics, dissociating organics and inorganics, emitted to 7 different emission compartments. Apart from the fate and exposure update, a new method to derive cancer and non-cancer human damage and effect factors of toxic pollutants was developed, with human damage factors expressed as Disability Adjusted Life Years (DALY). Human effect factors contain a disease-specific and a substance-specific component. To date, the new method has been applied to calculate combined human damage and effect factors for 1192 substances. Soon updated ecotoxicological effect factors will be published for more than 3000 chemicals based on the non-linear ecotoxicological response hybrid msPAF method.

Table 5.6: Summary Comparison of the Scope of Models							
Model	**Developer**	**Substance Types Covered**	**Receptors and Target Media Included**			**Notes**	**Comparison with Other Models**
			Human Health – Workers	**Human Health – Consumer**	**Environ-ment**		
Chesar	ECHA	Most organics. Not inorganics or metals	Yes	Yes	Yes	Evaluation version now available for review. Notes based on draft guidance information from ECHA. Currently, only planned to be available as IUCLID 5.2 (or higher) plug-in	ECETOC TRA as basis for human health assessment and EUSES as basis for environment assessment, including exposure via environment (tool to be used is indicated when inputting data). Allows for input of environmental release categories
EASE	HSE	Most organics. Not inorganics or metals	Yes	No	No	Uses enforcement and worst-case data and so known to produce high/precautionary values	Incorporated in EUSES and ECETOC TRA (but with adaptation including for over-prediction). Primarily Tier 1like EUSES and ECETOC TRA but may be adapted for Higher Tier estimations
MEASE	BauA	Inorganics and metals	Yes	No	No	Adapts EASE and ECETOC TRA for inorganics and metals. Not yet validated	Unlike other models MEASE allows occupational exposure estimates for inorganics and metals
EMKG-Expo-Tool	BauA	Liquids and solids (dust)	Yes, inhalation only	No	No	Extends UK HSE's COSHH Essentials work	ECETOC TRA 2010 adapted in line with principles of COSHH Essentials and EMKG-Expo-Tool
RISKOFDERM 2.1	TNO	Liquids and solids (dust)	Yes, dermal only	No	No	Version 2.1 of spreadsheet model refined in response to user feedback	ECETOC TRA 2010 adapted in line with data underlying the unrefined RISKOFDERM 1
Advanced REACH Tool (ART)	TNO, HSL, IOM, BauA, NRCWE, and IRAS	Most	Yes, not dermal, gas or fibres	No	No	Version 1.0 published 2010, no validation as yet.	Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES
INTAKE 2	FSA	Most	No	Yes, single pathway only	No	Simple tool that lacks the uncertainty and variability modelling possible with DEPM	Allows refinement to Tier 1 assessments of dietary exposure

Table 5.6: Summary Comparison of the Scope of Models							
Model	**Developer**	**Substance Types Covered**	**Receptors and Target Media Included**			**Notes**	**Comparison with Other Models**
			Human Health – Workers	**Human Health – Consumer**	**Environ-ment**		
Dietary Exposure Potential Model (DEPM)	US EPA	Most	No	Yes	No	Version 5.0 extensively tested and validated	Allows refinement to Tier 1 assessments of dietary exposure. Dietary intake patterns will need adapting for EU consumption
Stoffenmanager	Dutch Ministry of Social Affairs and Employment	Most	Yes, not from gas, fibres, abrasion of articles or hot working e.g. welding	No	No	Designed as Tier 1 tool from SMEs	Complement to other Tier 1 models such as EUSES and ECETOC TRA. COSHH Essentials principles applied. Update due in May 2010 to align with REACH and CLP
ConsExpo	RIVM	Most	No	Yes	No	Single substance, single product, single exposure scenario only. Version 5.0 available as evaluation version allows for multiple products and multiple exposure scenario assessments without a series of separate runs	ConsExpo may be run from EUSES, output from Consexpo may also be exported to EUSES and form the basis of further calculation. ECETOC TRA uses ConsExpo fact sheet data with adaptation e.g. some assumptions made more conservative. Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES
Exposure and Fate Assessment Screening Tool (E-FAST)	US EPA	Most	No	Yes, see CEM	Yes	Screen, ing Tier 1 tool. Includes assessment of endangered species	Tier 1 tool with specific consumer and environment focuses which may complement other Tier 1 tools. US focused tool therefore care needs to be taken to ensure exposure scenarios, endangered species etc. match EU
GExFRAME	JRC	Most	No	Yes	No	Single online access point for several consumer models, including E-Fast and ConsExpo and exposure data bases	Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES

Table 5.6: Summary Comparison of the Scope of Models							
Model	**Developer**	**Substance Types Covered**	**Receptors and Target Media Included**			**Notes**	**Comparison with Other Models**
			Human Health – Workers	**Human Health – Consumer**	**Environ-ment**		
Wall Paint Exposure Assessment Model (WPEM)	US EPA	Wall paints	Yes	Yes	No	Very flexible, externally validated tool that can also incorporate emission measurement data	Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES
Consumer Exposure Model (CEM)	US EPA	Most	No	Yes	No	Dermal exposure estimates less robust than inhalation estimates. Includes assessment of exposure from defined consumer products	Integrated into E-Fast
Multi-chamber Conscentration and Exposure Model (MCCEM)	US EPA	Most	No	Yes	No	Estimation tool for indoor estimations. Complicated for Tier 1	Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES
Atmospheric Dispersion Modelling System (ADMS 4)	Cambridge Environmental Research Consultants	Most	Yes, exposure from air	Yes, exposure from air	Yes, concentrations in ambient air	Short-range simulator of atmospheric dispersion. Commercial product (£1,850 annual single user licence)	Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES
CalTOX	California Department of Toxic Substance control	Most, including inorganics (site specific data needed). Not for surfactants and volatile metals	Yes, from soil only	Yes, from soil only	No	Models adverse health effects following exposure to contaminated soil	Highly focused exposure tool to complement Chesar, ECETOC TRA or EUSES
SimpleTreat	RIVM	Most	No	No	Yes, sewage treatment only	Models distribution and elimination from sewage treatment	Incorporated into EUSES and ECETOC TRA (via EUSES)

Table 5.6: Summary Comparison of the Scope of Models							
Model	**Developer**	**Substance Types Covered**	**Receptors and Target Media Included**			**Notes**	**Comparison with Other Models**
			Human Health – Workers	**Human Health – Consumer**	**Environ-ment**		
Geography-referenced, Regional, Exposure, Assessment, Tool for European Rivers (GREAT-ER)	CEFIC	Most	No	No	Yes, PEC distribution (spatial and temporal) in surface waters only	Resolution to river and catchment level. Recommended in ECHA guidance (R.16) for modelling adsorption, degradation and volatilisation in the water compartment. Product and sediment assessment extensions available	Higher Tier tool recommended in ECETOC TRA documentation
Generic Estuary Model for Contaminants (GEMCO)	CEFIC	Most	No	No	Yes, estuarine modelling only	Models sediment and water concentrations. Also models concentration and flux for different trophic levels	Higher Tier exposure tool to complement Chesar, ECETOC TRA or EUSES
OPS	Van Jaarsveld	Most	No	No	Yes, modelling emissions to air	Recommended (along with other Gaussian plume models (GPMs)) by ECHA guidance (R.16) for estimation of dispersion, deposition and chemical transformations in air.	Incorporated in EUSES. Higher Tier tool
Step 1&2	Fraunhofer-Institut for Molecular Biology and Applied Ecology	Developed for pesticides	No	No	Yes, surface water only	For the derivation of PEC values in water and sediment	Tier 1 and Higher Tier specialising in surface water modelling. Complement to Tier 1 models. Developed for pesticides therefore care needed when applying to other applications
Pesticide Root Zone Model PRZM (_GW and _SW)	US EPA	Developed for pesticides	No	No	Yes, groundwater (_GW) and surface water (_SW) only	Developed for pesticide transport in field soils. Version 3.2 is a FOCUS model for groundwater	Tier 1 specialising in groundwater and surface water modelling. Complement to other Tier 1 models. Particularly good for modelling run-off. Developed for pesticides therefore care needed when applying to other applications

Table 5.6: Summary Comparison of the Scope of Models							
Model	**Developer**	**Substance Types Covered**	**Receptors and Target Media Included**			**Notes**	**Comparison with Other Models**
			Human Health – Workers	**Human Health – Consumer**	**Environ-ment**		
MACRO	Swedish University of Agricultural Sciences (SLU)	Developed for pesticides	No	No	Yes, groundwater and surface water (drainage outputs), only	Developed for pesticide transport in field soils. Version 4.3 is a FOCUS model for groundwater (latest version 5.1)	Tier 1 specialising in groundwater modelling. Complement to other Tier 1 models. Developed for pesticides therefore care needed when applying to other applications
Pesticide Emission Assessment at Regional and Local scales (PEARL)	RIVM & Alterra	Developed for pesticides	No	No	Yes, groundwater only	Developed for pesticide transport in field soils and under different crop types. FOCUS model for groundwater	Tier 1 and Higher Tier specialising in groundwater modelling. Complement to Tier 1 models. Developed for pesticides therefore care needed when applying to other applications
PELMO	Fraunhofer Institute for Molecular Biology and Applied Ecology	Developed for pesticides	No	No	Yes, groundwater only	Developed for pesticide transport in field soils. Version 3.2 is a FOCUS model for groundwater	Tier 1 specialising in groundwater modelling. Complement to other Tier 1 models. Developed for pesticides therefore care needed when applying to other applications
RiskPoll	Ecole des Mines de Paris	PM, SO2, NOx, CO, aerosols and toxic metals	No	Yes	Yes	RiskPoll is being developed within the context of the European Commission's ExternE Project	Designed to provide realistic estimates for valuation of impacts and policy considerations rather than the more precautionary estimates used for risk assessment
Surface WAter Scenarios Help (SWASH)	Alterra	Developed for pesticides	No	No	Yes, surface water only	Designed to take outputs from models such as Step 1&2 for further surface water fate modelling	Tier 1 and Higher Tier specialising in surface water modelling. Complement to Tier 1 models. Developed for pesticides therefore care needed when applying to other applications

Table 5.6: Summary Comparison of the Scope of Models

Model	Developer	Substance Types Covered	Receptors and Target Media Included			Notes	Comparison with Other Models
			Human Health – Workers	Human Health – Consumer	Environ-ment		
Chemical Hazard Assessment and Risk Management (CHARM)	Industry and regulators	Oil and gas platform wastes. Not inorganics	No	No	Yes, from oil and gas platforms	Designed to model fate of waste from oil and gas platforms to water and sediment	Important source of exposure data for substances released from oil and gas platforms

5.7.2 GLOBOX

GLOBOX is a spatially differentiated multimedia fate, exposure and effect model. It is used for the calculation of spatially differentiated LCA characterisation factors on a global scale. GLOBOX is largely based on the European Union model EUSES (version 1.00). GLOBOX consists of three main modules:

- an impact-category independent fate module;
- a human-intake module, applicable to all impact categories that are related to human intake of chemicals; and
- an effect module, in which effect-related parameters can be introduced for every separate impact category.

GLOBOX is spatially differentiated with respect to fate and human intake on the level of separate, interconnected countries, seas and oceans. Alternatively, the user can choose to differentiate on a number of lower levels or to turn off spatial differentiation altogether. GLOBOX has been harmonised with the ecoinvent Life Cycle Inventory database which implies that all regional divisions distinguished in this database are also included as levels of differentiation in GLOBOX. The idea behind GLOBOX is that it should be possible to construct location specific characterisation factors for any emission at any location in the world, taking into account the summed impacts of such emission in all countries and at all seas and oceans among which it is dispersed during its lifetime.

5.7.3 TRACI

The Tool for the Reduction and Assessment of Chemical and other environmental Impacts to assist in impact assessment for Sustainability Metrics, Life Cycle Assessment, Industrial Ecology, Process Design, and Pollution Prevention (TRACI) model allows the examination of the potential for impacts associated with raw material usage and chemical releases arising from the processes involved in producing a product. TRACI allows the user to examine the potential for impacts for a single life cycle stage or the whole life cycle, and to compare the results between products or processes. The purpose of TRACI is to allow a determination of priorities or a preliminary comparison of two or more options on the basis of the following environmental impact categories: ozone depletion; global warming; acidification; eutrophication; photochemical smog; human health cancer; human health non-cancer; human health criteria; ecotoxicity; fossil fuel use; land use; and water use. TRACI is intended as an impact assessment tool that will support consistency in environmental decision making but it is recognized that additional tools may be useful to assess, prioritize and reduce potential environmental impacts. The user's guide presents information to assist in the use of, limitations and uncertainties associated with, and information concerning, the methodologies within TRACI.

To develop TRACI, impact categories were selected, available methodologies were reviewed and categories prioritized for further research. During the impact assessment methodology research phase, consistency with previous modelling

assumptions (especially those of the US EPA) was considered important for every category. The human health cancer and non-cancer categories were heavily based on the assumptions made for the US EPA Risk Assessment Guidance for Superfund and the Exposure Factors Handbook. For categories such as acidification and smog formation, detailed US empirical models - such as those developed by the US National Acid Precipitation Assessment Program and the California Air Resources Board - allowed the inclusion of the more sophisticated location specific approaches and location specific characterization factors. Where there was no EPA precedent, assumptions and value choices were minimized by the adoption of midpoints. TRACI's modular design allows for the compilation of the most sophisticated impact assessment methodologies that can be utilized in software developed for PCs. Where sophisticated and applicable methodologies did not exist, simulations were used to determine the most appropriate characterization factors representative of the various conditions within the US. As the research, modelling and databases for LCIA methods continue to improve, each module of TRACI is intended to be improved and updated.

5.7.4 Indoor Airflow and Exposure Model

Damage to human health as a result of exposure to contaminants emitted to indoor air is poorly addressed in life cycle assessment tools for dwellings. A new model has, however, been developed which calculates damages to human health caused by contaminants emitted from building materials. It is based on a multi-zone indoor airflow and exposure model. Ventilation rates and radon concentrations are simulated for a Dutch reference dwelling, and compared with measurement data from the Dutch Ecobuild houses and from average ventilation rates and radon concentrations in dwellings in the Netherlands. The ventilation rates and radon concentrations as simulated with the indoor exposure model are of the same order of magnitude as the ventilation rates and radon concentrations measured in the Ecobuild dwellings and in both radon surveys (except for the crawl space where the modelled ventilation rates are overestimated and the radon concentrations underestimated). Overall, the indoor airflow and exposure model has been shown to give a good reflection of actual ventilation rates and radon concentrations. However, for the crawl space the model requires further adjustment and the effects of mechanical ventilation on the model results need to be tuned.

5.7.5 RECIPE (LCIA method)

Life cycle assessment (LCA) is a methodological tool used to quantitatively analyse the life cycle of products/activities; ISO 14040 and 14044 provide the generic framework. After goal and scope are determined, data are collected and an inventory result is calculated. This inventory result is usually a very long list of emissions, consumed resources and sometimes other items. The interpretation of such a list is difficult but a LCIA procedure such as the ReCiPe method is intended to assist in the interpretation.

The primary objective of the ReCiPe method is to transform the long list of inventory results into a limited number of indicator scores. These indicator scores express the relative severity of an environmental impact category. ReCiPe uses an environmental mechanism as the basis for modelling. An environmental mechanism can be seen as a series of effects that together can create a certain level of damage to, for instance, human health or the ecosystem. For instance, for climate change it is known that a number of substances can increase radiative forcing; this means heat is prevented from being radiated from the earth to space. As a result, more energy is trapped on earth and temperature increases. As a result changes in habitats for living organisms may change and species may become extinct.

In ReCiPe eighteen such midpoint indicators are calculated as are three much more uncertain endpoint indicators. The motivation to calculate the endpoint indicators, is that a large number of midpoint indicators are very difficult to interpret, partially as there are too many, partially because they have a very abstract meaning. Thus, how can a comparison be made between radiative forcing and base saturation numbers that express acidification? The indicators at the endpoint level are intended to facilitate such interpretation as these are reduced to only three which have a more understandable meaning.

5.7.6 EDIP97 / EDIP2003 (LCIA method)

EDIP97 is a thoroughly documented midpoint-approach model covering most emission-related impacts, resource use and working environment impacts. It includes normalization based on 'person equivalents' and weighting based on political reduction targets for environmental impact and working environment impact as well as the supply horizon for resources. Ecotoxicity and human toxicity aspects are modelled using a simple key-property approach where the most important fate characteristics are included within a simple modular framework requiring relatively few data on a substance in order to calculate characterization factors. The update through EDIP2003 methodology supports spatially-differentiated characterization modelling and covers a larger part of the environmental mechanism than EDIP97 and also lies closer to a damage-oriented approach. This part of the general method development and consensus programme covers the investigation of the possibilities for inclusion of exposure aspects in the life cycle impact assessment of non-global impact categories (e.g. photochemical ozone formation, acidification, nutrient enrichment, ecotoxicity, human toxicity and noise).

5.7.7 Eco-indicator 99 (LCIA method)

The Eco-indicator 99 is a 'state of the art' impact assessment method for LCA, and incorporated many conceptual breakthroughs. The method is also the basis for the calculation of eco-indicator scores for materials and processes; these scores can be used as a user-friendly environment tool for designers and product managers to improve products. This impact assessment method is now widely used by life cycle assessment practitioners around the world.

Weighting is a controversial step in the impact assessment. Taking weighting as the starting point of the Eco-indicator 99, a 'top down' approach is used; this contrasts with the 'bottom up' approach used in traditional theme-oriented methods where a panel can be confronted with ten or more abstract environmental themes to weight. New damage models and three perspectives were developed to complete the method.

5.7.8 MSCE-POP 3.3.4 (2009)

Meteorological Synthesizing Centre – East (MSCE) includes a multi-compartment chemistry transport model that can be used to assess contamination with POPs of Europe (EMEP).

The MSCE-POP model has been used for the evaluation of POP contamination levels and trans-boundary transport under the UN ECE LRTAP Convention, as well as investigation of intercontinental POP transport, evaluation of POP candidates from the viewpoint of their long-range transport potential and persistence in the environment, and evaluation of POP redistribution between environmental media. In 2005, a validation of this model was undertaken by the European Monitoring and Evaluation Programme (EMEP). This estimated the uncertainty due to the model (not including emission uncertainties) at between 30% and 40%.

5.7.9 Use of Model Outputs for Probabilistic Evaluation

Many of the models considered above, particularly the normally-applied chemical risk assessment models, are deterministic in nature and produced only single values rather than probabilistic distribution functions. For example, EUSES 2.1 and ECETOC TRA both produce estimations for exposure, hazard and risk as single values.

It has been demonstrated recently (WCA, 2010) that it is possible to couple a spreadsheet version of EUSES 1.24 with a commercial programme capable of generating probabilistic output, as so generate probability distributions for PEC values.

The approach adopted by WCA automated the process of feeding exposure (as well as health effect) data into a risk assessment model, capturing the output and then using the data to generate a probabilistic output. It is noted that the ease with which spreadsheets may be adapted for automation make the use of spreadsheet-based models (such as the spreadsheet versions of EUSES and ECETOC TRA) particularly suitable for this type of adaptation. However, with sufficient programming expertise and access to source code, there is no theoretical reason why non-spreadsheet based deterministic models could not be adapted to a probabilistic evaluation in a similar way.

5.8 Review of Additional Other Assessment Models

So far the models considered relate to deterministic chemical risk assessment models or LCIA models that address a wider range of endpoints. In addition there exist other models that are used to inform on predictive (i.e. forward-looking) assessment for other environmental impacts; some of the main types are considered here in relation to their potential usefulness in providing information that could be of potential value in the preparation of a SEA.

An extensive review of such 'other' models was published in 2008 by the European Environment Agency (EEA, 2008). This considered 80 models which were allocated to 14 categories depending upon their thematic focus. Table 5.7 summarises the types of impact that the models were developed to addressed (using the thematic categories defined by EEA) and identifies the aspects for which they could find application within a REACH SEA.

On the basis of our review, only the following models relating to air quality were considered likely to be of potential relevance to some REACH-related SEAs:

- City-Delta (http://aqm.jrc.it/citydelta/);
- EcoSense (www.ier.uni-stuttgart.de/forschung/modmeth/ecosense/ecosense.html);
- GAINS (Greenhouse Gas and Air Pollution Interactions and Synergies; www.iiasa.ac.at/rains/gains.html);
- RAINS (Regional Air Pollution Information and Simulation; www.iiasa.ac.at/rains/gains.html);
- SMART (Simulation Model for Acidification's Regional Trends; www.macaulay.ac.uk/dynamo/smart.htm); and
- Unified EMEP Unified European Monitoring and Evaluation Programme model (http://emep.int/OpenSource).

