Institute for Environment and Health

A review of prioritisation methodologies for screening chemicals with potential human health effects as a result of low-level environmental exposure

IEH Web Report W13 **APRIL 2004**

The Institute for Environment and Health was established by the Medical Research Council at the University of Leicester in 1993. The Institute is principally funded by UK Government Departments and Agencies by way of specific research and consultancy contracts.

This report was prepared by the MRC Institute for Environment and Health for the Department of Health and issued as a Client Report in May 1999.

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Please cite as:
IEH (2004) *A Review of Prioritisation Methodologies for Screening Chemicals with Potential Human Health Effects as a Result of Low-Level Exposure* (Web Report W13), Leicester, UK, MRC Institute for Environment and Health, available at http://www.le.ac.uk/ieh/

ISBN No. 1 899110 74 7

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1 Aims and Objectives

Environmental chemicals are substances present in the environment as a result of human action, intentional or unintentional. They may be natural or anthropogenic in origin and organic or inorganic (Mücke *et al.,* 1986). This definition covers over 100 000 industrially used substances that are currently listed worldwide, and many preparations and mixtures, amounting altogether to several hundred million tonnes being emitted into the environment each year (Mücke *et al.,* 1986). Several hundred new substances are added annually.

Because of the large number of chemicals released into the environment annually, it is not feasible to conduct assessments of human exposure and possible associated health effects for all 'new' and 'existing' chemicals[a]. Even if the necessary resources were available, in most cases sufficient, reliable data on hazards of chemicals to human health, are likely to be absent (Dominguez, 1991). This has led to the development of schemes for prioritising compounds likely to be of significance to human health. A 'priority' chemical is one that, because of its importance, however defined, should be examined with greater urgency and in preference to other chemicals. Prioritising chemicals maximises the value obtained from limited resources for risk assessment by directing research towards those of greatest concern. Gaps in the data available may be identified during prioritisation. Clearly, there are complex difficulties in developing any prioritisation scheme and judgement must be used in establishing the criteria. As an example, if a substance is very toxic, but produced only in small quantities, how would it be prioritised against a substance that was only slightly toxic but supplied in high tonnage. Future research efforts may then be directed towards developing the essential information needed for regulatory activity.

This study was commissioned by the UK Department of Health (DH) as part of a broader research programme aimed at identifying key chemicals of concern at routine levels of exposure so that more detailed risk assessments could then be conducted on those compounds prioritised as being of greatest importance. This study aimed to review critically the existing screening methods for the prioritisation of environmental chemicals. The information obtained in this review was then used to produce a dedicated priority setting method capable of identifying chemicals in air, water, soil and foodstuffs that might cause significant adverse effects to human health following low-level exposure with a view to identifying data gaps and compounds that might require UK Governmental attention (IEH, 2004).

The IEH screening methodology was developed for existing chemicals only, as preliminary evaluations are required before new chemicals are made available commercially (see Section 2). The application of default categories in the prioritisation schemes for chemicals with no data was also considered. The priority list resulting from application of this screening method will potentially assist evaluation and implementation of activities for reducing environmental risks, although the costs of such risks to human health and the costs of concomitant reduction measures will also need to be taken into account.

This review includes an introduction to European Union (EU) legislation and existing governmental prioritisation schemes (Section 2), and an outline of the purposes and principles of prioritisation and the different methods and scoring systems used by different organisations for screening chemicals for human exposure and adverse human health effects (Section 3). Bearing in mind the purposes of the DH prioritisation scheme and shortage of reliable UK data, the advantages and disadvantages of different published methodologies are identified and evaluated in Section 4. Section 5 lists some recommendations for improving prioritisation methodologies. From the final evaluation, a prioritisation scheme is presented in Section 6 (also incorporating other published methodology where

[a] Substances placed on the European market after 18 September 1981 are classified as 'new' substances

appropriate) for the production of a priority list of chemicals for DH. Conclusions are presented in Section 7.