Table 5.7: The Potential Application to REACH-related SEA of Models Considered by EEA (2008)		
Thematic focus	**Impacts modelled**	**Application to SEA**
Agriculture	Socio-economic and environmental impacts from changes in fertiliser consumption and use, as well as of nutrient balance	None
Air quality	Socio-economic and environmental impacts from changes to emission of acidifying substances, ozone precursors, particulates and VOCs	Comparative assessment of wide range of impacts, some of which might be relevant to the use of a substance, alternative substances and/or alternative processes These models consider long-range transport, climate change and ozone depletion
Biodiversity	Changes in species diversity following climate change	Unlikely. However, should assessment of alternatives indicate significant differences in greenhouse gas emissions, assessment of change in species diversity as a result of climate change might be included through their use
Climate change	Climate change	Unlikely but may inform on other assessments
Energy	Energy consumption	None
Land use	Land use and cover, as well as changes to arable land cover	None
Forest	Forest	None
Transport	Demand for transport of different types, use of different fuel sources and car ownership	None
Waste and material flows	Municipal waste flow and volumes as well as recycling	Unlikely
Water	Water resource issues	Unlikely but may inform assessment where alternative(s) involve significantly different water usage
Demography	Population changes	None
Economy	GDP and fuel prices	None
Tourism	Tourist changes	None
Integrated socio-economic	Global modelling of many of the above	None

6. APPROACHES TO ASSESSING HEALTH IMPACTS

6.1 Outputs from Health Risk Assessment

6.1.1 Introduction

Assessment of the health impacts associated with a restriction or refused authorisation requires data on:

- current levels of exposure to the chemical and the anticipated changes in exposure due to risk management;
- dose-response or other data linking exposure to different health outcomes;
- data on the population exposed both prior to and after regulation;
- based on the above, estimates of the number of cases of a particular disease outcome attributable to exposure to the chemical of concern (or chemicals more generally); and
- data on the economic value of changes in health outcomes.

In addition, information is required on the limitations surrounding the different sources of data and thus the associated uncertainties surrounding their use in a SEA.

As indicated in Section 3, the output of the REACH risk assessment for each exposure scenario considered will be a Risk Characterisation Ratio providing an indication of the margin of safety between the DNEL (or in some circumstances DMEL) and the estimated exposure level (generally based upon worst case assumptions); all relevant exposure pathways considered of concern will be addressed. However, it is the data underlying the RCRs that are of most value to SEA (i.e. the hazard endpoints considered and level of exposures (or estimates of these)). Table 6.1 sets out the potential exposure pathways and risk endpoints that are likely to be most relevant; although not all of these may be a main driver for a restriction proposal or authorisation, more than one end-point or route of exposure may be relevant to the use of a particular chemical. The aim of the SEA is then to translate the information for each exposure pathway into the types of direct and indirect impacts listed in Table 6.1. Examples of direct and indirect health effects relevant to authorisation and restriction include mortality effects such as cancer and morbidity effects such as infertility and other reprotoxic effects, developmental effects, respiratory diseases and skin diseases. This includes consideration of both long-term and short-term exposures to the chemical of concern.

Table 6.1: Summary of Human Health Risks Considered for SEA		
At Risk Group	**Exposure Pathways**	**Direct and Indirect Impacts**
Workers Consumers Public health or man via the environment	Inhalation exposure Dermal contact Ingestion of particles or surface residues	• Fatalities or deaths brought forward • Morbidity effects – cases of disease / illness which may be chronic or acute in nature • Lost working days and non-working day opportunities • Health care costs • Changes in quality of life (e.g. DALYs or QALYs or other measure) • Stress effects related to pain and suffering

6.1.2 Statistics Used in Health Economics

In analysing health impact data, it is important to be clear on the nature of the statistics that are being used. From the review presented in the previous sections, the key health metrics and associated health statistics that are used in health impact are those set out in Tables 6.2 and 6.3.

Table 6.2: Summary of Key Health Metrics	
Health Metric	**Definition**
Epidemiological Studies	
Relative risk	The risk of disease in the exposed population over the risk in the unexposed population. Indicates the potential for a causal relationship
Attributable risk	The difference between the risk of disease in the exposed and the risk of disease in the unexposed groups. Provides a measure of the potential impact of a preventative programme once causality has been established. Can be converted to a relative risk ratio
Odds ratio	The potential for a causal relationship based on information on past exposure to possible risk factors, and is specific to particular population groups
Human Experimental Studies	
Dose-response function	Relationship between different exposures to a chemical and the level of health effect
Toxicological Studies	
N(L)OAEL	No (low) observed adverse effect level to define the point at which a response rises above a zero effect (i.e. the POD)
Benchmark dose	An alternative POD is provided by the benchmark dose (BMD) method which is normally defined in terms of an estimated dose equating to an effect in 5% or 10 % of the population (generally reported as $BMDL_5$ or $BMDL_{10}$, respectively)
Threshold of concern	A *de minimus* value may be identified for many chemicals in the absence of full hazard characterisation to identify a level of exposure at which the risk of adverse effects is considered very low

Table 6.3: Associated Health Statistics	
Statistic	**Definition**
Dose-response function	Direct probabilistic relationship that can be applied to the associated population
Derivable Estimates of Population Impacts	
Attributable fraction	The proportion of cases in a population in a defined period that can be attributed to certain risk factors. Calculation relies out relative risk ratios or odds ratios from epidemiological studies
Prevalence of an illness	Indication of disease burden, i.e. the number of people in a given population who have a disease at a particular point in time (for instance, number individuals with a disease out of 100,000 workers); derived from epidemiological studies
Incidence of an illness	Number of new cases of an illness over a given period of time period (for instance, if 300 new cases of a respiratory illness occur within the general population during a 12 month period, then the incidence within that population will be 300).
Margin of Safety	The ratio of the NOAEL (or other marker of POD) to the expected exposures

It is important to understand what health metrics are used with what statistics in trying to quantify health impacts. These links are as follows (drawing on the discussions in Sections 3 and 5), with the methods used to quantify the change in impacts ordered in terms of their likely reliability:

- dose-response functions: these provide a direct indication of the probability that someone exposed to a substance at a given dose level will contract the health effect of concern. Epidemiological data are frequently inadequate to inform their development and they are not linked to the usually available epidemiological health metrics (odds ratio, relative risk ratio or attributable risk). They can, however, be derived from benchmark dose and margin of safety estimates using models which extrapolate from the underlying animal data;

- attributable fractions: these provide an indication of the burden of disease within a population. Through the use of relative risk ratios or odds ratios, the impacts of changes in exposure – i.e. from current exposures to no exposure - on the attributable fraction can be calculated, indicating the associated reduction in the disease burden for the associated population;

- prevalence and incidence: in the absence of a dose-response function or relative risk and odds ratios, statistical data on the prevalence or incidence of a disease within a population can be used to provide a starting point for predicting changes in impacts. However, this requires additional assumptions on how a change in exposure may change prevalence or incidence. For example, by calculating the difference in prevalence or incidence for an exposed and an unexposed population; and

- the risk characterisation ratio (RCR) together with the margin of safety (MOS): the margin of safety data on its own provides no means of quantifying the change in health impacts that would arise from a regulatory measure; it is only possible to

quantify the change in impacts if the MOS data are fed into the various models that are available to allow extrapolation of a dose-response function.

The applicability of the different statistics can vary with circumstances. For example, sometimes prevalence is a more meaningful concept than incidence while in other cases it will be the reverse. If one is concerned with whether or not a change in regulation has been effective in reducing the number of cases of a certain illness, then one would compare the incidence of that illness over the past year and compare it with the incidence in previous years to see if it has changed. If instead the focus is more on whether the proportion of people currently suffering from a disease, such as a chronic respiratory disease, will decrease over time due to regulatory action, then prevalence may be more relevant.

6.1.3 Overview of Approaches

A number of approaches are available for assessing the health benefits of chemical risk management. The main approaches used to date are:

- cost-effectiveness analysis, with effectiveness measured in terms of disease cases avoided;
- cost-utility analysis, which is a form of cost-effectiveness analysis that relies on utility based measures instead of reductions in disease cases;
- cost-benefit analysis, with the potential to draw on a range of different valuation techniques; and
- risk ranking methods, which have been applied in the context of worker safety including in relation to chemical exposures.

We have not identified any formal multi-criteria analysis applications addressing worker, consumer or public health risks in relation to chemical risk. However, we have identified a range of risk ranking based methods which may be important to any future logic framework, given that they rely on hazard data only and do not also require the outputs of an exposure assessment. Given that these are the least data-demanding, we start with these and then review the potential use of the other methods listed above.

6.2 Risk Ranking and Other Comparative Methods

6.2.1 Introduction

As indicated above, risk ranking and other methods relying on hazard indices can provide a much less onerous and less costly method to derive policy choices, if not necessarily by quantitative means. Similarly, these methods can be an important prerequisite for the quantitative techniques discussed above, by focusing resources and identifying the most appropriate method for evaluating the health risk of concern. A number of tools have been developed to facilitate risk ranking of large numbers of

chemicals in order to prioritise those with the greatest potential to harm human health and/or the environment.

One such example is the EU risk ranking method (EURAM) which was used to identify priority chemicals for assessment under the Existing Substances Regulation. Application of the criteria for the identification of substances of very high concern (SVHC) that may be subject to authorisation set out in Title VII of REACH is a further example of a system for the identification of potentially harmful substances from a large list of chemicals. For the purposes of a specific SEA on a restriction or authorisation, however, it is likely that the number of substances to be compared will be limited to the substance subject to authorisation or restriction and a limited number of potential alternatives. Hence tools developed to screen large number of chemicals may not be the most appropriate.

The Scoring and Ranking Assessment Model (SCRAM) was developed for the US EPA to provide an analytical tool for ranking contaminants in the Great Lakes (Mitchell et al, 2002) constitutes another example of this type of method; this model is described further in Section 7 as it has a particular focus on persistence and bioaccumulation potential.

Another example is the approach developed by Brereton & Altenbach, which is described in more detail below.

6.2.2 Risk Ranking Matrices

Brereton & Altenbach (1998) consider risk matrices for their suitability as risk ranking tools for chemical substances (including substances in mixtures). The risks considered are in terms of accidental harm to worker health. A risk matrix is a matrix with units of frequency and consequences on opposing axes. A qualitative matrix uses descriptive terms to describe the units for both axes (a semi-qualitative matrix will use a numerical and a descriptive axis), as shown in Figure 6.1 overleaf.

As can be seen from Figure 6.1, a qualitative matrix enables differentiation of the highest risks (red) from the lowest risks (green). However, comparative assessment of substances that fall into any other block (orange) may be possible along a row or column of the matrix but not otherwise. For example, the unlikely-trivial box may be considered to contain lower risks than the unlikely-extreme box but it would not be possible to compare risks from the unlikely-minor box with those from the certain-trivial box.

Brereton & Altenbach (1998) take this argument one stage further and state that, due to the uncertainties associated with the assignment of risks to qualitative criteria, often the only robust distinction is between highest and lowest risks. In order to allow all boxes in a matrix to be compared to all other boxes, a fully quantitative matrix could be constructed, with actual consequence values (e.g. deaths) plotted against the likelihood with a set time scale (e.g. years).

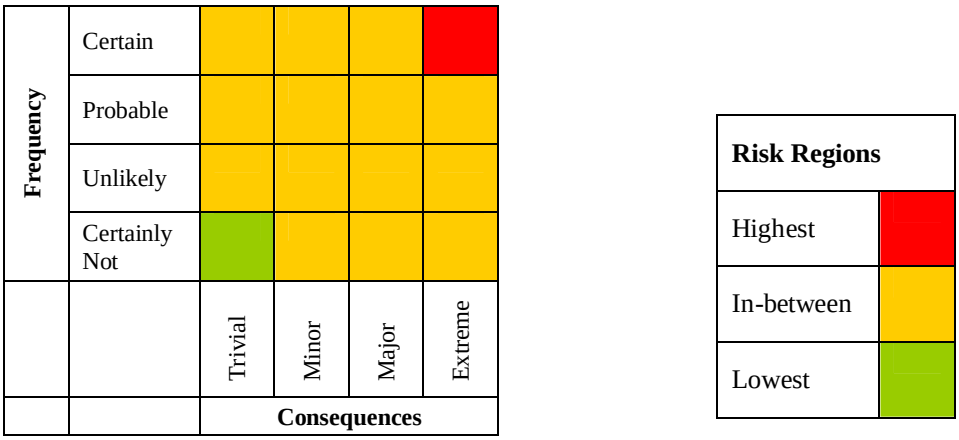

Figure 6.1: Qualitative Risk Matrix

Where the amount of data needed to construct such a quantitative matrix is not available, other approaches may also be of value. However, Brereton & Altenbach (1998) report that it is possible to achieve very similar outcomes by constructing 'relative risk' matrices based on a limited categorisation of available data. This allows for the impacts and risks to workers from different substance releases to be compared, as well as those to the public. This is done through construction of two side-by-side matrices, one for workers and one for the public using identical frequency categories, as shown in Table 6.4.

Table 6.4: Frequency Categories for Workers and the Public	
Frequency category	**Definition for Workers and the Public**
A	Between 10^{-6} and 10^{-4} per year (lowest)
B	between 10^{-4} and 10^{-2} per year
C	between 10^{-2} and 0.1 per year
D	between 0.1 and 1 per year (highest)

Common consequence categories were also set but here workers were assumed to be protected (at least to some extent by appropriate protective equipment) when working with substances and so the ambient exposure level necessary to cause a specified level of harm was assumed to be higher for workers than would be the case for the (unprotected) public. Therefore, the consequence axis of the worker and the public matrices were assigned different values representing equivalent effect consequences.

For example, no noticeable impact to workers from a substance would be assumed to occur if the exposure level is less than the established safe exposure threshold level (assuming appropriate protective equipment is in place), such a threshold level in working environments is generally defined in terms of occupational exposure limits[45].

[45] Brereton & Altenbach (1998) considered such occupational threshold levels (OELs) in terms of Threshold Limit Values Time Weighted Average (TWA) values and Emergency Response Planning Guide Levels. It would generally be assumed that the most relevant OELs for comparison to scenarios

In order to provide a sufficiently precautionary approach to address risks to the public (i.e. man via the environment), Brereton & Altenbach (1998) divided the worker threshold levels by a factor of ten. This factor size was chosen for illustrative purposes only in this example; in practice, the actual size of the protective factor required would need to be carefully determined before applying this technique. The consequence categories used in their example are set out in Table 6.5, with the resultant relative risk matrices reproduced in Figure 6.2.

Table 6.5: Consequence Categories for Workers and the Public

Consequence Category	Definition for Workers	Definition for the Public
I (No noticeable impact)	≤ OEL	≤ OEL/10
II (Minor impact)	OEL to $OELx10^2$	OEL/10 to OELx10
III: (Significant impact)	$OELx10^2$ to $OELx10^4$	OELx10 to $OELx10^2$
IV (Severe impact)	$OELx10^4$ to $OELx10^8$	$OELx10^2$ to $OELx10^4$

Quantitative Risk Matrix for Workers

Frequency (Years)	Category I	Category II	Category III	Category IV
D (0.1 - 1)	13	14	15	16
C (10^{-2} to 0.1)	9	10	11	12
B (10^{-4} to 10^{-2})	5	6	7	8
A (10^{-6} to 10^{-4})	1	2	3	4

Consequences (Multiples of Threshold)

Quantitative Risk Matrix for the Public

Frequency (Years)	Category I	Category II	Category III	Category IV
D (0.1 - 1)	13	14	15	16
C (10^{-2} to 0.1)	9	10	11	12
B (10^{-4} to 10^{-2})	5	6	7	8
A (10^{-6} to 10^{-4})	1	2	3	4

Consequences (Multiples of Threshold)

Figure 6.2: Quantitative Risk Matrices

The Risk Level can then be calculated for each substance as the multiple of frequency and consequence. Risk Levels for substances may be compared directly or can be used to assign substances to blocks of the risk matrix. Blocks can then be assigned a Risk Level that reflects the highest Risk Level for that block or the average Risk Level for the block, as appropriate to the circumstances being considered. For example, block 14 of the Workers' matrix could be assigned the highest Risk Level of 100 (frequency of 1 x consequence of 100) or the average Risk Level 25 (frequency

relating to the general population would be the 8-hr TWA values, rather than short-term exposure levels (STELs).

of 0.5 x consequence of 50). Blocks of substances may then be compared or grouped according to derived Risk Level.

The use of threshold values as the basis for assigning to 'units of consequence', rather than predicted exposure concentrations enables different substances, with potentially markedly different hazard properties and potencies, to be directly compared with one another. Importantly, the consequence categories used for both the worker and the public matrices are equivalent, and so the blocks within those matrices are equivalent. For example, the risk to workers expressed by block 9 in the workers matrix will be equivalent to the risk to the public expressed by block 9 in the public matrix.

The use of Risk Levels allows for the comparison of risks from different substances but they do not equate to actual risk values. Thus, these risk matrices are comparative and illustrative tools only, and do not produce outputs consistent with those of a formal risk analysis. However, such an approach could have value in those cases where a threshold value is available (or definable) for a substance but for which other risk data, such as N(L)OELs or alternative markers of the POD may be lacking. Thus, this technique allows for the comparison of substances where there are variations in the nature and extent of risk data available for some or all of the substances being considered, a situation entirely possible when comparing alternatives under SEA.

6.2.3 Benchmarking Based Approaches

An exhaustive review of potential benchmarking approaches has not been undertaken, but a recent example is described here to highlight the potential of such methods.

Yuan and Dornfeld (2009) adopt a three tier process to characterise the impact of the release of a substance from intake, toxicity and persistence. This method is found to be comparable to the Human Toxicity Potential (HTP) method of impact characterisation used in the USA but requires far less hazard and exposure data. The method described is suitable for the characterisation of chronic impacts on human health only.

Yuan & Dornfeld (2009) define toxicity in terms of the threshold value for an acceptable daily intake (ADI). The persistence of a substance is defined in terms of a substance's rate of decay in the environment (rather than the length of time that the substance will be available to cause impacts and which can be measured in terms of half-life). Intake following the release of a chemical substance is the product of the substance concentration and the appropriate intake factor for inhalation, ingestion and/or dermal contact. Intake from all sources and all relevant intake routes must be combined to provide the overall intake.

The potential impact of a substance on an individual is determined by intake over time. To standardise, the 'individual' receiving the impact and the time interval overall intake is defined in terms of the intake of a standard size (70kg) person over a 24 hour period. Intake is then calculated in terms of the average individual daily intake where:

$$\text{Daily Intake (DI)} = \frac{E \times IF \times 10^6}{N \times BW \times P} \quad \text{(mg substance / kg body weight / day)}$$

Key:
E = Amount released;
IF = Intake fraction;
N = Total number of people exposed;
BW = Average body weight (70 kg); and
P = Persistence = $\sum\left(\frac{\text{Mass of substance in environment}}{\sum(\text{Mass of substance in environment x rate of decay})}\right)$

The intake and toxicity are then combined into a single a dimensionless 'individual daily risk ratio' (R) derived by dividing daily intake by the acceptable daily intake. The output of this exercise are used to develop a system for benchmarking chemicals by plotting them on a graph of risk ratio (R) against persistence (P) and separating the data points by lines with a gradient (S) of -1 drawn from the risk axis at appropriate intervals[46].

The application of this approach to the characterisation of industrial solvents is illustrated in Figure 6.3 (see Yuan & Dornfeld (2009) Figure 3).

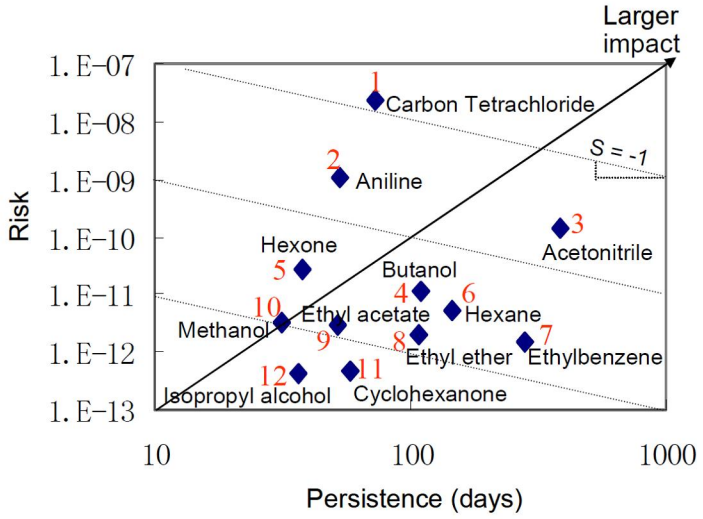

Figure 6.3: Benchmarking of Substances for Human Health Impacts

6.3 Physical and Utility Based Indicators of Impact

6.3.1 Role in SEA under REACH

Within the context of REACH restrictions and authorisation, there is the potential to use either physical based measures of impact or utility based measures.

[46] Mathematical justification not shown for brevity.

For example, a simple, single-dimension, physical unit of measure of effectiveness would be estimates of the number of deaths avoided or cases of disease or illness avoided as a result of either restrictions or a refused authorisation.

Physical units of measure have been used within health-related cost-effectiveness analyses for many years in regulatory decision making and a number of studies have been carried out in the US for example to develop benchmark cost-effectiveness values to guide decisions on when the cost per physical unit reduction in health risk would appear to be unjustified (Tengs et al, 1995).

Requirements were introduced in the US in 2003 for cost-effectiveness analysis to accompany regulatory cost-benefit analyses by the Office of Management and Budget for all major regulations. The early studies focused on the number of preventable deaths averted as the single-dimension measure of effectiveness. However, dissatisfaction with the ability of this type of measure to reflect variations in disease severity and duration, led to the use of calculations of years of life saved as a preferred unit of measure by some departments (Board on Health Care Services, 2006). The life-years approach provides more weight to averting deaths among persons who otherwise would have longer remaining life expectancies; in particular, an intervention that prevents deaths among children will generally lead to larger estimates of life years gained than an intervention that prevents deaths among adults.

More recently the trend both in the US and in Europe appears to be towards use of a utility based measure of effectiveness and, in particular, measures of the number of years lived in full health by the beneficiaries through the use of either DALYs or QALYs. Such utility based measures may be more appropriate than the use of physical units of measure for diseases associated with chronic impacts or with cancer for example, where the health effects may be experienced over prolonged periods of time. This is because utility based measures can be used to reflect changes in quality of life not just changes in the incidence of a disease outcome. Effects over time can therefore be taken into account more easily. This has obvious attractions in relation to the types of health impacts that may be associated with chemicals subject to either restriction or authorisation.

The key advantage of DALYs or QALYs over a single-dimension measure is that it enables a number of possible disease endpoints to be considered within a single assessment. In other words, by converting the information on the number of disease cases reduced for different diseases to DALYs, the information can be aggregated to derive an estimate of the total number of DALYs gained. This has obvious advantages where risk management would result in reductions of, say, cancer cases, chronic respiratory effects and dermal sensitisation due to reduce exposures.

6.3.2 The Basis for QALYs and DALYs

Although there is a range of different health utility measures that are applied to assess the benefits of an intervention, the most commonly used ones are Quality Adjusted Life Year (QALYs) and Disability Adjusted Life Year (DALYs)[47]:

- a QALY represents disease-specific health gain by taking into account both quantity and the quality of life generated by healthcare interventions. It is calculated by combining the years gained by an intervention and a measure of the quality of the life-years gained;

- a DALY represents health loss connected to a specific disease, a specific risk factor (e.g. smoking, air pollution). In relation to an intervention (e.g. promoting healthy nutrition), it rather indicates health gain, like the QALY. It is calculated as the sum of years of life lost (YLL) and years lived with disability (YLD) weighted for severity of the disability (or disease) in question, all related to the specific disease etc. in question. In terms of concept and calculation DALY and QALYs are each other's counterpart.

The quality-adjusted life year (QALY) is a measure of the burden of disease covering the quality and the quantity of life lived. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death. If the extra years would not be lived in full health, a disability weight is assigned and the extra life-years are given a value between 0 and 1 to account for this. These in-between states could stem from a hearing impairment, reduced sight, reduced mobility, etc.

DALYs (disability adjusted life years) were first developed as a concept by Murray and Lopez with the World Health Organisation and the World Bank (1996), and they combine the effects of premature death and disability on society into a number to enable comparison across different effects. DALYs are derived as follows:

DALY = Years of life lost (YLL) + Years lived with disability (YLD), where

> YLL = annual Number of deceased (mortality) * remaining age group Life Expectancy, and
> YLD = annual Number of diseased (new cases) * Severity weight * Duration of disease.

As can be seen from the above, DALYs are the reverse of QALYs, whereby 0 = no health problem, rather than death. A range of different approaches exist for eliciting the weights assigned to different health states. However, standardised systems, such as the EuroQol Group's EQ5D, now exist which can be used to categorise many, but

[47] Other measures include Healthy Life Expectance, Health Adjusted Life Expectancy and Healthy Year Equivalent. These measures do not appear to be used for regulatory purposes as much as QALYs and DALYs and we have not found any relevant applications during the literature review due to various problems in applying the concepts in practice.

not all, health states according to the following dimensions: mobility, self-care, usual activities (e.g. work, study, homework or leisure activities), pain/discomfort and anxiety/depression.

Examples of DALYs for 49 non-communicable diseases, representative for the world in 1990, have been developed by Huijbregt et al (2005a). However, a number of issues need to be taken into account when attempting to interpret these values:

1. The DALYs developed by Huijbregt et al are based on world averages. Thus, for developed regions or countries, the DALYs gained or lost may be lower than those given, as medicine is more advanced than the world average. Hence in the context of REACH, world-based values may overestimate the benefits of banning or authorising the substance;
2. The DALYs were calculated without applying age-specific weighting and without discounting future health damages, which may overestimate the number of DALYs gained or lost. As a subject of some debate, this issues should be acknowledged; and
3. The use of YLDs includes subjective judgment of the weighting of health disabilities. For cancer, 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, but 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, cited in Huijbregt et al, 2005), it is expected that the influence of any subjective judgment as to 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 follows:

$$Damage\ (as\ DALY\ caused\ by\ a\ number\ of\ diseases) = Npop * \Sigma DALYe * Re$$

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.

6.3.3 QALY and DALY Based CEAs

Traditionally, neither QALYs nor DALYs have been used in the context of chemical risk management, with this possibly due to the fact that neither are risk dependent. However, there has been increasing interest in their use as a means of conveying more

information on health benefits and to provide a means of enabling better comparisons across and aggregation of information on different health endpoints.

In 2003, the World Health Organisation (WHO) issued a guide to cost-effectiveness analysis of health interventions. Although the guidance is not focused on chemical risks, it does provide some valuable discussions on cost estimation, where benefit transfer approaches are not considered appropriate, and other aspects of health impact assessment and appraisal of options. The guide reviews issues concerning the assessment of mortality and morbidity related impacts. It recommends the use of DALYs for assessing the population effectiveness of an intervention, although measures such as QALYs and HYLs are also considered appropriate. However, the guide is aimed at the assessment of major health interventions, i.e. those that will have an impact at a national population level, rather than issues of concern in relation to granting an authorisation for the limited use of a chemical or the assessment of targeted restrictions proposals.

More recently, the OECD has scoped their use in the context of health risk to children. This was in response to the need to consider environmental risks to children from chemicals (OECD, 2006). The OECD study concluded that although WTP values may be more appropriate than QALYs to reflect affected individuals' preferences (as they do not impose a selection between longevity and health), QALYs may be more appropriate to reflect those aspects of risk like duration of effect. However, the OECD work also concluded that additional difficulties in the case of children relate to cognitive ability, practical and legal autonomy, and the fact that there may be a greater social interest in protecting children than adults (Hammit, 2006).

QALYs have also been calculated for different policy contexts with some of them related to chemical exposure. de Hollander (2004) gives examples of Euros per QALY values for various conditions and health protection related policies, with these presented in Table 6.6.

Unfortunately, cancer is not covered by Table 6.6 but some cancer screening programmes are included. Such costs would be equivalent to the benefits, i.e. costs avoided, if a specific chemical risk reduction option reduced the need for such treatment. It is interesting to note that most of the health protection measures included in this list reproduced in Table 6.6 have higher costs per QALY gained.

The recent study by RIVM on *Health impact assessment of policy measures for chemicals in non-food consumer products* produces estimated DALYs gained from undertaking risk reduction measures on specific chemicals included in consumer products, examining nine case studies spanning from cosmetics to cleaning products and DIY products.

Table 6.6: Overview of Cost-effectiveness Calculations	
Costs: euro/QALY[a]	**Intervention**
< 0 (cost-saving)	National vaccination programme (DP)[b] Smoke detector in the home (HPt) Help with addiction for Smoking HP Removal of lead from petrol and paint, stripping lead-based paint coats (HPt)
0-1,000	Mandatory safety belt (HPt) Disease coping training for asthma (MC) Practical test for moped and autocycle (low-speed moped) riders (HPt)
1,000-10,000	Chlorination of drinking water (HPt) Influenza vaccination for all elderly people (DP) Cholesterol test and dietary advice (DP) Bypass operation (MC) Mammography population survey (DP)
10,000-100,000	Controlling Legionella in (health) care facilities (HPt) Pneumococcal vaccination for the elderly (DP) Kidney replacing treatments (dialysis) (MC) Smear and treatment for cervical cancer (DP) Periodic automobile test (HPt) Airbags (HPt) Ban on asbestos in brake blocks (HPt)
10,000-1,000,000	Reduction of radon in existing dwellings (HPt) Neurosurgery for malignant brain tumours (MC) General measures for controlling Legionella in water distribution systems (HPt)
> 1,000,000	Measures for reducing industrial benzene emission in the USA (HPt) Measure to reduce dioxin emissions from waste incinerators (HPt) General measures to reduce exposure to ELP associated with electric power lines (HPt)
a. QALY: according to quality-adjusted life-year. b. BP: disease prevention, HPt: health protection, HP: health promotion, MC: medical care. Source: de Hollander (2004): Assessing and Evaluating the Health Impact of Environmental Exposure. Available at: http://igitur-archive.library.uu.nl/dissertations/2004-0511-152200/full.pdf	

The RIVM study calculates DALYs for a range of different health outcomes:

- for carcinogenicity: the study assumes 65% of cancer cases are due to exposure to chemicals and an average of 8 DALYs per cancer case are assumed (based on incidence of different types of cancer and total number of DALYs related to each type); and

- for acute effects: the study uses the EuroQoL scores, based on six dimensions: mobility, self-care, daily activities, pains and other complaints, anxiety/depressions and cognition.

The report acknowledges that the main uncertainties related to the use of DALYs stem from the exposure assessment derivations and toxicological data. The approach is said to be based on the use of LCA techniques to estimate the mass of the chemical released to the environment, but in practice exposure is assessed using a range of methods. In this regard, it is interesting to note that the report suggests that the method should be based on an exposure estimate equating to "a 10% response over

background", which is essentially synonymous with a $BMDL_{10}$ (see Section 3). Other health metrics used in predicting exposure include reference to the NOAEL, the MOS, dose-response functions for cancer effects and RIVM's ConsExpo model. This wide-ranging choice of methods for model exposure is important as it illustrates the potential need to call on a range of approaches to provide the outputs needed for quantification of different types of health effect.

Other uncertainties identified in the RIVM report (2008a) concerning the assignation of DALYs include the following:

- limited information on incidence and duration – or alternatively, prevalence – of disease or health effects;
- the assessment of weighting factors for severity of disease and health status; and
- projection of retrospective incidence and mortality data on evolution of incidence and mortality in the future.

The study does not consider the health impacts from a shift to alternatives so the net health gains may be lower than those given in the report. It also concludes that the estimates are rough and that impact assessments of physiological and toxicological effects may require the development of a more adapted framework rather than the 'clinically oriented' DALY framework.

Also relevant is the series of volumes that have been produced under HELI, the Health and Environmental Linkages Initiative[48]. Under HELI, the WHO has coordinated the preparation of practical guidance for the estimation of the burden of disease for selected environmental and occupational disease factors. This guidance offers a step-by-step approach to estimating the size of the environmental health problem which can then act as an input to decision making. Publication No. 6 of the series concerns occupational exposure to carcinogens. The disease outcomes considered are lung cancer, leukaemia and malignant mesothelioma, and the disease burden is described both in terms of deaths and DALYs. This includes a description on how to calculate the disease burden. This is set out as follows:

- data on exposure;
- information on the relative risk for cancer for each carcinogen;
- estimation of the population attributable fraction (AF), which is calculated by combining the above data to estimate the impact in each country of occupational exposures to carcinogens. AF estimates are presented as fractions of the deaths and disability that are caused by occupational exposures to carcinogens and are used to give an indication of how much ill-health might be avoided is exposure to the risk factor did not occur; and
- the number of deaths attributable to the occupational exposures to carcinogens are then estimated by multiplying the AF by the number of deaths in the country. The

[48] HELI is also supported by UNEP; information and downloadable guidance are available at www.who.int/heli.en

extent of disability can also be estimated by multiplying the AF by disease-specific estimates of DALYs.

An example given in the guidance is reproduced in Table 6.7. Owing to the nature of the data provided in the guidance series No 6, i.e. exposure and DALY by WHO sub-regions, it is likely to be more applicable to the restrictions process.

Another example of the explicit use of DALYs as an input to an assessment for regulatory decision making is given by ESPREME[49]. The aim of this research was to carry out a cost-benefit analysis of different strategies for reducing the public health impacts associated with atmospheric emissions of a range of heavy metals (arsenic, cadmium, chromium, lead, mercury and nickel) to the environment. As part of the modelling work carried out in this study, human health impacts were quantified using a series of dose-response relationships for different health endpoints, including cancer effects IQ decrements, etc. Impacts on human health are quantified first in terms of DALYs for both non-cancers and cancers, based on an approach using the International Life Sciences Institutes classification scheme for human health impacts.

The approach proposed used in ESPREME considers three different categories of effect to take account of the reversibility and life-shortening potentials of the respective impacts, with the results replicated in Table 6.8.

Table 6.7: Approach adopted by ESPREME to Derive DALYs for different Health Effects

Criteria	**Category 1 Irreversible /Life-shortening effects**	**Category 2 Probably irreversible /Life-shortening effects**	**Category 3 Reversible / Non life-shortening effects**
Examples	• Cancer • Reproductive effects • Teratogenic effects (birth defects) • Acute fatal or acute severe and irreversible effects (e.g., fatal poisoning) • Mutagenicity	• Immunotoxicity • Neurotoxicity • Nephrotoxicity (kidney damage) • Hepatotoxicity (liver damage) • Pulmonary toxicity (lung damage) • Cardiotoxicity (heart damage)	• Irritation (eye, skin, mucosal; that is transient) • Sensitisation (allergy) • Reversible acute organ or system effects (gastrointestinal inflammation)
Weight	1	0.1	0.01
$DALY_{personal}$	12.8	$12.8 \cdot 0.1 = 1.28$	$12.8 \cdot 0.01 = 0.128$
$YOLL_{personal}$	12.5	1.25	0.125
Source: ESPREME (2007)			

[49] Estimation of willingness-to-pay to reduce risks of exposure to heavy metals and cost-benefit analysis for reducing heavy metals occurrence in Europe.

Table 6.8: Calculation of Lives Lost and DALYs Lost Due to Occupational Lung Cancer

The Attributable Fraction (AF) for occupational lung cancer for males is based on Levin's Equation using the proportion of the total male population 16 years or older ever exposed and the relevant relative risks. The following assumptions are used:

Proportion of the male workforce currently exposed in sector i = 0.048
Turnover factor = 4
Partitioning factors (high exposure, low exposure) = 0.5, 0.5
Male employment participation proportion = 0.85

The step-by-step calculations are then:

Proportion of male workers ever exposed = 0.048 × 4 = 0.192
Proportion of male workers ever exposed (low level) = 0.192 × 0.5 = 0.096
Proportion of male workers ever exposed (high level) = 0.192 × 0.5 = 0.096
Proportion of the male population ever exposed (low level) = 0.096 × 0.85 = 0.082
Proportion of the male population ever exposed (high level) = 0.096 × 0.85 = 0.082
Proportion of the male population never exposed = 1.0 – (0.082 + 0.082) = 0.836

Males level	**Workers currently exposed Population ever exposed by level**		**Workers ever exposed RR mean**	**Pi × RRi**	**Workers ever exposed by**	
	0.048	0.192				
Unexposed			0.0	0.0836	1.00	0.836
Low			0.096	0.082	1.3	0.106
High			0.096	0.082	1.9	0.155
∑Pi × RRi						1.098
AF						0.089

AF= **(∑Pi × RRi -1)/ ∑Pi × RRi**

Therefore, for males in AFR D, the AF (IF) for lung cancer arising from occupational exposures to lung carcinogens is 0.089, or 8.9%. Then:

Male deaths from lung cancer due to occupational exposures = total deaths from lung cancer in males 15 years or older × AF for lung cancer in males from occupational exposures. E.g.: 6600 × 0.089 = **590 deaths** dues to lung cancer from occupational exposure. This information could be used as the starting point for a single dimension CEA, where risk management would reduce the number of occupational exposures.

In order to estimate the burden of the disease, we also need DALYs. DALYs for lung cancer in males due to occupational exposures = total DALYs from lung cancer in males 16 years or older × AF for lung cancer from occupational exposures. Eg: 67 000 × 0.089 = **5960 DALYs lost due to lung cancer from occupational exposure**. In this case, the estimated DALYs lost would be the starting point for a CUA assessing the change in DALYs lost due to reductions in occupational exposures.

Source: HELI, the Health and Environmental Linkages Initiative, www.who.int/heli.en

6.3.4 Relative Advantages and Disadvantages of Physical Units versus Utility Measures

The use of physical units of measure has advantages over the use of QALYs or DALYs in that it is more straightforward to apply. As effectiveness is measured in terms of changes in the number of cases of the actual health effect, it is a readily understood measure of impact. However, it also has disadvantages in that the simpler single-dimension indicators of effectiveness cannot capture the effects of illness on an

individual's well-being prior to death. This has led to the increased interest in the use of QALYs or DALYs (or other measures of impact that include consideration of quality of life).

On the other hand, the meaning and usefulness of the QALY (or the DALY) is debated as 'perfect' health is hard, if not impossible, to define. Some argue that there are health states worse than death, and that therefore there should be negative values possible on the health spectrum. Determining the level of health depends on measures that some argue place disproportionate importance on physical pain or disability over mental health.

Schultz et al (2006) list several key differences between QALYs and DALYs:

1. They are complementary, and changes to their values are inverse to each other ($\Delta QALY = -\Delta DALY$);
2. Different methods are used to calculate the weightings for quality of life and disability;
3. DALYs take perfectly healthy people who die after the average expected lifetime as a reference. QALYs consider typical old-age disabilities and actual lifetime expectancies; and
4. DALYs can deal with an evaluation dependent on age, which cannot also be undertaken using QALYs, which assume constant proportional trade-off behaviour.

A number of articles discuss the advantages and disadvantages of using QALYs and DALYs relative to other approaches such as cost-benefit analysis. For example, they are favoured by some because they are not as dependent on income and are therefore considered to be more equitable in assessing health outcomes. Anand et al (2006) note though that a year of life may not be equal depending on factors other than illness, for example age. DALYs take this partly into account while QALYs do not; DALYs assign different values to life according to when the measures to extend life would occur, e.g. a working adult is given a greater value than a child for the same period of time gained. This is argued as being justified because people of a working age tend to have more dependants, and they are contributing to society (even though this assumption may lead to problematical ethical issues).

In the context of REACH, DALYs in particular may be useful as they can be used to reflect problems in society that relate to time lost but that do not cause deaths, for example, neurological conditions which together with psychiatric conditions account for 28% of years lived with disability but only 1.4% of deaths and 1.1% of years of life lost.

The use of either QALYs or DALYs results in valuing some form of *life years*, rather than the number of lives saved. The report produced by the US Committee to Evaluate Measures of Health Benefits for Environmental, Health and Safety Regulation (2006) provides a table highlighting the difference between treating all deaths prevented equivalently and estimating losses and gains in longevity across the

affected population. Table 6.9 below reproduces a table given in the report which shows that the use of lives (i.e. a single dimension measure of effectiveness) as an impact measure assigns the same value to preventable mortality regardless of whether the individual is middle aged or elderly. In contrast, the use of life years can show that such mortality may more significantly affect younger individuals. Adjusting for quality of life increases the relative differences between older and younger people slightly, as shown by the ratios in the rows for life year and QALY estimates. However, the standard practice of discounting to reflect the timing of the impacts and the general preference for receiving gains sooner and deferring losses would reduce the relative difference between life years and QALYs.

Table 6.9: Lives, Life Years, and Quality-Adjusted Life Years (QALYs)

	Preventable Deaths	**Life Years[a]**	**QALYs[b]**
Age (in years)			
5	1	73	65
35	1	44	37
75		12	9.1
Ratio of values by age			
5/35	1	1.7	1.8
5/75	1	6.1	7.1
35/75	1	3.7	4.1

a Based on age-specific life expectancy for 2002 (NCHS, 2005).
b Based on EQ-5D norms for the U.S. population (Hammer et al, 2006).

RIVM (2008a) used DALYs as the means of generating health impact estimates that are suitable for comparison across a range of effect types. They note the limitations of DALYs as a metric (e.g. in relation to the assumptions made on the impact of cancer, difficulties in assessing acute effect impacts and the dangers in attempting to compare DALY scores for very dissimilar endpoints) but the authors concluded that '*to be prevented DALYs/year*' are the most appropriate health impact metric for use.

Finally, it is important to note that a QALY- or DALY-based SEA can reflect only impacts on health and longevity. This will not take into account the nature of the risk itself and societal perceptions and values related to it. Knowledge of risks, degree of personal control over risk exposures and other features of risks may affect an individual's perception of a risk and hence their values towards reducing that risk. This is a weakness relative to the methods offered by cost-benefit analysis. It has also been argued that the use of QALYs or DALYs does not take into account the effects of a patient's health on the quality of life of others (e.g. caregivers or family), which may also result in an underestimate of the social costs of chemical exposure (Remoundou and Koundouri, 2009).

6.4 Monetary Valuation Based Approaches

6.4.1 Introduction

As noted earlier, the aim of cost-benefit analysis it to place a monetary value on the benefits of a change in action. From the health economics literature, a number of different potential economic impacts can be identified, and these can be categorised in terms of those who may bear the impacts:

- **individuals/workers and their families**: financial costs, which consist of loss of earnings as a result of absence from work or the loss of a job and any extra expenditure required, for example on drugs or the need to attend hospitals; 'human costs' which relate to the loss of quality of life or of general welfare, and may include pain and suffering to the affected individual, and worry and grief caused to family and friends;
- **employers**: loss of output; payments related to sick leave; administrative costs related to a worker's absence[50] including additional recruitment costs; loss of experience/expertise; overtime working; compensation payments (although this is usually covered by some form of employer's liability insurance); and insurance premiums; and
- **taxpayers:** costs borne by taxpayers for national health care provision, disability and other social security benefits.

From a welfare economics perspective, the total social costs of either occupational diseases or illnesses affecting consumers and the general population are the sum of the impacts listed above for taxpayers, together with lost output (including productivity losses), gross wage and the non-wage labour costs of absent workers (such as loss of experience), administrative costs and the human costs. These represent the direct and indirect resource costs and the non-market 'external' costs of illness. The other costs listed above (e.g. insurance premiums) relate to what are commonly referred to as 'transfer payments', which do not give rise to net welfare effects. As a result, they are not considered in economic analyses, even though they may be important in financial terms to an individual worker or an employer.

There are essentially three sets of methods for estimating the benefits from intervention (whether a restriction proposal or refused authorisation):

- direct and indirect resource cost methods;
- revealed preferences methods including wage risk premia[51]; and
- stated preferences methods.

The theory underlying these methods is not discussed in detail here. Within the context of chemical risk management, some detail is given in the ECHA Guidance

[50] Clerical and management related costs. Legal costs may also be relevant where compensation payments are required in the case of disablement, for example.

[51] This is equivalent to hedonic pricing in the context of environmental impacts.

document on SEA and restrictions with further discussion provided in the OECD Technical Guidance Document on Chemical Risk Management (Postle et al, 2001).

The aim here has been to provide an indication of how the methods have been applied in the past to the types of health impacts relevant to restriction and authorisation.

6.4.2 Direct and Indirect Resource Costs

Direct and indirect resource costs can be estimated using market-based information, for example, data on health care costs, and estimates of lost output and employees' wages. For these impacts, the benefits of a change in regulation can be calculated using a 'cost of illness' approach which involves multiplying the medical costs and lost output per individual case of a given illness by the number of cases occurring 'with' and 'without' the proposed change in regulation. The difference between the two sums provides the estimate of the benefits delivered by the change in regulation. The approach requires estimates of the number of cases of an illness that would be avoided from an exposure assessment and observed data on costs. Costs associated with lost output are usually valued at the wage rate, and are relevant whenever there is lost productivity, either as a result of a change in an individual's productivity rate in the same job or due to an individual only being able to undertake less productive work. 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.

The calculations also require data on the average length of a 'disease event' in terms of the number of days of medical care and number of day's absence from work. This can be a key issue in trying to develop cost of illness estimates, as data on the average number of days of medical care required per case or the average number of days that a worker with a particular illness is not at work are likely to be limited.

Other potential problems include the absence of readily available data on medical costs for a particular type of illness, and difficulties in estimating the resource costs associated with fatal illnesses. In particular, there can be difficulties in establishing the boundaries between fatal and non-fatal cases in terms of hospital treatment costs, as the treatment costs may not differ significantly. There can also be problems associated with predicting how many currently non-fatal cases may result in deaths in the future (in order to avoid double-counting).

The use of cost of illness based estimates would appear to be the most frequent approach for placing an economic value on health effects in the EU. Outside the field of hazardous chemicals, one can find numerous examples of the use of these types of estimates. For example, in relation to air quality policy, Pearce (2000) provided estimates of per day output losses to employers for various EU countries based on wage costs to employers. A wider search of the health literature highlights that estimates exist for a range of illnesses (from cancers to various morbidity effects), including those which can be linked to chemicals exposure, suggesting that it may be possible to find readily available estimates for disease end-points of concern to a restriction proposal for example.

By way of example, many of the valuation studies concerning the implementation of REACH have involved the calculation of direct and/or indirect resource costs. Perhaps one of the best examples in terms of how these approaches can be applied is given by the study carried out by the University of Sheffield (Pickvance et al, 2005) for the ETUI. The aim of this study was to estimate the benefits of focused on dermatitis and respiratory diseases including asthma and chronic obstructive pulmonary disease.

The study first determined the disease burden for each of the disease endpoints using data on the incidence of the disease and predictions of the proportion of cases that would be avoided in the future (i.e. incidence) due to the various provisions in REACH. The authors then analysed the costs associated with skin and respiratory diseases in terms of the associated health service costs, productivity costs, and the value of the lost health-related quality of life to the individual using QALYs (see previous Section).

Health service costs were calculated using evidence from other studies in the published literature (Pickvance et al, 2005). For valuing production losses, two alternative methods were used, the human capital approach (the traditional approach) and the friction-cost method. The monetary values of the prevention of reductions in health-related quality of life for individuals with occupational asthma, chronic obstructive pulmonary disease (COPD) and dermatitis was approximated by multiplying an estimated utility decrement over an assumed duration of symptoms by the value of a QALY (assumed to be between €28,000 - €43,000, see also discussion below under cost-benefit analysis). The mid-point estimates of costs incurred due to productivity losses, health care costs, and monetary valuations of the impact of lost health relating to chemicals covered by REACH were calculated for 10-year and 30-year time horizons following implementation of REACH, compared to a scenario in which REACH has not been implemented.

A study carried out by COWI (2004) for the Danish EPA also applies a cost of illness approach to value the direct and indirect costs of five diseases (asthma, headache, contact allergy, lung cancer and skin cancer). Direct costs were calculated using data available from the literature and expert judgements, with a patient's own lost earnings included in the calculation (well being forgone). In this case, as the aim was to value the costs associated with the burden of disease, estimates were based on the prevalence of the disease in the population. Transition probabilities were used to estimate the migration of patients from one disease state to another, based on survival data given in the literature. Rates are then multiplied by individual disease 'state' costs of treatment, etc. to generate the direct costs. Social welfare costs were then based on a benefits transfer based approach using available willingness to pay values.

A US study by Burtraw and Krupnick (1999) examines the use of different methods to value the benefits of health improvements stemming from the clean-up of hazardous chemicals in the Great Lakes region. Although this study also draws on the use of stated preferences methods, it highlights the potential for using cost of illness estimates to generate valuations for impact such as fertility and child/embryo

development. In the case of fertility, the study actually uses a contingent valuation survey to derive estimates of WTP, however, the payment vehicle used in the study is the cost of IVF treatment; it is obvious that these costs could be estimated directly using the techniques described above. The study does apply a lost productivity approach to derive a valuation of both the morbidity costs associated with low birth weight children and the costs of caring for children with birth defects. IQ loss is valued in a similar way; however, it should be recognised that use of future loss of earnings to value changes in IQ is a human capital approach which does not account for any of the benefits of being brighter.

Other studies have also used the cost of illness approach to value the benefits of reduced exposure to chemicals such as mercury. The NESCAUM (2005) report sets out an approach for valuing the health related changes in children's intelligence (IQ), neurological decrement, and adverse myocardial events due to exposures of mercury emissions from coal-fired power plants. The report notes that there is little research available with regard to individual's WTP to avoid a decrease in infant IQ. As a result they developed a four step approach to derive estimates based on a small but permanent change in IQ on lifetime earnings:

1) Estimated proportional impact of a 1 point change in IQ on lifetimes earnings – Cost of Illness (COI) used to value impact, before calculating marginal rate by differentiating with respect to IQ and the participation rate in the workforce. The present value is representative of the lifetime costs. The impact of a 1 point IQ change on years of schooling, workforce participation and wages was then calculated through a regression analysis using survey data. Impacts are then valued using the calculated coefficients impact on earnings in each period;

2) Quantified average lifetime earnings for US individuals in 2000 - the baseline from which changes could be measured (i.e. impact of schooling etc. compared to average);

3) Combined stages 1) and 2) outcomes to calculate absolute impact of a one point change in IQ on lifetime earnings; and

4) Considered the impact of changes in IQ on the costs of remedial education. Assumes IQ in the population is normally distributed, with an IQ score below 70 indicating a degree of mental handicap. A shift in the normal distribution by 1 IQ point is modelled; with the proportional change in the population falling below 70 calculated. The net impact is then applied to the population to give the number affected. Assuming the costs are equal to the costs of providing part-time special education, the impact is quantified and discounted accordingly.

IQ is continuing to be used in this manner to measure the impacts of mercury on human health. The most recent research conducted at a global level by Sundseth et al (2010) uses assumed decreases in IQ due to mercury exposure to derive the annual damage costs (i.e. lost earnings) from intentional and unintentional emissions of mercury. The study's authors do however point out that the variation in damage costs

between different population groups is not reflected in this type of analysis (i.e. small-scale gold miners using mercury are likely to suffer much more severe health consequences and damage costs than many other groups). A case for more distributional analysis of impacts is therefore highlighted in SEA.

A relevant non-REACH study is that carried out by the University of Lancaster (Giacomello et al, 2006) which applied a cost-of-illness based approached to estimate the economic benefits to the general public as a consequence of the ban on PCBs. The analysis covered health service costs as well as lost of productivity. The dose-response model used in the analysis is basically a historical analysis of human health impacts for the past sixty years based on a number of factors including the varying levels of exposure and the estimated dietary intake. Health care costs are estimated with reference to UK National Health Service reference costs.

As noted above, the study carried out by Pickvance et al (2005) used two different approaches to value production losses, the human capital approach and the friction cost method. It is of note that research is currently underway with the aim of improving the measurement and valuation of productivity costs. Research carried out by Erasmus MC and the Institute for Medical Technology Assessment (Koopmanschap, 2009) is examining methods for improving the derivation of estimates for efficiency losses, administrative costs and interestingly the impact of productivity losses on a workers quality of life (using the EQ5D).

6.4.3 Revealed Preferences and Willingness to Pay Approaches

There are essentially three approaches to estimating individuals' WTP for a reduction in the risk of morbidity or mortality (or, alternatively, their *willingness to accept* (WTA) an increase in risk). The first two are essentially willingness to pay estimates based on individuals' revealed preferences, while the third relates to individuals' stated preference. The approaches are:

- by examining the actual voluntary expenditures made by households on items that reduce the risk of death from certain activities, or by examining the costs associated with any avertive behaviour aimed at reducing risks;

- by examining the increased compensation individuals need, other things being equal, to work in occupations where the risk of death at work is higher (an estimate of the WTA compensation); and

- through the use of experimental markets and survey techniques to directly elicit individuals' WTP for a reduction in the risk of death.

Two key measures used in these studies is the value of a statistical life – a VOSL – and the value of a life year lost – a VOLY. The VOSL is essentially a measure of a change in the risk of fatality, where this is found by determining individuals' willingness to pay for a small change in risk which is then summed across the population at risk. A VOLY (sometimes also referred to as a VSLY – value of a

statistical life year) is usually derived from the VOSL. In the simplest case, where it is assumed that the value is constant, the VOLY is the VSL divided by the number of life years saved by the reduction in risk (Chestnut and De Civita, 2009), with the values for future years then discounted.

Voluntary Expenditure

Voluntary expenditure, for instance, would include the expenditure by either a worker or a consumer on protective equipment – gloves, masks, etc. – prior to the use of a hazardous chemical or product containing a hazardous chemical; it has been argued that this can be viewed as an indication of the individual's willingness to pay to reduce the risks associated with the use of the chemical / products. However, this avertive expenditure approach has several drawbacks with regard to its application to chemical risks. Firstly, an individual's assessment of the probability of a risk outcome occurring may differ significantly from scientific estimates of those probabilities. In the case of workers, the level of expenditure may be determined by an employer and not by the worker, invalidating the assumption that the use of such equipment reflects a willingness to pay to avoid the risk of a disease. Furthermore, use instructions, including details of appropriate personal protective equipment, may substitute for any consideration of the associated risks. For consumers, the assessment of risk may consider several different types of illnesses simultaneously, making it difficult to separate out the value associated with avoidance of different types of health effect (with this potentially giving rise to double counting or misuse of expenditure estimates).

An example of the existence of such problems is given by responses to consultation for the dichloromethane risk reduction strategy (RPA, 2008). Workers were aware of the health risks of exposure to dichloromethane, and of the need to wear appropriate personal protective equipment but the majority of consultees indicated that they either did not use the appropriate equipment or did not use any. The choice of equipment was not always up to the worker but determined by the employer. In this case, this finding led to the development of an option requiring the use of more protective gloves and masks.

A product premium based approach has been used to value health risk reductions associated with pesticide residues on food. Nijkamp et al (2002) assessed a dataset of 27 pesticide risk related studies. This includes studies involving an analysis of purchasing decisions and price: risk trade-offs to infer the value assigned to the reduction of risks associated with 'safer' food. It also includes analyses of demand for eco-labelled and organic produce at different price premia.

Wage Risk Premia

The wage-risk method is essentially used to calculate a VOSL for workers employed in hazardous occupations. It relies on the assumption that there is enough labour mobility to permit individuals to choose their occupations so as to reflect all of their preferences, one of which is the preference for a level of risk and, thus, the level of

compensation required to accept that risk. For a detailed review of the use of this approach and the wage risk premia literature more generally Viscusi and Aldy (2002), who discuss varying issues regarding latency, age effects etc.

Most hedonic labour market studies focus on the risk of accidental death or accidental injury, although there are studies which have attempted to explore the effect of occupational disease. Lott and Manning (2000) evaluated the effect of carcinogen exposure on workers' wages within the context of changing employer liability laws. In lieu of the standard mortality risk measures, the authors employ the Hickey and Kearney carcinogen index, which represents worker carcinogen exposure at the 2-digit SIC code level. Lott and Manning convert their results into a value of a statistical life assuming that the index is a proportional representation of the actual probability of getting occupational-related cancer, that 10 – 20 percent of all cancer deaths result from occupational exposures, and that the probability of a worker getting cancer ranges from 0.04 to 0.08 percent per year.

Cole et al (2009) carried out an investigation into existence of wage premium for working in a pollution intensive environment. Results for the economy as a whole suggest a small wage premium of approximately one quarter of one percent associated with the risk of working in a "dirty" job. This premium rises to over fifteen percent for those individuals who work in one of the five dirtiest industries. The authors also found evidence of a fatal risk wage premium, suggesting estimates of the value of a statistical life of between £12 million and £19 million (2000 prices). The approach used in this study is based on the use of Threshold Limit Values to weight the toxicity of 21 different industry pollutants, from heavy metals to traditional local air pollutants to other pollutants.

However, Pearce and Koundouri (2004) note that it may not be appropriate to include a VOSL based valuation of worker related occupational health benefits in a cost-benefit analysis of chemicals regulation. If the above studies are correct and workers in a given job already receive a wage premium for the risks that they take in working with hazardous chemicals, then to place a value on a reduction in the risk of death due to exposure to carcinogens, for example, would result in a double counting. This suggests that only direct and indirect resource costs should be taken into account when considering changes in occupational health impacts. However, the article by Pearce and Koundouri (2004) prevaricates to a degree and also notes that one of the aims of REACH is to deliver occupational health benefits, suggesting that the situation is not clear cut.

Stated Preferences Techniques

Stated preferences techniques such as the contingent valuation (CV) and the contingent ranking (CR) method are used to develop direct estimates of an individual's WTP to avoid a particular health effect. These valuations are based on the creation of experimental markets and use surveys to elicit individuals' willingness to pay (WTP) to reduce the risk of death, of injury or of experiencing a particular illness. For example, the derivation of WTP with regard to deaths (mortality) is based

on establishing what those who could be affected by a specified risk would be willing to pay for a small reduction in that risk (or improvements in safety); the resultant amount when aggregated across the whole at risk population provides an estimate of the 'value of a statistical life' (VOSL). In the case of illness or disease (morbidity effects), people are asked how much they would be willing to pay to avoid certain symptoms or a day's illness.

The key advantage of these techniques over the cost of illness method is that the resulting WTP values will include an estimate of the value of pain and suffering but an estimate of individuals' willingness to pay to avoid having a minor case which might last for many years. These survey methods can provide a valuation that incorporates not only benefits to the individual him/herself but also related to the protection of future generations (bequest values) and to knowing that others can benefit from a service (existence values).

Cost of illness and WTP values can often be combined to fully value the direct and indirect consequences of an illness or disease or in cases of mortality (NESCAUM, 2005). The difficulty in relation to workers is that both measures may reflect the risk premia associated with the occupation in question (wages/income should reflect premia, as should the individual's WTP to avoid the risk), therefore double-counting is possible. This problem will not arise in relation to valuation of changes in public health risk.

With reference to assessing the impacts of public health risks due to environmental exposures (man via the environment), contingent valuation studies of respondents' WTP to reduce the risk of developing a fatal or chronic degenerative disease through exposure to environmental pollution have revealed that WTP is dependent on a number of factors. These include the type of disease (WTP to reduce the risk of cancer was estimated to be about one-third larger than WTP to reduce the risk of a similar chronic degenerative disease), as well as the affected organ, environmental pathway, or payment mechanism (WTP to reduce the risk of lung disease due to industrial air pollution is twice as large as WTP to reduce the risk of liver disease due to contaminated water) (Hammit and Liu, 2004). The results of the study also suggest that WTP should be reduced to account for a latency period between exposure and manifestation of disease[52] (in agreement with an earlier study which states that the long latency period for cancer and other chronic health conditions should be discounted in the benefit analysis- see Viscusi and Aldy, 2002).

Burtraw and Krupnick (1999) examined the use of different methods to value the benefits of health improvement, focussing on the Great Lakes Cleanup. This study is interesting because it applied a range of methods to derive economic valuations covering a range of effects. The use of cost of illnesses estimates has been discussed above but the study also included use of contingent valuation and conjoint analysis to

[52] WTP to reduce the risk of a fatal disease with a 20 year latency period is about one-quarter smaller than WTP to reduce an immediate risk of the same disease, which implies that WTP falls at a rate of about 1.5 percent per year of latency.

estimated individual's WTP for increases in fertility and for valuing WTP to avoid a statistical case of cancer. In the case of fertility, individual's WTP for an increased probability of success was elicited, with the payment vehicle being the costs of IVF treatment as paid through either taxes or insurance. Conjoint analysis was also used to examine the trade-offs people were willing to make in terms of funding IVF and reduced highway fatalities. In relation to cancer effects, the study estimated the direct and indirect health costs using the cost of illness approach but concluded by suggesting the use of conjoint analysis to obtain WTP to avoid statistical case of cancer.

A meta-analysis carried out by Nijkamp et al (2002) further highlights the use of these methods to value different levels of health risk reduction but in relation to pesticides. This includes studies valuing consumers WTP for organic produce and for pesticide residue free produce, as well as studies that analyse preferences for various food safety attributes related to pesticides exposure. A key issue with some of these studies is that the actual level of risk reduction is never explicitly specified. It is also difficult to link the resulting valuations with specific health outcomes, as many of the studies also incorporate other issues such as consumer choice and the environment within the bundle of benefits being valued. The health benefits are also generally related to one-off events rather than longer-term, chronic impacts.

Benefit Transfer

Undertaking studies (such as a contingent valuation survey) specific to individual health end-points would is a resource intensive exercise and can take many months to complete. As a result, researchers have turned to the use of existing data to provide an indicative measure of individuals' willingness to pay to avoid a particular type of health effect. This process is known as benefits transfer and it is increasingly used to provide insight into the economic gains that may result from the introduction of a new policy or a change in policy.

Benefits transfer can be carried out using either value transfers or function transfers (see Defra, 2010 for further discussion). In general, a function value transfer approach is considered preferable to the use of unit value transfers (when carrying out the process across a range of sites with differing characteristics) as it is believed to reduce the level of error inherent in the transfer process. Unfortunately, there do not appear to be any studies available relevant to chemical risk reduction that would provide the basis for applying a function value transfer approach. Instead, the ECHA Guidance on SEA and Restrictions provides a summary of potential benefit transfer estimates that could be used in REACH SEAs. This includes transfer values for both a range of morbidity effects (mostly linked to the types of health effects associated with air pollutants) and mortality effects, with the latter values being relevant to cancer effects.

A recent example applying the transfer values quoted in the ECHA guidance to a chemical risk management decision relevant to REACH is given by the study on cadmium in brazing sticks and jewellery carried out by RPA (2010) for DG

Environment. The data from the cadmium risk assessment prepared under the Existing Substances Regulation provided the starting point for this work, which then required further work to predict exposure levels for both professional and non-professional (consumer) users. These data were then combined with information on populations exposed in each group of users, current OELs, and relevant risks ratios for low and high exposed individuals (in the form of a standardised mortality ratio) to predict numbers of individuals likely to contract cancer under the baseline and a no exposure scenario. VOSLs of €1.2 and €1.8 million were then applied to the predicted number of cases avoided for the no exposure scenario to develop lower and upper bound benefit estimates. Note that the worker population assumed to benefit from measures in this case mainly relates to the self-employed and/or small workshop based operations, or to situations where no occupational exposure limits are in place. There is no evidence to suggest that these individuals would be benefitting from any wage risk premia associated with their use of brazing materials.

Valuation of QALYs and DALYs

Finally, it is important to highlight the fact that there is an increasing trend towards the use of DALYs or QALYs as the basis for quantifying health impacts followed by the conversion of these to a monetary value.

For example, the UK Health and Safety Executive calculates the money value of a year of ill-health as the product of the number of QALYs lost and the money value of a 'full health life year'. They take the component of the UK VOSL related to pain, grief and suffering (WTP to avoid the risk of death) and equate this to the value of one QALY. Assuming that the WTP component of the VOSL is £550,000 and that an accident results in the loss of 39 years of life, at a 4% discount rate, the resulting VOLY is £27,150.

Pearce and Koundouri (2004) argue that for chronic exposures the issue is one of morbidity, if chemicals induce ill-health before death, and premature mortality. Thus, one would be seeking a measure of future gains in life expectancy, and the notion of a 'value of a life year' (VOLY) seems more appropriate as the basis. They base their approach on one developed by Lvovsky et al (2000)[53], who calculate the number of DALYs lost per 10,000 cases for each of several health end-states: premature mortality, chronic bronchitis etc. On the assumption that one premature death is equivalent to 10 DALYs, this permited them to derive WTP values for each health end-state. From this overall average WTP values per DALY can be inferred, with Pearce and Koundouri concluding that the appropriate value for a DALY in Europe/UK is around €90,000 per DALY (based on a starting value of $US 1.6 million in 1990 prices).

In earlier work Pearce (2000) shows that for a 40-year-old, the VOLY would be around €40–50,000 for a VOSL of €1.5 million or, say, €45–55,000 for a VOSL of

[53] Not yet reviewed.

€1.67 million. Such values fit neatly with the UK Department of Health procedure of valuing a 'QALY' (Quality Adjusted Life Year, which is akin to a DALY) at £30,000, and reasonably well with other work carried out in the UK on VOLYs which provides a range of £27,000 (Chilton et al, 2004) to £42,000 (Markandya et al, 2004).

The EuroQuol study is also looking at the valuation of a DALY but has yet to report its conclusions.

6.4.4 Advantages and Disadvantages in the Context of REACH

Although the above discussions highlights that all three types of monetary valuation methods have been applied at some time to estimate the benefits of reductions in health risks, they have been applied to a varying extent and to different types of health endpoints. Overall the COI approach has been used to the greatest extent and covering the widest array of health endpoints, in part due to the fact that it relies on actual or observed data. It is also likely to be the least resource intensive method as it does not require the use of surveys or complicated statistical analyses.

Benefit transfer based approaches for using existing VOSLs, whether based on wage risk premia or stated preferences studies, are also used extensively. However, the limited number of studies relevant to the type of health endpoints associated with the chemicals of concern under REACH will restricts the degree to which benefit transfer methods can be used as a valuation method for morbidity effects and effects associated with exposures to mutagens and reproductive toxins. There is also the issue of whether the application of a monetary valuation to occupational health benefits could result in some level of double-counting due to the possibility that workers already realise a premia for their exposure to hazardous chemicals.

Further considerations in trying to apply these methods under REACH are as follows.

- while most studies valuing benefits focus on adults, children are more vulnerable to some hazards and therefore some illnesses that are chemical related are more prevalent in the infant population, even if mortality amongst children is much lower. Policy based on adult values consequently does not take into account the exposure and susceptibility in children, potentially resulting in a loss of social welfare and inefficient policy making (Scapecchi, 2006).

- the main issue concerning the use of a COI based approach is that it will not cover the intangible social costs of morbidity impacts; neither will it be a good indicator of such impacts in the case of fatalities. As these social costs may be significant for certain types of health impact, and in particular may be important in relation to carcinogenicity, mutagenicity and repro-/developmental toxicity, then use of COI estimates alone may significantly underestimate the benefits of action.

- the use of a QALY or DALY based measure of health effects assumes that health and longevity preferences depend on only health consequences, independent of the characteristics of the individual or the risk involved. This assumption may not

hold when applying these methods to the types of public and consumer health impacts associated with hazardous chemicals. In contrast, a WTP based approach – and in particular one based on the use of stated preferences methods – would allow for preferences to vary due to different characteristics such as wealth, age and whether the risk in known, unknown, dreaded, etc. (Hammitt, 2006).

- there are standard WTP values available for the value of a statistical life and the value of a life year lost. These values can be applied to predictions of the number of cancer deaths avoided or the reduction in the number of life years lost due to controls on the use of a chemical. However, it may be important to review the basis for those VOSL with respect to the types of regulatory decisions that are being made under REACH as part of any longer term research. Previous studies have suggested that a cancer premium should be applied to any VOSL. Recent work for a US EPA Workshop (van Houtven et al, 2006) concludes that individuals have a strong preference for avoiding cancer risks relative to automobile fatalities (one of the early sources of VOSL values) of the same magnitude (a common finding). However, this preference decreases as the cancer latency period increases (e.g. individual loses out on less). Individual preferences for avoiding cancer risk are also found to be positively related to their chances of surviving until the onset of illness due to the fear and dread involved. On average, the study found that preferences to avoid cancer risks were two to three times larger than for accidents but that for periods of latency greater than 30 years this affect was largely mitigated.

6.5 Implications for a Logic Framework for REACH

Table 6.10 summarises the methods covered above as potentially providing the basis for assessing human health impacts in SEAs under REACH. These methods include different approaches under CEA and CBA, as well as risk ranking methods and benchmarking techniques that could form the basis for a multi-criteria analysis.

As can be seen from the table, it may be possible to establish a hierarchy for the use of these methods within a logic framework starting with the implications that the different methodologies and techniques within them have with regard to the outputs of the risk assessment:

1) if the most that can be provided from the risk assessment is a RCR based on a Margin of Safety (MOS with the associated NOAEL, LOAEL or BMD), then the SEA may be limited to drawing on some form of risk ranking or benchmarking exercise; in some cases there may be the potential for valuation using stated preferences methods. Reliance on these statistics would result in a degree of precaution, providing a stimulus for those carrying out an authorisation SEA to try and develop better dose-response information from the available health studies;

2) if dose-response data, relative risk or odds ratios, prevalence or incidence data are available, and exposure modelling enables predictions of the number of cases

avoided, then the two CEA approaches could be applied as a first step towards quantification. At this time a decision would be made as to whether it was necessary to progress to the use of DALYs (in preference to QALYs) in order to take into account chronic effects or benefits across multiple diseases;

3) if it has been possible to quantify the number of cases avoided, then consideration could be given to placing a monetary value on the health benefits for a restrictions SEA and should be carried out for an authorisation SEA. Where the metric for measuring health effects is based on lives saved or life years saved, then standard VOSL and VOLY values could be applied to provide a monetary value of the health benefits. Where the metric is DALYs, then consideration could be given to valuation using a standardised € per DALY estimate;

4) if the total value of the health benefits (discounted over an appropriate time period) are not greater than the costs of risk reduction, then consideration could then be given to the ability to estimate health care costs and lost productivity. Note if DALYs are being used as the metric of 'effectiveness' in terms of health benefits then it may be preferred to restrict this assessment to health care costs only.

Under this type of logic framework, MS Authorities and authorisation applicants would not undertake original WTP valuation studies. That does not mean that there would not be a role for such studies. Instead it assumes that the most appropriate level for such work to be carried out would be at the EU level with the aim of developing transferable WTP values specific to the types of chemicals likely to be subject to restrictions and authorisation.

It is clear that the trend in CEA is for the use of a more sophisticated measure of effectiveness than just lives saved or cases of illness avoided. For the reasons highlighted above, in particular the ability to reflect chronic effects and effects that cannot be easily characterised in physical units (e.g. impacts on neurological function) there may be a role for the use of DALYs in particular under REACH. The recently published report by RIVM highlights that more work needs to be carried out to ensure that the disability weights used to determine the number of DALYs lost due to an illness are appropriate to a chemicals regulation context. Finally, the above framework may not give adequate consideration to other factors that can inform on whether or not adverse health effects may result from an exposure. In particular, it may have to be tailored further for consumer and general population exposures and risks, where there may be difficulties in predicting the level of exposure, the frequency of exposures and the duration of those exposures.

Table 6.10: Summary of Methods for Assessing Health Impacts

Methodology	Underlying Data	Metrics and End-Points	Impacts not Captured	Other Comments
Risk Ranking	- Classification - Dose-response	- Qualitative assessment of severity - Likelihood of effect	Does not require quantification of the number of cases of a disease or take into account the social costs associated with impacts	
Benchmarking	- Hazard data, including persistence - Exposure data (e.g. intake)	- Qualitative comparison of risk vis a vis other substances	Does not provide an estimate of number of cases of a disease or take into account the social costs associated with impacts	
Physical Measure of Disease Cases	- Dose-response - Risk or Odds ratio and Attributable Fraction - Prevalence - Incidence - Exposure data	- Lives saved – cancer effects - Life years saved – cancer effects - Disease cases avoided – mutagenic effects, reprotoxic effects, morbidity effects	Secondary health effects not captured – may be an issue with e.g. carcinogens where exposure may also lead to other chronic or acute effects. Does not take into account health care costs, lost productivity or social costs.	Does not readily allow consideration of benefits related to both morbidity and fatality effects.
Utility based measure using QALY or DALY	- Dose-response - Risk or Odds ratio and Attributable Fraction - Prevalence - Incidence - Exposure data	- QALYs or DALYs for: - Fatality effects - Life years lost - Morbidity effects taking into account impacts on quality of life	Does not take into account health care costs or social costs, included costs to carers; may overlap to some degree with lost productivity estimates.	Can better account for e.g. neurological diseases which impacting on ability to function and hence of quality of life. Takes better account of impacts on longevity.
Cost of Illness	- Dose-response - Attributable Fraction - Prevalence - Incidence - Exposure data	- € Health care or medical costs - € Lost productivity	Does not take into account the social costs associated with impacts on the quality of life or impacts on other carers.	Calculations required data on the average length of a disease event and other observed data that may not be available
Revealed Preferences	- Dose-response data to link change in risk to wage premia - Relative risk or similar to assess € per unit risk avoided for avertive expenditure - Exposure data	- € Wage risk premia -> Value of a statistical life - € Avertive expenditure	Does not take into account the social costs associated with impacts on the quality of life or impacts on other carers.	Unlikely that wage risk premia data would be available for a specific case. Avertive expenditure method does not provide a true valuation of economic benefits.
Stated Preferences	- Data on prevalence (?), starting risk levels and after policy risk level -> could be linked to NOAEL, LOAEL and related statistics, together with exposure data	- € WTP for fatality - Value of a statistical life (VOSL) or value of a life year lost (VOLY) - € WTP to avoid a morbidity effect – a disease or disease event	Does not take into account health care costs, but may incorporate a measure of lost productivity and will capture social costs to individual and can capture those to carer.	Benefit transfer as an alternative to original studies. However, lack of original studies constrains ability to value morbidity effects and raises uncertainty over application of existing VOSLs.

7. APPROACHES FOR ASSESSING ENVIRONMENTAL IMPACTS

7.1 Introduction

7.1.1 Outputs from Environmental Risk Assessment

Assessment of the environmental benefits associated with a restriction or a refused authorisation requires data on:

- levels of emissions of the chemical and the changes in emission due to risk management;
- substance and environmental characteristics to predict the environmental fate and behaviour of emitted substances; and
- dose-response relationships that link exposure to different environmental outcomes.

As indicated in Section 4, the output of the REACH risk assessment for each exposure scenario will be a Risk Characterisation Ratio (RCR) providing an indication of the margin of safety between the predicted no effect concentration (PNEC) and the predicted environmental concentration (PEC). The PNEC will represent the most sensitive marker of effect for an environmental compartment based on endpoints such as mortality, reproduction, hatching, growth, spawning frequency or abnormalities.

However, it must be remembered that the value of the PNEC is the product of the sensitivity of the effect (i.e. the POD) and the magnitude of the applied assessment factor (AF). The size of AF will depend on data robustness, variability within/between species, the specific endpoint and the duration of the study on which the finding was based. Hence, potentially the lowest POD might not be the one ultimately selected in the risk assessment to form the basis for the PNEC where another somewhat less sensitive endpoint is identified but is found to warrant a much larger AF. This is illustrated by the fact that PNECs based on single species studies may be subject to generic AFs ranging between values of 1000 to 10, depending on the nature and type of the supporting study(ies) (ECHA, 2008d). Thus, it is possible that although the risk characterisation for a given scenario is based on a PNEC value derived for a particular toxic endpoint, there may be other end-points which are also relevant to the use of a chemical; some of these may be of potential environmental and economic importance than the effect used to support the RCR.

For example, while the lowest PNEC might be established for an effect in algae, the dataset for a substance under consideration may also include evidence of an effect being possible, at somewhat higher concentrations, on hatching in rainbow trout. While this is not relevant to the objectives of a risk assessment, within a SEA – where the focus is on capturing the range of potential impacts – the effect on trout may offer a greater possibility of providing a quantitative indication of impact (and possibly one that could be valued). As a result, it may be important to consider not only the particular effect underlying the PNEC used in the risk assessment to establish a RCR, but to also consider if there is a need to address other endpoints of toxicity identified in the experimental dataset.

It must also be appreciated that, because of dataset limitations, in environmental risk assessment it may be that it is necessary to extrapolate from toxicity data for one compartment to another (e.g. freshwater species data are often used to derive extrapolated PNECs for the terrestrial or marine compartments). This practice obviously poses a particular problem with regard to assessing impacts in relation to a compartment for which no direct data are available.

There is also a need to consider if the output from other environmental risk assessment approaches, such as species sensitivity distributions (SSD), may not provide better information on the overall impact on an ecosystem than reliance on a PNEC based upon a single test.

In such situations, additional exposure assessment work could then be undertaken using the types of models discussed in Section 5 to provide predictions of the environmental impacts that would be associated with particular scenarios. This would need to include consideration of the potential for both long-term and short-term exposures to the chemical of concern. The aim of the SEA would then be translate the information for each risk conclusion into the types of direct and indirect impacts listed in the last column of Table 7.1, so as to allow translation of the outcome from the risk assessments into an indicator of significance and potential economic value.

Table 7.1: Risk Outcomes and Links to SEA

Environmental Compartments and Risk Conclusions	**End-Point**	**Direct and Indirect Impacts (based on ecosystem services)**
Freshwater - Aquatic organisms and fish Marine waters - Aquatic organisms and fish Terrestrial environment - Earthworm and other invertebrates - Soil - Plants Secondary Effects (non-compartmental) - Fish eating predators - Worm eating predators - Top predators, other mammals and birds Atmosphere Sewage Treatment Works	• Survival • Growth • Reproduction (including endocrine disruption) • Abnormalities	• Provisioning services: food, water, energy, medicines • Regulating services; atmosphere and climate regulation, waste processing • Supporting services: nutrient cycling, soil fertility, air • Cultural services: culture, amenity, recreation including ecotourism • Biodiversity

7.1.2 Statistics from Environmental Risk Assessments

In analysing environmental impact data, it is important to be clear on the nature of the statistics that are being used. From the review in previous sections, the key environmental metrics that are generally used in environmental impact assessment are those set out in Table 7.2.

Table 7.2: Summary of Key Environmental Metrics

Metric	Definition
EC_{10} / EC_{50}	Effective Concentration for 10 or 50% of the population – The amount of a chemical that causes a given effect to a given percentage of the experimental animals exposed to it
NOEC	No Observed Effect Concentration
Species Sensitivity Distribution	Extrapolation of test results from single species tests to other species, based on at least 10 species and 8 taxonomic groups
Risk Characterisation Ratio	The ratio of PEC/PNEC

It is important to understand how these metrics may be used to try to quantify environmental impacts. These links are as follows, with the methods used to quantify the change in impacts ordered in terms of their likely reliability:

- dose-response functions: these provide a direct indication of the probability that a given effect will occur following exposure to a substance at various dose levels – dose-response data can be used to determine a POD (e.g. no observed effect concentration, NOEC);

- species sensitivity distribution: the SSD provides a probabilistic extrapolation of NOEC data from test species to other species; and

- risk characterisation ratio: the RCR on its own provides no means of quantifying the impacts; it is only possible to quantify the environmental effects if the RCR data are fed into the various models that are available to allow extrapolation of a dose-response function. RCR does not quantify the environmental impacts; a RCR greater than one for a given scenario will not clearly identify and quantify the potential impacts in terms of damage to the ecosystem overall.

7.2 Physical Measures of Impact

7.2.1 Introduction

Within the context of REACH Restrictions and Authorisations, physical measures of impact could be used as a proxy for benefits (and could provide the basis for the development of a cost-effectiveness analysis).

Different approaches could be taken to developing a physical proxy for benefits:

- a simple measure of change could be adopted, for example, based on tonnage used, emissions to the environment, etc.; or
- a more sophisticated measure of change which reflects contribution to environmental burdens could also be developed, for example, to take into account bioavailability in the environment or the location of emissions; and/or
- scoring and weighting systems could be used to develop more complex proxies of impact, where emissions may occur to more than one environmental compartment.

Use of a single physical measure of 'effect' may be particularly relevant to restriction proposals where the aim is to provide a relative comparison of the cost-effectiveness of different risk management options. It may also be relevant for substances without a threshold, say vPvBs.

Both the first and second approach have been applied to chemical risk management in the past, drawing on the need to reduce emissions so as to deliver a level of risk reduction that would result in an acceptable RCR ratio (i.e. PEC/PNEC > 1). The main advantage of using emissions or change in environmental burden as a proxy for benefits is the reduced amount of data required to quantify 'effects'.

7.2.2 Impact Score as a Proxy for Effect

A study by Entec (2006)[54] sought to develop a generally applicable approach to evaluating environmental benefits from regulation of chemicals. In this method, estimates of environmental exposure levels (derived using a series of runs of a model such as EUSES in which assumptions are modified to match each management option considered) are compared with the PNECs used in the risk assessment. For each scenario, an estimate of the predicted concentration (PEC) is compared to the PNEC, i.e. a series of risk characterisation ratios (RCR) are generated. The method then attempts to equate the resultant RCR estimate with an environmental impact to generate an effect-impact score.

Importantly, RCRs are banded into a series of 'effect categories'. These are theoretical 'bands' developed on the assumption that the magnitude of generic AFs as established in the Technical Guidance Document[55] are predictive of the scale of impacts. For example, it is assumed for a PEC to PNEC ratio of >1 to 10 for acute toxicity that there would be little or no effect at the PNEC (with no more than 5% of species affected), but at a PEC to PNEC ratio of greater than 500 that there would be severe lethal effects rendering the ecosystem non-functional (effective ecosystem death). It is further assumed that such an impact can be directly translated to specific parts of an ecosystem, such as fish stocks. The model therefore simplifies the read-off between effect and impact by assigning ranges of RCR-values to 'effect categories' which in turn equated to a 'impact score'.

[54] Entec (2006): New Approaches to Evaluating and Quantifying the Benefits of Chemicals Regulation, a study for Defra, April 2006.

[55] In which they are based on the nature of the endpoint and robustness of the dataset

Table 7.3 illustrates the scoring system developed in the study for aquatic toxicity and impacts on fisheries. The extent of impact is then translated into an economic valuation using a willingness to pay value for avoiding such an impact. Other environmental impact scores included in the study are for freshwater invertebrates (in surface water and in sediment), for fish and invertebrates in marine water, and for deposition on crops via the atmosphere.

Table 7.3: Impact category: surface water, freshwater – Impact on fisheries
Marker of impact: toxicity estimates for freshwater fish species

Impact Levels Description	Impact Score	Effect category	Risk Characterisation Ratio PEC/PNEC
No impact	0	No effects	<1
Sensitive species (salmonids) population impacted	1	5% species	>1-10
Effects on coarse fishery	2	10% species	>10-50
Impacted – sensitive species in decline or absent	3	20% species	>50-100
Poor or unviable fishery	4	50% species	>100-500
No fishery or very few species	5	95% species	>500-1000

Although highly attractive in terms of its simplicity and ease of application, the approach depends upon a series of questionable biological assumptions, several of which are recognised by the authors themselves. These include:

- prediction of the scale of effects at a particular estimate exposure is based on the PNEC value and generic AFs alone (i.e. there is no adjustment for the actual nature of effect or dose-response shown by that substance);
- 'banding' of effects is based on very simplistic assumptions that do not necessarily reflect the true nature of any biological responses that might arise; and
- considering the fisheries example presented, there appears to be little scientific basis for the extrapolation from the magnitude of the RCR-value to a species population effect (an aspect also identified in WCA, 2010) and the attempt to interpret such an effect score as an impact on fisheries is effectively arbitrary.

Overall, therefore, the adoption of a 'safety factor'-based approach without any consideration of the toxicity that underlies the RCR value or of actual dose-response relationships for the substance means that this methodology cannot be considered to be risk-based in nature. Furthermore, the model is clearly unsuited to assessment of the impact of substances without known toxic properties but for which other environmental properties of concern have been established, e.g. as is the case for vPvB substances.

7.2.3 Indices and Multi-criteria Based Approaches

The use of indices has constituted a popular practice in ecological valuation and management (Nunes et al, 2001). These are discussed here with particular reference to the role that they might be able to play in carrying out a comparison of the risks associated with the adoption of alternative chemicals, processes or products.

An early example of a multi-criteria rating system is the method proposed by Randwell (1969) (in Nunes et al, 2001). This method was used to evaluate coastal habitats and combining the use of eight criteria into a single score, the Comparative Biological Value Index (CBVI). Each of these criteria are rated according to a scale and the final score is obtained by summing up the scores for all the nine criteria. The maximum potential value is 28 and the minimum value is 7. The higher the CBVI value, the greater is the requirement for site protection. This valuation approach relies on input criteria that require some subjective valuation but allows comparison of different policies. Although this instrument was designed for the assessment of conservation policies, a similar system could apply to chemical policies where chemicals could be scored against the different types of environmental risks affecting different biological indicators of value, e.g. diversity, physicochemical properties, optimum populations, etc. This would provide an indication of the potential impacts of chemicals.

Another example of how MCA has been applied in a chemicals context is given by *Eco-efficiency Analysis*, which was developed by industry in 1996. Combining an MCA type of approach and a Life-Cycle Assessment (LCA) approach to the assessment of impacts, the goal of eco-efficiency analysis is to quantify the sustainability of products and processes. Eco-efficiency analysis does not utilise concepts such as avoidance costs or other costing approaches but uses weighting factors indicating the relevance or how important the environmental compartment is for a particular eco-efficiency analysis and/or the alternatives are to the GDP of the region/country. Following normalisation or normalisation and weighting with regard to emissions and economic activity, the corresponding arithmetic values are plotted to illustrate the footprint of the substance in question.

A related method is the so-called SEEBalance, which is aimed at better taking into account the social (including wider economic) aspects of sustainability and incorporating them into the eco-efficiency analysis. The SEEBalance method uses a system of social indicators, e.g. company benefits, freedom of association, number of part-time workers, impacts on other economies, etc. that are also weighted.

The DHI study on the environmental benefits of REACH also used a ranking system, based on the EURAM[56] method. The scores (which were estimated) are measures of environmental exposure (EEX-values), of environmental effects (EEF-values) or measures combining exposure and toxic properties of the chemicals (environmental scores, ES- values). Persistent toxic substances that are produced in large amounts are ranked very high. The method resulted in a very high number of substances being ranked similarly (DHI, 2005). However, it may provide a means of benchmarking substances in terms of their relative risks and hence the potential need for precaution.
A study by RIVM (2008b) on organotins also included the use of a MCA-based methods. The study focused on the situation that might be expected for substances for which restrictions were being proposed under REACH. Rather than developing full

[56] European Union Risk Ranking Method, which was developed for prioritising EU high production volume chemicals for risk assessment.

EIAs for the two case study compounds (and the assumed alternatives for each), the exercise was limited to considering environmental impacts relating to surface waters.

For each restriction scenario examined, the estimated environmental water concentration (**Cw**) was calculated for the organotin and its alternatives. A risk assessment was then conducted in which these Cw values were compared against standard compound-specific parameters (which can define the toxicity profile of the chemical):

- Maximum Permissible Concentration (**MPC**) – level which protects 95% of the species potentially present, derived in various ways depending on extent of experimental data available;
- Species Sensitivity Distribution (**SSD**) – based on a normal distribution function based on experimentally-defined aquatic chronic (NOEC) or acute (ED50) effect levels;
- Hazardous Concentration for 5% of species (**HC_5**) – based on 5^{th} percentile of SSD; and
- Fraction Affected (**FA**) of species – i.e. fraction of species exposed to levels above the EC_{50} or NOEC.

Risk quotients based on the maximum permissible concentrations were then compared for the organotins and the alternatives, with similar comparisons also undertaken for the other key statistics. An assessment of PBT properties of alternatives was then undertaken using an online QSAR-programme. The authors suggested that use of a simple continuous scoring system for key properties may be of potential value in distinguishing between alternatives where there is only a restricted dataset available. In the example given, this comprised scoring each substance (or in the case of a mixture, adjusting for % composition) for its P, B, long-range transport and FA.

Another approach, the SCRAM model, has been suggested as providing a potential basis for risk ranking or chemicals benchmarking (Mitchell et al, 2002). As previously described in Section 6, this model was been designed to evaluate and score the persistence, bioaccumulation and toxicity of chemical contaminants present in the Great Lakes, based on limited datasets. To operate the model, available information is entered into a spreadsheet that calculates the 'chemical score' of a substance based on the toxicity and potential exposure determinants of the chemical. The toxicity element of the model requires, at a minimum, 1 data point relating to either acute or toxic ecotoxicity endpoints supplemented by information on the NOAEL or LOAEL value relating to mammalian toxicity. It should be noted that this model places emphasis on the environmental fate, particularly on environmental persistence, and hence includes scoring for the extent of bioaccumulation, persistence and environmental half-life. This reflects the model developers particularly interest in developing an approach that would allow comparison of chemicals with known toxicity against others for which the toxicity profile is not yet known but for which there were concerns that it might show environmental persistence and later be found to possess toxic properties. Interestingly, in addition to generating a 'chemical score', SCRAM also includes a score for the degree of uncertainty surrounding the information used. This could potentially be important when attempting comparisons

between substances with significantly different sized datasets as it provides a means of taking into account – for each substance – the uncertainty that might arise from data gaps for some endpoints or where the available data are judged to be of poor or variable quality.

7.3 Approaches for Economic Valuation

7.3.1 Market or Resource Based Approaches

These approaches rely on the use of market prices to value the costs/benefits associated with changes in environmental quality, and are various referred to as the effects-on-productivity (or production function) approach or the dose-response technique. The aim of this type of approach is to determine the economic value of changes in environmental quality by estimating the market value of the impact that changes in quality have on changes in output of an associated good.

Application of this type of method is limited by the fact that it can only be applied to goods which are traded in the marketplace and in cases where it is possible to define a dose-response relationship between the presence of a chemical or chemicals and a change in either costs, yield or population levels. This limits its applicability to valuing the environmental impacts of chemicals likely to be regulated through a restriction or authorisation.

The study by DHI (2005) on the environmental benefits of REACH used the avoided costs approach (as a form of market-based approaches) to estimate the benefits from chemical regulation. In this study, avoided costs included the costs of water purification, sludge and dredged sediment disposal and cleaning of fish. The starting point was that excess levels of chemicals in a specific environmental compartment would restrict the possibilities of using it, thereby implying a loss of potential future income or value and/or costs for treatment or cleaning. Although this approach generated the smallest estimates of environmental benefits, it was also considered the most robust of the methods applied. Table 7.4 summarises the valuations derived from this study.

Other examples of the use of this type of method include the work by Lancaster University (Giacomello et al, 2006) which derived estimates of the damages costs associated with the use of TBT anti-fouling paints. The assessment is based on a production function approach and a value of the projected landings is taken as a surrogate of the value of the impacts. The method used to calculate the projected landings is based on the difference in volume of landings prior to 1986 and after 1986 (annual and average volumes) multiplied by the nominal prices and then deflated to account for inflation and time preference. Different percentages are applied to account for causality (100%, 50% and 10%).

Table 7.4: Potential Benefits of REACH on the Environment			
Receptor/Impact	**Basis for valuation**	**Total benefits (2017-2041)**	**Comments**
Sewage treatment plants	Avoided costs of upgrading a STP to nutrient removal as a result of less chemical stress €29-98 per person equivalent (2005 prices)	€131-€440 m	Values may underestimate the potential costs savings
Water cleansing	€0.05/m^3 in the UK and €0.02-0.10/m^3 in Denmark	€896-€5,564 m	5% of current treatment costs are due to chemical contamination
Sludge disposal	Costs of incineration avoided €200/t Value of lost fertiliser €98-130/t	€1,520m	Includes incineration costs and fertiliser value of sludge
Fish cleaning	Cleaning of fish products for fish feed, costs avoided €18/t	€16m	Figure doubled to account for more contaminated fish catch from the North Atlantic
Dredged sediment	Costs of disposal of contaminated sediment avoided (60% reduction in contaminated sediment). Costs varying from €4/m^3 to €24/ m^3	€241-1,450m	Benefits may be underestimate

Similar approaches have been applied in the context of pesticides and impacts on bee populations. Bees are essential to many economic activities, which depend on their services, such as pollination. They not only generate indirect values in the form of ecological services, they also provide direct values, such as honey production. Various studies have estimated the value of a bee colony and have tried to predict the economic damages due to impacts on bee populations for exposures to pesticides. For example, the study by Giacomello et al (2006) tried to estimate the magnitude of the benefits that regulation of a generic insecticide may have in terms of pollination and honey production. They considered different causality levels ranging from 5 to 70% for the annual loss of colonies due to the generic insecticide. Based on a series of assumptions, Giacomello et al (2006) assume that the failure to ban the generic insecticide causing such losses could result in economic damages due to reduced pollination and honey production of £2 million per annum, and assuming a causality level of 50%. If the impacts on pollination services were also accounted for, the losses could be 10 times higher (as honey production is generally assumed to account for around 10% of the value of a colony).

There are a few examples where such approaches have been used in the context of chemical risks and the environment. For instance, stated preferences studies have been carried out in relation to pesticides. The study by Travisi (2004) used a meta-regression framework to account for inherent differences in the WTP values for reduced environmental risks from exposures to pesticides. The study found strong evidence for the WTP for reduced risk exposure to increase by approximately 15% and 80% in going from low to medium and high risk-exposure levels, respectively. The results for the income elasticity seemed to indicate that the income elasticity is positive and the relationship is elastic. The results also revealed however that a meta-analysis was unable to provide a consistent and robust picture of the large range of WTP assessments across different environmental target types.

7.3.2 Revealed Preferences Methods

The two main revealed preference approaches in relation to the environment are the hedonic pricing method and the travel cost method. Both of these have limited applicability to valuing the environmental (as opposed to health) benefits of regulating hazardous chemicals:

- the hedonic pricing method is usually applied to determine the premium placed on the price of a good, such as residential properties, associated with different environmental attributes. In a chemicals context, the focus of such studies would be on the premium that people are willing to pay for products with different environmental characteristics, for example, products which are free of a particular chemical or have met eco-labelling criteria;

- the travel cost method is similar but in this case recreational users demand for sites of varying qualities is modelled to determine their willingness to pay for particular environmental quality attributes. Again it is unlikely that the types of chemicals likely to be regulated under restrictions or authorisation in the future would have such significant impacts on the quality of a recreational visit that the use of this approach becomes relevant (with the only potential exception being significant impacts on the quality of recreational fisheries due to, for example, high aquatic toxicity potential or perhaps endocrine disrupting effects).

A review of the literature highlights that there are numerous studies which have estimate the premium that people are willing to pay for products with different characteristics; for example, there are numerous studies which have estimated the price premium associated with organic produce.

We have also identified a range of other types of studies which have looked at particular product types and attributes. For example there a various studies relevant to sustainable products for the construction sector, including treated wood products for main construction purposes, wooden decking for outdoor use, methods of construction (brick based or steel framed), different building design elements, and valuation of avoidance of toxic molds and mildew in properties, etc.

This highlights the potential for applying this type in the context of consumer products, although care would be needed to ensure that any premium was related to the presence or absence of a particular chemical rather than other more general environmental attributes.

7.3.3 Stated Preferences Methods

There are two sets of methods which essentially involve the use of hypothetical (or experimental) markets to elicit individuals' willingness to pay for environmental improvements. These are the contingent valuation method and attribute-based stated preferences methods. Under the contingent valuation method (CVM), individuals are surveyed to determine their willingness to pay for a specified change in the quality or

quantity of an environmental good (or how much compensation they would expect for an increase in risk or in environmental damages). The mean willingness to pay value across all valid bids is then used to provide an indication of the economic value of the specified change. Stated preferences methods (covering conjoint analysis and contingent ranking) involve the elicitation of individuals' ranking of preferences amongst a bundle or 'basket' of different environmental outcomes. Values for changes in environmental goods are derived by 'anchoring' preferences to either a money sum or the real market price of one of the goods included in the bundle/basket of outcomes.

These two methods are the only valuation techniques that can be used to derive both environmental use and non-use values. As a result, they are the most commonly applied technique to valuing the impacts of regulations (or projects/programmes), particularly where the aim is to reduce impacts on ecosystems.

ABT Associates (1995), in a report to the Canadian Government, assessed the environmental benefits of restrictions on the use of perchloroethylene using a contingent valuation survey. The median amount a respondent who used dry cleaning services was prepared to pay was an additional 8.42 Canadian dollars per household per year (at 1995 prices) to eliminate perchloroethylene-related environmental damages, while respondents who did not use dry cleaning services expressed a willingness to pay of 5.23 Canadian dollars.

Von Stackelberg et al (2005) investigated the willingness to pay to avoid ecological and human health effects of PCB exposure in interviews with respondents from across the US. The ecological endpoints used in this study were changes in effects on bald eagle fecundity from 20% of animals affected to 10% or 5% affected, and changes in the percentage effect on a species sensitivity distribution (SSD) of reproductive effects across several avian species from a 50% to a 25% chance that 20% of species will be affected. The willingness to pay for reductions in risks to eagles and the SSD was similar at $139 for eagles and $157 dollars for the SSD (both as one-off payments at 2005 prices).

In relation to pesticides, Mourato et al (2000, see also Foster and Mourato, 1997) valued the multiple environmental impacts associated with pesticide use in the UK. Respondents were asked to view the various consequences of pesticide use in bread production as product attributes which should be taken into account in the decision to purchase a loaf of bread and to rank the value of those attributes. The results indicate an estimated mean willingness to pay (WTP) to protect bird species of around 6 pence per loaf (1997 values), with this being six times higher than the meant WTP to avoid a case of human ill-health (valued at 1 pence per loaf). WTP per household per year was then estimated at £16.30 for the protection of bird species and at £2.40 for the avoidance of a case of human ill-health[57]. Estimated total WTP across all households in the UK is then around £300 million per annum.

[57] In order to transform these values into WTP per household per year, data on the volume and bread consumption and an elasticity of demand of -0.09 (based on MAFF, 1999) were used.

Giacomello et al (2006) applied a benefits transfer based methodology to value the benefits from a ban on two pesticides, methiocarb (in use) and DDT (banned). The aim of the study was to identify, quantify and where appropriate monetise the environmental benefits arising from regulation by seeking to develop hazard-benefit relationships for substances based on historical evidence. The objectives were to: identify suitable example substances, based on historical evidence, to be used as case studies; collect the evidence establishing a link between the substance and effects reported in the environment; quantify the link between the substances and the effect(s) reported in the environment and on human health; and, where possible, monetise such impacts.

For methiocarb, the economic valuation of benefits from a ban was based on the economic value of certain species associated with methiocarb poisonings but only for selected components, where data were available. A series of willingness to pay studies were used to provide the benefit transfers estimates on which the valuation exercise is based (further details of the source studies are provided below). These are presented in Table 7.5.

For DDT, two scenarios were used:

- Scenario 1, which is the most conservative scenario, considers only observed impacts. This includes impairment of the reproduction system in a number of predatory birds. Here it is assumed that if DDT use had not been restricted only these predatory birds would have been affected; and

- in Scenario 2, which is less conservative, potential impacts are considered in addition to observed ones. In this case, the possibility that other impacts would have occurred is considered, assuming DDT had not been banned. These include: a) further reproductive impairment in other avian species; b) reproductive impairment of fresh water fisheries and mammals such otters, seals etc.; and c) the risk to human health.

For DDT, the focus for Scenario 1 was to quantify and identify the economic implication associated with change in those top-predator birds populations (merlin, sparrowhawk and peregrine falcon), which have shown a clear sensitivity to DDT in the UK. The non-consumptive use value of birds was calculated from the size of the market for bird-watching in the UK and the market for marine wildlife in the UK. The indirect use value of birds – in terms of their ecological function – was based on work by Costanza et al (1997) (the biological control service provided in crops by birds is equivalent to £21 per hectare annually (at 2004 price)). The non-use value was based on existing WTP studies for the preservation of particular species in relation to Biodiversity Action Plans.

The impacts considered under Scenario 2 are based on long-term study results. The study considers a subset of impacts which are the further reproductive impairment in avian species and reproductive impairment of freshwater fisheries and mammals. The main missing data are the dose-response relationships between DDT usage and

potentially affected species. For illustrative purposes causality relationships were assumed. These arbitrary causality relationships were chosen mainly to show the potential range in the magnitude of costs that a delay in regulating a chemical may have. Therefore, the estimations obtained using these causality levels are considered to be only indicative of the real values.

Table 7.5: Values of Wildlife Species in Valuation of the Costs from Methiocarb Poisonings

Species	Use value			Non-use value		Unit value (£/head)	Total value (£)
	Direct use (consump-tive)	Direct use (non consumptive)	Indirect use	Option value	Existence & bequest value		
Wild mammals							
Badger		x	x	x	x	32	142
Deer	x	x				162.25	859
Fox	x					191	532
Hare	x (partial)					3.13	235
Wild birds							
Buzzard		x				6.4	7
Mallard	x (partial)					2.19	132
Pheasant	x					7	119
Livestock							
Cow	x					571	858
Sheep	x					43	1,488
Companion animals							
Cat		x				2,856	13,839
Dog		x				4,905	290,372
Total							***308,583***

Source: Giacomello et al, 2007

The average annual benefits that the regulation of DDT might have generated in terms of the observed impact that the protection of the three bird species could have had ranged from £19 million to £57 million assuming a causality level of 10% (using the estimates reported above from Mourato et al, 2000). In the £19 million estimate, the value of protecting three farmland bird species is assumed to be equivalent to the value of protecting only one farmland bird species. In contrast, the £57 million estimate assumes that the value of protecting one bird species as reported in Mourato et al (2000) should be aggregated across all three of the bird species which are known to have been at risk of extinction.

Richardson & Loomis (2008)[58] provide an updated meta-analysis of studies carried out using the contingent valuation method to place an economic value on threatened,

[58] 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.

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 7.6. 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 7.6: 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 within the context of this study, however, is an understanding of what changes were being valued. As can be seen from Table 7.6, 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 where concentrations are found at levels below those which could lead to impacts on populations. It would also be necessary 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 a single chemical.

A willingness to pay survey carried out in the UK (NERA, 2005) in relation to the WFD was designed to elicit willingness to pay to achieve good status within surface water bodies; by its scope, this includes reducing loads of Annex 10 priority and priority hazardous substances to the environment. However, there is no means of decomposing the WTP values elicited through the survey to develop a valuation that only covers reductions in loads of Annex 10 substances compared to other chemical contaminants or other physical or biological pressures.

We have also identified a study which uses stated preferences methods to elicit individuals' willingness to pay for eco-labelled household products. This was carried out in England and Norway for certified and eco-labelled wood furniture (Veisten,

2006)[59]. The piece of furniture used in the survey was a pine table, with the hypothetical eco-labelled alternative being one which carried a certificate of origin of the wood used for the table from a sustainably managed Nordic forest.

The study used two different approaches to estimating willingness to pay: choice-based conjoint analysis and open-ended contingent valuation. The surveys were carried out in IKEA stores in both questions, with the aim of determining customers' willingness to pay a price premium for the eco-labelled furniture. The findings were as follows:

- Conjoint analysis: the additional median willingness to pay was $54 (16%) of the price of the unlabelled alternative in England and $4.3 (2%) in Norway;
- Contingent valuation: the additional median willingness to pay was a $25 (7.5%) price premium for England and a $13.8 (6%) price premium for Norway.

7.3.4 Ecosystem Services Based Approaches within CBA

Increasingly ecosystem approaches have been called on to encapsulate the wide range of benefits, good and services that the natural environment offers. Indeed, ecosystem approaches have been used within the context of WFD and hazardous substances in the still on-going Aquamoney project[60].

The main stages in the approach are summarised in Figure 7.1 below, beginning with initial characterisation, consultation and mapping, moving onto service valuation and classification and then via further consultation and use of transfer values etc. to complete the Ecosystem Services Approach and Ecosystem Services Valuations (ESV).

[59] Veisten, K (2006): Willingness to pay for eco-labelled wood furniture: choice-based conjoint analysis versus open-ended contingent valuation. Journal of Forest Economics, 13, 29-48.

[60] See Internet site http://www.aquamoney.ecologic-events.de/

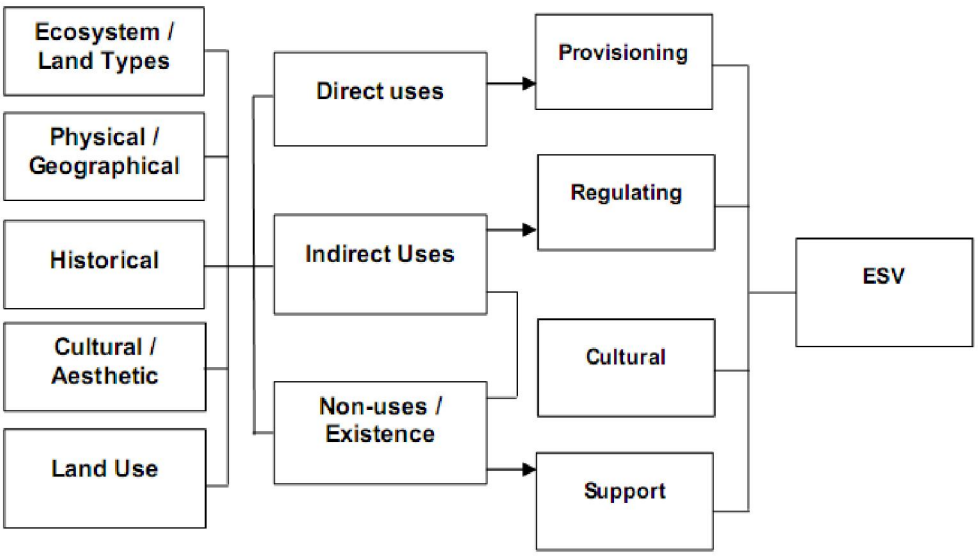

Figure 7.1: Framework of Ecosystem Services
Source: Glaves et al (2009)

The description of the services is based on the Millenium Approach where:

- provisioning services: include products obtained from the ecosystem and sometimes with a market value, e.g. food, fuel, ornaments;
- regulation services: such as air-quality maintenance, natural flood protection, disease regulation, pest protection, etc;
- cultural services : these refer to the non-material benefits that people obtain such as spiritual value, recreation, cognitive development, tourism, etc; and
- supporting services: necessary for the production of all other services, e.g. habitat provision, water cycling, soil formation, nutrient cycling.

More recently, work has been undertaken for the European Environment Agency to provide the basis for a Common International Classification for Ecosystem Services (Haines-Young et al, 2009). This system combines a range of different thinking with regard to how ecosystem services should be defined, building on the Millenium Assessment and other more recent work. It defines 10 different groups of potential 'services', with these related to provisioning services, regulating services and cultural services. It then links these groups to different service classes which can be more directly linked to outputs and products. Although not all of these groups and classes 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.

The Ecosystem Services Approach has been applied in a wide range of countries, at either regional or site specific scales. The study discussed above by Lancaster University (Giacomello et al 2006) started from an ecosystem services based approach by examining the services and good provided by the species affected by TBT. In addition to valuing the market benefits to shellfisheries of the partial UK ban on TBT anti-fouling paints for small boats, it also considered the value of nutrient

cycling services provided by natural shellfisheries. This aspect of the analysis also considered different levels of contribution to marine nutrient cycling as a whole based on a value of US $21,100/ha/yr (1994 prices) of estuarine ecosystems (based on Constanza et al, 1997)). The advantage of such an approach is that it takes uncertainty into account with regard to how causality is linked to the level of evidence. On the other hand, it does result in a fairly subjective assessment.

The Aquamoney project is aimed at developing guidelines based on an ecosystem approach (pers. comm. 2010). The guidelines are, at the time of writing, not yet available. Different case studies conducted under the project however have included stated preference studies to elicit the benefits from water quality improvements.

7.3.5 Key Issues

CBA requires consideration of both the costs and the benefits of a change in regulation. Ideally, all costs and benefits would be quantified and then valued in money terms. The main issue concerning the use of approaches under the umbrella of CBA is thus the existence of evidence of impacts so as to inform on the quantification of the benefits. In addition there are specific issues concerning each of the above methods, such as:

- market based approaches: these approaches may fail to account for those services that cannot be valued in the market place, e.g. recreational services and non-use related values, but will capture impacts on production from different levels of environmental quality related to chemical emissions;
- revealed preferences: this approach may be valid in accounting for impacts that are observable by users but will under estimate non-use benefits; and
- stated preferences and/or contingent valuation exercises are expensive to conduct and it may be difficult to convey information on chemical risks in a manner that can be understood easily by the interviewee.

On the other hand, the advantages of CBA over other methods is that it allows the comparison of benefits and costs in a same unit, that of money. This advantage is increasingly being recognised by policy makers; hence the increasing interest in impact assessment methodologies that include benefit estimates to inform policy making.

7.4 Other Comparative Methods

7.4.1 Life-Cycle Impact Assessment Based Methods

Other comparative methods include LCA and LCIA**,** as discussed in Section 5, or integrated assessment as described by Briggs (2008). The ESPREME (2007) study is based on the use of integrated assessments and also draws on varying methods to provide the basis for quantifying the benefits of reducing atmospheric emissions of heavy metals. One of the approaches discussed in the study is the Ecotax method which is a combination of environmental taxation with LCA/LCIA outputs. This

method relies on two basic assumptions where the first one is that the members of the Swedish Parliament represent the will of the people, and the second is that the environmental tax system represents the priorities of the Parliament. It is based on the principle that if a tax level is set optimally based on governmental objectives, then it should reflect the social value per unit of emission reduction.

The different environmental taxes and fees existing in the Swedish tax system are shown in Table 7.7. In cases where the tax or fee used is not on the reference substance, calculations are made according to the principle that a contribution to an impact category can be considered equally harmful independently of what caused it. For example, an emission of 1 kg of methane is, according to IPCC (1995), equivalent to 56 kg of carbon-dioxide over a 20 year time frame. Emissions of carbon-dioxide have a tax value of 0.041 Euro per kg and, thus, the emission of methane warrants a damage value of (56 kg/kg * 0.041/kg) = 2.30 Euro/kg.

Table 7.7: Environmental taxes and fees existing in Sweden in 1998	
Impact category	Taxes and fees (1 Euro= 9 SEK)
Ecotoxicological effects and human health	2.2 €/kg pesticide
	3333.3 €/kg cadmium
	1.1 – 11.1 €/kg benzene
	20-38.9 €/kg lead

In applying the Ecotax method together with Swedish taxes and fees, different weighting factors are then estimated for:

- aquatic ecotoxicity: based on aquatic ecotoxicity potentials (AEPs[61]) for emissions to water from Jolliet and Crettaz (1997, not reviewed for this study);
- aquatic ecotoxicity for metals released to soil and air; and
- terrestrial ecotoxicity for metals released to soil and air.

In the case of aquatic ecotoxicity, Table 7.8 shows the calculated values based on AEPs for emissions to water and the tax on the active substance in pesticides. As can be seen from the table, mercury has the largest impact (as in the case of human health) followed by cadmium. The impact of the other heavy metals is comparatively marginal. When it comes to the aquatic ecotoxicity for metals released to soil and air, the damage costs for mercury are the largest at 8,333 €/kg for emissions to soil and 6000 €/kg for emissions to the air; this same process was then applied to terrestrial ecotoxicity (see Table 7.9).

[61] AEP is derived fora substance (sub) by normalization to a reference chemical (RC) by the formula

$AEP_{sub} = APAF_{sub} \div APAF_{RC}$

where APAF is the potentially Affected fraction of species per unit of emission.

Table 7.8: One-step Weighting Factors for Aquatic Ecotoxicity Based on AEPs		
Substance	**Characterization factor**	**One step weighting factor (€/kg)**
	AEP emission to water	**Based on 2.22 €/kg * copper**
Arsenic	0.52	0.2
Cadmium	520	222.2
Chromium	2.6	1.1
Lead	5.2	2.2
Mercury	1300	555.5
Nickel	0.79	33.3

The main issues related with these values stem from the assumptions concerning the internalisation of external costs by taxes and fees. Although one may argue that taxation can correct externalities, it is unlikely that they will be an accurate valuation of them. In this regard, it is of note that the Swedish values are higher however than the average in EU and the suggested levels in EC. It has not been possible to check the basis for such taxation system, so there are some doubts about the basis for the approach in this regard.

Table 7.9: One-step Weighting Factors for Aquatic Ecotoxicity for Metals Released to Soil and Air					
Substance	**Emission to soil**		**Emission to air**		
	Character-isation factor	**One step weighting factor Euro/kg**	**Character-isation factor**	**One step weighting factor Euro/kg**	
	AEP	**Based on 3333.33 €/kg) cadmium**	**AEP**	**Based on 180 Euro 20/kg lead 93 octane**	**Based on €/kg 38.88/kg lead 98 octane**
Arsenic	0.24	3.3	0.08	1.2	2.3
Cadmium	240	3333.3	79	1222.2	2444.4
Chromium	1.2	16.6	0.4	6.1	12.2
Lead	3.9	54.4	1.3	20	38.9
Mercury	600	8333.3	200	3111.1	6000
Nickel	0.4	5	0.12	1.9	3.7

Currently there are several methodologies, models and assumptions available for LCIA. However, in comparison to traditional risk assessment methods, LCIA requires more innovation to deal with the additional impact categories. Therefore modelling within LCIA depends on a variety of factors such as: impact categories; indicators; the level of acceptable uncertainty; expert judgement; etc. An optional element in the LCIA phase of an LCA study is a weighting portion, where the results from the different impact categories are weighted against each other. This can be useful in order to reach an overall ranking in comparative assessments. The combination of LCA and MCA type of approaches is described further below.

LCIA is suitable to assess the impacts of hundreds of substances at various locations and with various levels of impacts. The assessment will provide a basis for comparison upon which a procedure for the classification and characterization of the different types of impacts is possible. The data requirements to do this however are substantial.

7.5 Summary

Within the context of both restrictions and authorisation, it is likely that many SEAs will be limited to the use of a non-economic approach. This highlights the potential importance of developing some form of risk ranking or benchmarking procedure that can be used as base reference. The problem with this type of approach is the ability to develop meaningful 'references' for different types of environmental risk and exposure levels. This remains a major challenge, although there are examples as presented above, of approaches that have been tried in the past.

Table 7.10 summarises some of linkages that can be made between the outputs of risk assessments and the potential for using the different SEA methodologies.

Table 7.10: Comparison of Methods for Assessing Environmental Impacts

Methodology	Potential Underlying Environmental Statistics	Metrics and End-Points	Impacts not Captured	Other Comments
Single-Dimension (physical units)	-Risk ratio	PEC/PNEC NOEC LC_{50} LD_{50}	Secondary environmental effects not captured	Does not readily allow consideration of benefits
Revealed Preferences	-Dose-response -Species sensitivity distribution (SSD)	Impacts on specific species or ecosystems. Specific properties (e.g. endocrine disruption or vPvB)	Will exclude non-use	Emphasis on human perception and may underestimate risk
Stated Preferences			Will normally exclude production functions	
Ecosystem based approaches	-SSD -Dose-response -Production functions	Impacts on marketed goods or services; ecological services such as water cleansing, fish cleaning, etc	Can include use and non-use so most impacts covered	Data requirements likely to be significant and dose-response data needed as well as understanding of ecosystem functioning
LCA	-Environmental fate and behaviour -PEC/PNEC -NOEC -LC_{50} -LD_{50}	- Resource needs, raw materials, depletion of biotic/abiotic resources - Emissions,	Can include a wide variety of impacts but this could be subjective	Better when there are a few alternatives

Table 7.10: Comparison of Methods for Assessing Environmental Impacts				
Methodology	**Potential Underlying Environmental Statistics**	**Metrics and End-Points**	**Impacts not Captured**	**Other Comments**
		including transport and greenhouse gases; - waste arisings - acidification - euthrophication		
MCA based scoring and weighting methods	-environmental fate and behaviour	- impact of species - toxicity - bioaccumulation persistence		

Multi-criteria approaches may be of value in relation to both restrictions and authorisation, where the aim is to develop a comparative assessment of the environmental risks of alterative substances. These approaches were essentially designed for this purpose and not for the purpose of demonstrating that the benefits of using a chemical outweigh the risks to health and the environment. Issues are likely to arise with the derivation of the importance weights assigned to the different impact categories, particularly as these would need to reflect EU preferences as well as the regulatory aims of REACH. For example, would a weight of 20% for toxicity potential be appropriate for the purpose of an authorisation and/or a restriction? Similarly, issues could also arise should the assessment not consider a wide enough range of impacts when considering both the costs and benefits of restrictions or failed authorisations.

There may be scope under both restrictions and authorisation to use changes in physical measures of impact, such as emissions or environmental burdens, as a proxy for benefits; indeed, in many cases this may be more feasible than the use of cost-benefit analysis techniques but it will not provide information on whether benefits outweigh costs within the context of authorisation.

Monetary valuation using CBA techniques in the short-term is only likely to be feasible when: 1) there is a clear dose-exposure relationship and enough information about environmental impacts; and 2) there are production functions that can be linked to a specific market.

In the longer term though, there is no reason why stated preferences methods could not be used with the aim of eliciting people's willingness to pay to reduce certain types of impacts on the environment. For example, a study could examine people's willingness to pay to avoid endocrine disrupting effects in certain species, or to reduce emissions of vPvBs into the environment for precautionary reasons. he key issue in trying to use such surveys will relate to developing valuations which are transferable and not specific to a particular chemical, so that they are relevant to more than one risk management decision.

Thus, the choice of approach will depend on numerous aspects, including the specific adverse effects under consideration. The DHI study concluded that the possibilities for estimating the benefits of REACH on the environment suffer from a lack of a sufficiently developed methodology and from a lack of data.

8. CONSIDERATIONS AT THE EXPERT WORKSHOP

8.1 Background

As part of the study, an Expert Workshop was convened on 19th May 2010 to discuss the findings of the scoping phase of the project and review the preliminary versions of logic frameworks for human health and environmental impacts, that had at that tuime been developed to facilitate the conduct of SEAs. The workshop also discussed the initial work that had been undertaken on two case studies (HBCDD and TCEP) that are used to exemplify and validate the logic frameworks (see also Part 2 to this report).

The workshop was organised by the RPA project team and hosted by DG Environment, and brought together leading international experts from the fields of environmental economics, human and environmental risk assessment, epidemiology, impact assessment and life cycle analysis, with individuals drawn from government, industry and academia, specialist consultancies and representatives of the European chemical industry.

The objectives of the workshop were to:

- critically review the scientific and methodological basis of the draft logic frameworks for health and the environment;
- comment on the application of the initial drafts of the frameworks to two case study chemicals, tris (2-chloroethyl) phosphate (TCEP) in relation to human toxicity and hexabromocyclododecane (HBCDD) in relation to environmental concerns; these are candidate chemicals for authorisation and were selected from a short list in discussion with DG Environment and ECHA; and
- gather opinion on the suitability and limitations of the scientific or socioeconomic understanding and methods, so as to identify further research needs both within the study and more generally.

The key conclusions and recommendations of the Workshop are discussed further below. The specific recommendations concerning the proposed logic frameworks were reported on in the Second Interim Report. As the logic frameworks have developed significantly since that report, there is little value in repeating the Workshop conclusions on the preliminary frameworks here. However, it is important to note that the feedback received was extremely valuable to the study team in further developing, amending and adapting the frameworks.

8.2 Considerations on Risk Assessment and SEA

8.2.1 General Issues

It was noted that there was a fundamental difference in the ways datasets are used for risk assessment (RA) and for SEA. In RA, the risk characterisation ratio (RCR) approach ensures that only 'safe' chemical exposures are allowed through incorporation of assessment factors in the DNEL/PNEC (to allow for established or potential inter- and intra-species differences, scientific uncertainty and dataset limitations where applicable) and conservative assumptions in the exposure assessment. The result is that the conclusions from RAs are, of necessity, precautionary in nature as they are based on 'reasonably worst case' scenarios.

There was a lengthy discussion of the application of precaution in the context of a RA in combination with SEA; divergent views were apparent with some strongly supporting the existing approach embodied in the REACH risk assessment method and others suggesting that there may be an excessive reliance on default assessment factors in RA even where scientific evidence suggest they may be overly precautionary. It was also questioned if it might be more appropriate to only apply adjustment factors at the final stage of the RA since this was suggested to be more in line with the precautionary principle. For the SEA, it was considered essential to consider not only the 'realistic worst case' scenarios as used by RA but to also address more 'realistic' or 'best' estimates, the latter being based on mean or average values of exposure and hazard potential. In addition, within a SEA there was a clear need to include detailed sensitivity and uncertainty analyses to inform decisions.

It was noted that although some while valuations based on 'willingness to pay' (WTP) exist, few of these are directly linked to chemical exposures or effects. However, it was noted that in the absence of WTP estimates, the use of market data alone (e.g. medical treatment costs) may significantly underestimate the full economic 'value' of impacts; it is therefore important that WTP estimates are developed over the longer term. In practice, other health based metrics (e.g. D/QALYs) were considered to be more likely to be available in the short-term although these are not yet comprehensive and will not cover all of the health endpoints of potential relevance to REACH.

A possible danger that was recognised by participants is that the outputs from a SEA could be misinterpreted if the assumptions varied significantly from those in the RA (i.e. realistic versus worst case). However, it was suggested that this danger could be reduced by including clear statements on the uncertainties identified and the assumptions made.

There was concern that SEA methods may not adequately address the need for a balance between societal and individual risks (i.e. distributional fairness). The question was also raised as to whether it was appropriate to always consider single substances since groups or mixtures may be of greater relevance (although it is also unclear how this could be applied within a REACH-specific situation). The question of whether and how enforcement should be considered within REACH SEAs was

raised but not resolved (this was illustrated by an example on the influence of enforcement on future cancer burdens).

Terminology was noted to vary significantly between disciplines and chemical regulatory areas, and the same term may have quite different meanings in different contexts. It was a suggestion that there should be uniform adoption of REACH terminology but others considered it not to be a significant issue provided adequate explanation and definitions were given.

8.2.2 Novel Approaches

The potential use in SEAs of advanced impact estimation techniques, such as statistically-derived estimates of disease burden using epidemiology data or the use of LCIA techniques, was recognised.

In LCIA, the focus is to provide a **comparative** assessment of selected chemicals (or processes) using a series of substance-by-substance analyses. Also, through use of multiple runs (or in some models, a series run of multiple chemicals), it is possible to assess dynamic changes and to assess the potential impacts of various risk management scenarios. Although LCIA allows a much wider set of endpoints (e.g. energy use and greenhouse gas emissions) to be addressed, concern was expressed as to the lack of transparency of the models and their outputs (e.g. the basis on which estimates are derived), the ease of model application, and the availability of suitable datasets for the chemicals of concern. However, the ability to develop scenarios so as to reflect dynamic changes (i.e. temporality) was considered of particular value when addressing issues such as bioaccumulation. It was suggested that there was a need to agree on the 'receptors' that should be considered and on how outputs would be valued within the context of SEAs for REACH.

8.2.3 Assessment of Human Health Impacts

The significant problems that exist when attempting to use experimentally-based hazard data (as derived during the RA) to infer the nature and scale of human health impacts was emphasised (the TCEP case study was considered to illustrate the typical problems that could be anticipated). Also the significance of some of the endpoints that are included in toxicity tests, to human morbidity was considered unclear.

The development of approaches such as bench mark dose (BMD) techniques in addition to linear extrapolations was welcomed as a means of informing on dose-response. Possible alternative approaches such as use of proxies of effect (e.g. exposure/emissions) to inform expert judgement of impact, were also suggested to be important.

It was noted that in some circumstances, information on effects and exposures may also be obtainable via non-industry sources, such as Trade Unions and NGOs.

8.2.4 Assessment of Environmental Impacts

Our current ability to quantify any identified environmental impact was noted to be very limited.

The potential value of species sensitivity distribution (SSD) techniques was recognised. However, SSD was considered probably unsuitable for PBT and vPvB substances where the focus should be to address the concern about environmental transport. Also, there was noted to be methodological and interpretation issues with SSD, particularly as to how to extrapolate output to environment consequences and it was suggested that robust impact determinations from SSD-type approaches may be possible only at specific localities (presumably by drawing on additional information regarding locality). There were also disparate views on how estimates of environmental impact should be valued (e.g. was it appropriate to value effects in terms of impacts on a single species, rather than on an ecosystem more generally).

Possible alternative approaches to the use of SSDs that were suggested included: use of proxies of effect (such as volumes of exposed media); and consideration of dose-response of individual species to inform expert judgement of impact. It was also suggested that the SSD may not provide the information actually needed to estimate impacts and that it may be important to actually look at the dose-response functions for individual species that underlie the overall distribution. It was suggested that these single species dose-response functions may provide better indicators of the types of ecosystem or single species effects that could occur, that the use of a SSD. In general, this was identified as an area requiring further study.

One participant mentioned the potential value of mapping emissions and impacts against ecosystem services and provided a UK example concerning managed realignment (i.e. River Blackwater[62]). However, it is uncertain that this approach will be fully applicable to the REACH context although in some instances specific services may be relevant. This possibility requires further investigation.

8.2.5 Assessment of Persistent or Bioaccumulative (i.e. PBT and vPvB) Substances

It was noted that there was as yet no generally accepted approach to valuation of the presence within the environment and biota of persistent or bioaccumulative substances where there was absence of any known or inferred toxicity. Suggestions on possible ways to addressing this issue included: use of mapping and or fate and transport models incorporating a probabilistic approach; drawing on understanding from similar substance such as the polychlorobiphenyls (PCBs); and use of emissions (and changes in these) as a proxy for risk.

[62] For further information see Internet site http://www.comcoast.org/index.htm

9. SUMMARY AND RECOMMENDATIONS

9.1 Findings from the Literature Review

The aim of this study is essentially to develop logic frameworks for assessing the health and environmental benefits associated with regulation of chemicals under the restriction and authorisation processes under REACH. Rather than just focusing on the risk assessment or SEA component of a potential framework, this study is trying to adopt a more holistic approach so as to start the work required to bridge the existing gaps between risk assessment and risk management.

The literature review has identified a number of different issues which require consideration in trying to bridge the existing gaps and developing a framework for future SEAs in both the short and the long term. Our key conclusions from the review for both health and the environment are summarised below.

9.1.1 Human Health: Key Findings

Hazard data for human health effects may be generated using a range of approaches, from epidemiological studies to toxicological studies. These approaches can be used to produce different health statistics, which can in turn be used in varying ways to predict exposures.

Key issues regarding human health hazard data include:

- data developed through epidemiological studies may be historic and not reflect current exposure levels; but more generally, such studies may not be available for many of the chemicals likely to be subject to REACH; even fewer direct human studies are likely to be available to provide a dose-response function;

- the outputs of toxicological studies will result in the calculation of a DNEL and a range of supporting metrics. These will incorporate assessment factors to reflect uncertainty and to ensure that the resulting figure is a protective estimate (i.e. reflects a level of precaution). For impact assessment purposes, however, these assessment factors mean that the DNEL value does not in reality reflect an exposure level at which a toxicological effect ceases to occur but probably some level below this. In order to quantify impacts, it may be more appropriate to consider the LOAEL or the BMD and to also collate data on effect levels above these where data are available;

- in any event, uncertainties surrounding NOAELs, LOAELs and the BMD levels should be made clear and quantified where possible; this is important as an impact assessment should not only consider 'worst case' assumptions but also consider 'best estimates'; and

- finally, there are also likely to be some cases where the risk characterisation will be qualitative, e.g. for some carcinogens and for certain irritants and sensitisers.

With regard to the exposure assessment component of the work, numerous methods can be applied. The choice of method is likely to be driven by the available data and the health metric stemming from the hazard assessment. The approaches to predicting exposures are similar for workers, consumers and public health, but data availability problems and the need to make additional assumptions when modelling consumer and public health introduce further uncertainties into the end estimates. Even though models are available for carrying out the exposure assessment, it is also clear that non-model based approaches are likely to be needed for some aspects of consumer exposure. In addition, considerable work has been undertaken into the development of LCIA approaches for assessing public health impacts; although these are not yet in a form that is consistent with the risk assessment approaches used under REACH, there is the potential for in the longer term for greater use of such models once suitably developed.

With regard to the SEA methods that are available, there is a spectrum ranging from hazard based risk ranking methods to the more quantitative approaches provided through the use of DALYs and monetary valuation within a CBA framework.

- Risk ranking methods are used in other fields to provide a non-economic way of assessing the acceptability of risks to both workers and the public. There may be merit in exploring how these approaches could be applied within the context of REACH to provide some form of decision matrix or a set of benchmarks for use by decision makers.

- Both single-dimension and multi-dimension measures of effectiveness are used in the field of health impact assessment. Both have their merits and may be appropriate depending on the health risk issues being considered. Increasingly, analysts are turning to the use of DALYs and QALYs to measure both the change in the number of cases and the impacts that the associated health effects have on an individual's well-being prior to death. In the context of REACH, DALYs in particular may be useful as they can be used to reflect problems in society that relate to time lost but that do not lead to death, for example, neurological conditions which together with psychiatric conditions account for 28% of years lived with disability but only 1.4% of deaths and 1.1% of years of life lost.

- Of the monetary valuation methods, the COI approach has been used to the greatest extent, in part due to the fact that it relies on actual or observed data. Collection of COI data is also likely to be less resource intensive than the use of surveys or complex statistical analyses. This type of approach could also be combined with the use of either DALYs or with VOSL or VOLY data, as long as care is taken to ensure that there is no double counting in so doing (e.g. checking to ensure that a VOSL reflects only willingness to pay and not also some measure of productivity losses).

- Benefit transfer based approaches using existing VOSLs (or VOLYs derived from these) are also used extensively, drawing on wage risk premia or stated preferences studies. However, the limited number of studies relevant to the type

of health endpoints associated with the chemicals of concern under REACH will restrict the degree to which benefit transfer approaches can be used as a valuation method for morbidity effects and effects associated with exposures to mutagens and reproductive toxins.

9.1.2 Environment: Key Findings

As for health, a variety of different statistics is used to reflect the level of environmental hazard associated with a given chemical. In this case, the issues are complicated by the range of different environmental compartments that may need to be considered and the number of different species that may be relevant. Furthermore, information on selected species may still be a poor predictor of impacts at the ecosystem level, due to the potential for food chain effects and secondary poisoning issues.

The key outcome of the environmental risk assessment is the risk characterisation ratio (RCR - reflecting the ratio of the predicted environmental concentrations (PEC) to the predicted no effect concentration (PNEC)). As previously discussed this provides sufficient information to inform decisions within the context of a risk assessment. However, it provides no real information on the environmental effects which may occur in terms of their nature, magnitude or ecological importance. For instance, derivation of a RCR greater than one for a given scenario only indicates that there is a potential for an adverse impact of some type. Importantly the size of the RCR cannot be used to infer, even in a comparative sense, the extent of the resultant ecosystem damages. As such, the interpretation of the environmental risk assessment findings poses a significantly greater challenge than the situation for human risk assessments, where the target species is precisely defined (i.e. humans) and the toxic endpoint on which the DNEL is based and which is used to define the RCR will allow one to infer at least in broad terms the nature of the potential impact that might occur (e.g. in terms of risk of acute toxicity, sensitization, target organ toxicity or cancer).

In addition, the ability of substances to persist and bioaccumulate in the environment means that these chemicals pose a particular concern as their long-term effects cannot be predicted and any effects would be difficult to reverse; simply stopping emissions of the chemical into the environment would not solve the problem if reserves have built up over time. As a result, PBT and vPvB substances cannot be adequately assessed with traditional environmental risk assessment methods, which rely on a chemical's toxicity to determine risk.

Key issues identified with regard to the environmental hazard and exposure assessment and the development of SEAs are as follows:

- the use of PNECs and comparing these to environmental concentrations appears simple and straightforward, however, there are many underlying assumptions, such as different endpoints, acute vs. chronic effects, safety margins and species sensitivities;

- the need to ensure that all effects are properly assessed and that uncertainties as well as safety/assessment factors are explicit (to avoid the comparison of a 'worst case' with a 'most realistic' scenario, for instance);

- the potential role for single and multi-species studies which may help understand the impacts on ecosystems, however, the need to also ensure that the underlying assumptions would appear to be valid if used as a proxy for ecosystem effects; and

- the need to ensure that if any methods are developed which involve a comparison of PBT and vPvB substances to other substances with well known toxic properties, that these methods take into account the fact that concern does not just arise from toxicity.

Traditionally, the assessment of environmental impacts in the chemical context has been based on cost-effectiveness analysis, with some examples also available of the use of market-based approaches. The Aquamoney project, in its review of existing methodologies, concluded that:

> *Linking economic values to bio-indicators is not common practice, […] Although it is somewhat of a commonplace nowadays that valuation should involve both natural scientists (ecologists and water scientists) and economists, some guidelines such as the ones provided by Emerton and Bos (2004) also mention bio-economic models. Bio-indicators as proxies for water quality are mentioned in USDA/NRCS (1995), but these guidelines do not link these indicators to economic valuation and economic values*

Although there are considerable gaps between the outputs of environmental risk assessments and the types of dose-response functions generally needed for monetary valuation, there are studies which have tried to bridge these, for example, using Species Sensitivity Distributions (SSD) combined with willingness to pay surveys. However, it is currently unclear the degree to which this type of survey would have to be specific to a given chemical and its properties or could be developed to provide transferable benefit estimates.

In any event, it is unlikely that willingness to pay surveys would be used in the short-term by Authorities or companies in response to either the restriction or authorisation processes.

More generally, problems that will affect the further development and application of any methodology, whether based on benchmarking, risk ranking, and multi-criteria methods versus more economics based concepts include:

- a chemical's persistence being the key reason for concern with regard to its presence in the environment, as the fact of this persistence makes it difficult to quantify any changes in impacts over time;

- an absence of environmental monitoring data (together with transport, fate and behaviour data in some cases) that would enable one to establish the geographic extent of environmental concentrations above the no effects level; and

- difficulties in linking data on toxicity for most sensitive species to other species or to ecosystem effects.

9.2 Lessons Learnt on the Logic Framework and Case Studies

9.2.1 The Logic Framework

The overall aim of the logic frameworks developed as part of this study, and presented in Part 2 of the report, has been to provide the basis for ensuring that SEAs prepared under REACH generate the types of information required by decision makers to make robust decisions on risk versus socio-economic trade-offs.

The logic framework was developed specifically with the aim of providing a step by step approach to assessing human health and environmental impacts to account of differences in starting information on risks, the availability of further data on exposures and the ability to link exposures to actual effects on humans and the environment. Given the problems that may arise in making such linkages and the potential lack of different types of information, the logic frameworks also set out a range of approaches that could be used as part of each step.

The logic framework was also designed to be consistent with the ECHA Guidance on preparing SEAs for Restriction and Authorisation. 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). In other cases, use may be made of surrogates for impact quantification, such as might be derived from extrapolations based on use of SSD-type approaches to estimate the level of adverse impact that may result from particular levels of exposure within a compartment. In some instances, however, it may not be possible to perform any form of toxicity-based quantification

or semi-quantification analysis. In such instances, the analyst may still be able to provide policy makers with insights into the potential for adverse impacts to occur, through development of surrogate indicators based on aspects such as potential consequences that may arise as a result of, for example, the bioavailability or persistence characteristics of a substance and/or trends in its usage pattern.

The final stage (Step 5) in the logic framework is 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.

The framework was tested on two case study 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.

9.2.2 Data Accessibility

One of the key findings to emerge during development of the logic framework and its application to the case studies on TCEP and HBCDD is that the process relies on collation of range of information from existing sources such as the REACH Chemical Safety Assessment and associated exposure scenarios; however, it also demands additional information in order to produce robust information for use by decision makers. This includes information on:

- amounts of substance produced/used and the supply chain patterns;
- numbers of workers exposed within particular sectors;
- occupational and environmental exposure patterns and available exposure measurement data;

- efficiency of personal protective equipment (PPE or LEV) that is available to workers and levels of worker use compliance;
- where environmental exposure is of concern, the locations at which releases occur (which would, for example, inform on nature and size of water bodies impacted) and particular local environmental factors (e.g. actual receiving water dilution rates);
- realistic derived minimum effect characteristics; and
- for toxicological and ecotoxicological aspects, detailed information on endpoint-specific dose-response characteristics (as metrics such as the RCR or PNEC are likely to be of only limited value when attempting to derive impact estimates for an SEA).

Data on the relative importance of EU production and use compared with imports in articles from outside the EU may also be helpful in placing the impact of EU industry activities in context against the overall (global) exposure patterns.

The extent to which the above types of information will be available is likely to vary. For example, production and use pattern information – together with information on site locations – may be readily available from REACH Registration dossiers to authorities preparing restriction SEAs, or to an industry consortium; it will be harder for a downstream user to place their use within the wider EU context, but some of this information may be available from relevant Annex XV dossiers.

Importantly though the availability of other types of information, such as toxicity/ecotoxicity dose-response relationships, could be improved for use by all involved in preparing SEAs by more importance being given to the presentation of such information in the REACH risk assessments.

9.2.3 Expertise Required to Develop SEAs in Support of REACH

The development of robust and comprehensive qualitative and/or quantitative assessments of health or environmental impacts requires a multidisciplinary approach. Depending on the issues that need to be addressed, this may necessitate individuals possessing the following skill sets:

- economics – to provide an economic context to qualitative descriptions of impacts or to predict the monetary value of the human health, environmental and/or ecosystem service impacts;
- exposure assessment – to develop realistic occupational/environmental exposures, taking into account fate and transport through the environment (including geographical and temporal patterns);
- toxicology – to identify, from amongst the toxicological dataset, effects that could inform estimates of human health/well-being impacts (or potentially, impacts on other mammalian species) and to determine if dose-response data are adequate to allow extrapolation to specific effects;
- epidemiology – to interpret epidemiological data (if available) to derive estimates of attributable fraction (or other suitable metric) to estimate impacts on exposed populations; and

- ecotoxicology – to identify, from the ecotoxicological dataset, species and effect data that could inform estimation of environmental damage and to establish if dose-response data are adequate for extrapolation.

Additional input may also be required on a case-by-case basis from:

- mathematical modellers – to model dose-response estimates and, potentially, to run and interpret outputs from exposure models;
- medical/clinical professionals – to advise on the interpretation, in terms of human disease, of particular toxicological findings and to facilitate comparisons between particular conditions (thereby potentially allowing 'read-across' to overcome data gaps);
- public health professionals – to advise on the population-level consequences of predicted changes in health parameters;
- occupational hygiene specialists – to advise on realistic estimates of workplace exposure and the influence of different LEV and PPE;
- ecological population modellers – to inform on potential community and ecosystem consequences of estimates of ecosystem disturbance; and
- life cycle impact and environmental modelling specialists – to undertake specialist modelling of geographical and temporal patterns of environmental exposure.

9.3 Areas for Future Research

A number of areas with regard to the need to develop the underlying science or economics to support the preparation of SEAs have been identified during the course of this study. This includes areas where there is a need to develop better consensus on the approaches to be applied, as well as areas where more fundamental research is required.

The key areas for further development or research identified here are:

1. Interpretation of significance of certain toxic endpoints in relation to human health impact

2. Interpretation of ecotoxic effects in relation to environmental impacts

3. Methods and data for estimation of exposure

4. Further development of more REACH specific benchmarking approaches

5. Further development of Life Cycle Impact Assessment models so as to be more consistent with concepts and methods under REACH

6. Development of more hazardous chemicals relevant ecosystem services concepts

7. Commissioning of willingness to pay studies that are specific to REACH restriction and authorisation contexts.

9.3.1 Interpretation of Toxic Endpoints in Relation to Human Health Impacts

There is a need to establish agreed linkages between a number of toxicity endpoints routinely included in test designs used for risk assessment, and the human health outcomes to which they may be correlated; it is suggested that this might be best addressed through an expert workshop.

The development of guidance on appropriate methods to undertake inter-species extrapolation in the context of SEA (as opposed to risk assessment) would also be helpful. This should include consideration of value of approaches such as allometric scaling and the more involved PBPK modelling, as well as the use of techniques such as linear extrapolation and benchmark dose (BMD) modelling. Provision of guidance as to what level of assessment factors might be appropriate within the context of SEA would also be of value.

9.3.2 Interpretation of Ecotoxic Effects in Relation to Environmental Impacts

There is a generic need to develop a greater understanding as to what constitutes an 'acceptable' degree of risk with regard to potential effects on the environment; in part this may be achieved through multidisciplinary discussions at venues such as workshops. However, primary research may also be necessary to better inform discussions as to the potential ecosystem consequences of effects on single species or groups within various trophic levels for each of the main media of concern (i.e. freshwater, marine and soil and sediment environments).

Both the species sensitivity distribution (SSD) based approach and single-species based dose-response functions are considered potentially valuable tools, depending on circumstance, to aid the development of estimates of the nature of the ecological consequences of chemical exposures. However, there is a need for further research in these areas to clarify the interpretation of outputs with regard to ecosystem impacts, and to establish best practice with regard to the development of sensitivity analyses and estimation of degree of uncertainty (e.g. the HBCDD case study demonstrates the wide differences in output that may arise depending on approach and assumptions used). In particular, there may be a need to reach a consensus between ecologists and risk assessors (and potentially economists) as to the appropriate size of dataset necessary to establish a SSD suitable for SEA purposes.

Despite these reservations, we believe further consideration should be given to the value to policy making of the use of SSD-based estimates as surrogate indicators of impacts, where quantification through other means is not feasible.

Further research is also needed to establish linkages between the statistical outputs of such assessment methods and environmental impacts and, in turn, to link these impacts to meaningful measures of economic value.

It is also suggested that consideration should be given to building on experience gained to date in applying methods, such as SSD, LCIA and other approaches, to chemical groups, such as metals and pesticides. Examples of such experience include the work done to date to predict the movement through and build-up within particular geographical or environmental compartments and biota, including consideration of temporal patterns, for those chemicals that are persistent and/or bioaccumulative (P/B) .

An outstanding issue remains for chemicals that are very persistent and very bioaccumulative but for which no particular toxicological concerns have yet been identified (i.e. vPvB). For such substances, even if information can be derived on geographical and temporal patterns of exposure, there is no suitable metric of effect (i.e. toxicity to particular organism(s)) against which to establish an impact valuation. Research could be carried out on combining temporal exposure predictions with the known (limited) toxic potential of the substance (or a similar surrogate that is better characterised) to provide estimates of potential future impacts of the substance at predicted environmental levels.

However, there may also be merit in further developing the type of model that the US EPA uses to predict the build-up and transport of such chemicals over time, so as to provide forecasts of potential future exposures in the absence of regulation. Such model outputs could then provide a context to the possible scale of any damages that may occur should new forms or currently unresearched toxic effects be identified in the future.

9.3.3 Estimation of Exposure

The limitations of existing models and the difficulties in establishing robust estimates for the various sectors of the human population (including workers) as well as of environmental media have been highlighted during this study. Further research has been suggested to establish the real usefulness of the various available approaches; it is also suggested that this should include consideration of the use of Delphic techniques and read-across approaches based on expert advice, although these are likely to need to the support of some actual exposure data.

The need for further population-based studies of cross-sectional, cohort or case-control design that involve the collection of detailed information on occupational and/or environmental exposure histories is also recognised. Such studies may provide data to support the development of exposure matrices with expert input. Some valuable examples of this approaches already exist, particularly for the Nordic populations and an example of the type of exposure matrix that may be possible is the ‘job-exposure’ matrix; but similar matrices might also be developed that inform on exposure related to consumer products or environmental chemicals (e.g. the basic data for the UK’s Biobank project has now been enhanced with special modules

addressing diet and occupational history[63]). Furthermore, inclusion of additional data collection within existing large cohort studies might be considered to support the development of exposure matrices. There should also be greater attempts to define the limitations and uncertainties that surround the different models and approaches.

In respect of both the effects of substances and the estimation of exposure, there may be benefit in undertaking further research to establish the added value gained by adopting a probabilistic (non-deterministic) approach when estimating exposures and then linking these to effects.

With respect to both of the above suggestions, there may be merit in developing a series of short examples of the application of different methods/models to illustrate:

- the processes involved including the types of assumptions that may have to be made;
- the level of data required by the different approaches and where the data can be sourced from;
- the uncertainties involved in applying the different methods; and
- the different ways in which their outputs can be used.

Although there have been studies which provide examples of the use of different approaches, these tend to apply the same type of method with no cross-comparison provide as part of the discussion. We have tried to address this to a limited degree in this study, but it has not been possible to provide a thorough discussion of the outputs that are needed from the exposure assessment to enable improved quantification of impacts in SEAs.

9.3.4 REACH Focused Benchmarking Methods

Benchmarking has been identified as being of potential value in providing a context to the level of hazard associated with the continued use of chemical, and in particular where it is hard to link a particular property or study finding to a concrete health or environmental outcome. In this regard, benchmarking the chemical of concern against other chemicals with better specified health or environmental risks may help in providing information on the potential severity of the effects from continued use (after also taking the potential for exposures into account).

Within the context of this study, it was not possible to carry out a comprehensive review of all the different models that have previously been developed as aids to benchmarking. For convenience, in the Case Studies presented in Part 2 of the Report, we have illustrated the potential strengths and weaknesses of such approaches through the application of one such model, SCRAM. This model was chosen because it already included a full dataset for HBCDD within its standard set of comparator substances. However, it should be noted that the case studies identified some potential weaknesses in this particular model regarding the grouping and scoring of

[63] Additional information on the UK Biobank project is available at Internet site http://www.ukbiobank.ac.uk/

information across different health and environmental endpoints. In particular, the scores assigned under the model criteria were felt to not necessarily reflect an ideal approach for application outside the scenario for which it was originally developed (i.e. study of contamination of the American Great Lakes).

It is suggested that there may be some value in carrying out a comprehensive review of the various model approaches that have been published to assess the extent to which these may meet the requirements for a system to conduct benchmarking under REACH. Such a review would need to include consideration of the types and level of information that may be of most value to decision makers, the need to provide information on specific health indicators and on a chemical's hazard profile in relation to health and the environment overall, and how best to address uncertainty and the relative weighting that should be given to particular properties that may be possessed by chemicals.

9.3.5 Life Cycle Impact Assessment

As part of the study, the potential for using the existing LCIA models to support exposure and impact assessment has been reviewed. This was also a topic for discussion at the expert workshop.

The conclusions are that for such models to be applicable to REACH, they may need to be reconfigured or modified so that they are more consistent with the concepts used in REACH risk assessments. This could start with a review of data underlying both REACH and LCIA, for example, as part of a workshop between chemical risk assessors and LCIA specialists. Recommendations on future research and the steps required to bridge the gap between these two areas could then be developed for further consideration.

9.3.6 Development of a Hazardous Chemicals Ecosystem Services Concept

The 'ecosystem services' approach is recognised as a powerful tool for establishing the potential socio-economic importance of the goods and services provided by the environment. However, it is not necessarily easy for those unfamiliar with the concept to make linkages between the types of impacts that hazardous chemicals can have on the environment and the outputs from risk assessments.

This suggests that there may be value in developing more explicit guidance on how to link the two. For example, this would include identifying those classes of services most relevant to the hazardous chemicals context and more specific details of the potential implications for the different functions and services falling into the classes. A series of practical examples would also help illustrate these linkages.

9.3.7 Valuation of Changes in Health or Environmental Impacts

The study has highlighted:

- the potential value of having more comprehensive tables setting out valuations developed in the past for both different health and environmental effects. A starting list of these has been provided in Part 2, but further work should be undertaken to develop a more consistently based set of figures and to carry out a more systematic review of the literature. In this regard, care should be given to identifying valuations derived through the different valuation methods and to make clear any caveats that should be attached to the use of different valuations (e.g. when it may be appropriate to use a VOSL and when a VOLY would be more appropriate);

- in the case of health, the development of more comprehensive data sets should include figures for DALYs (or QALYs) assigned to different disease cases; this should include data not only on the development of clinical diseases but also other possible chemical mediated changes which may influence 'well-being' or life-chances, such as infertility and minor IQ loss;

- that the most work is required in relation to the environment, where there would appear to be both a lack of relevant valuation studies but also a lack of previous studies examining how some of the techniques used in risk assessment can be applied within an impact pathway approach to provide the basis for increased economic analysis. This includes both a lack of species specific to mesocosm studies, as well as studies concerning the impact of reductions in low levels of chemical contamination to environmental quality improvements and the implications of these for habitats and ecosystems; and

- the study has also highlighted a need to carry out new WTP studies with the aim of developing valuations for the types of effects most likely to be addressed by the restriction and authorisation processes under REACH. In particular, there may be value in carrying out studies into people's willingness to pay to avoid the unknown future damages, such as those that might be associated with vPvB chemicals. However, there is also a need to undertake more general studies into people's willingness to pay for reductions in environmental exposures for particular types of ecosystems to toxic chemicals and for avoidance of certain types of health effects that are not currently covered by the wider health valuation literature.

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