2 Background Information on European Union Legislation Relating to Prioritisation of Environmental Chemicals

Over 100 000 commercial chemical substances have been declared as supplied to the European Union (EU) market between 1 January 1971 and 18 September 1981. These are listed on the European Inventory of Existing Commercial Chemical Substances (EINECS[a]) as 'existing' substances. Substances placed on the EU market after 18 September 1981 are classified as 'new' substances.

Before a new substance can be introduced into the EU market it must be tested and notified to the appropriate Member State authority. In addition, regulatory agencies require the collection of extensive further documentation on safety, including toxicity testing, before a chemical can be used in foods or certain types of commercial product. This information is studied by the relevant authority in order to assess the intrinsic hazardous properties of a substance and, using the limited information normally supplied about exposure, to conduct a preliminary evaluation of human health risk (Shillaker, 1992).

Regulatory appraisal of new substances supplied to the EU market is achieved through the 7th Amendment (92/32/EEC) to the Dangerous Substances Directive (67/548/EEC). In the UK the requirements of this directive are implemented by the Notification of New Substances Regulations 1993 (NONS 93[b]) (TSO, 1993). Specified technical information is required for new substances on the basis of tonnage, in order to evaluate possible foreseeable risks, whether immediate or delayed, that a substance may pose to man and the environment. In the case of substances notified under this scheme, suppliers must provide a 'base set' of data for all new substances supplied at 1 tonne per annum, a more limited data set for substances supplied at 100 kg per annum, and for those supplied at 100 and 1000 tonnes per annum, more extensive data are required. The exact toxicological information required is dependent on tonnage but the base set includes the following.

- **Physicochemical properties:** melting point, boiling point, relative density, vapour pressure, water solubility, and *n*-octanol–water partition coefficient.
- **Toxicological data:** acute toxicity via oral, dermal or inhalation routes, skin sensitisation potential, irritancy, subacute toxicity (28 day study), mutagenicity (two tests), reproductive toxicity and toxicokinetic information.
- **Ecotoxicological data:** acute toxicity to fish and daphnia and growth inhibition of algae.

The Existing Substances Regulation (Council of the European Communities, 1993) requires data on existing substances produced/imported in amounts exceeding 10 tonnes per annum to be submitted to the European Commission (submission deadline determined by tonnage). Implementation of the regulation can be divided into four main stages: (1) data collection, (2) priority setting, (3) risk assessment and, if necessary, (4) risk reduction. All risk assessments of new and existing chemicals must be conducted in accordance with guidelines set out in the Technical Guidance Document on risk assessment of new and existing chemicals (European Commission, 1996[c]).

[a] See http://ecb.jrc.it/existing-chemicals
[b] See http://www.hse.gov.uk/hthdir/noframes/nons/nons2.htm
[c] The second edition of this document is available [April 2003] at http://ecb.jrc.it/tgdoc

The Existing Substances Regulation also requires that manufacturers/importers provide a base set dossier of information on a substance. The regulation aims to identify priority substances for further evaluation (DoE, 1993); however, no guidance or methodology on how this should be achieved is provided. A European Union Risk Ranking Method (EURAM) was published by Hansen *et al*. (1999) in response to the priority setting requirement of the Existing Substances Regulation. The objective of this scheme was the ranking of EU existing substances on the basis of their potential risk to the environment and human health using an exposure–effect model. Data for this method are obtained from the International Union Chemical Information Database (IUCLID) (Heidorn *et al.,* 1996). The application of formalised priority setting procedures reduces the large number of substances and associated data sets that need to be fully evaluated to meet the requirements of the regulation. Clearly, priority setting is a critical preliminary stage of any effective, systematic programme for dealing with existing chemicals.

The number of substances likely to fall within the scope of the Existing Substances Regulation has been estimated to be about 100 500, of which approximately 2000 substances are produced or imported into the EU in quantities exceeding 1000 tonnes per annum (i.e. high production volume chemicals (HPVCs)) (Shillaker, 1992). Clearly, it is not feasible to conduct risk assessments on all substances to identify those of concern and the use of a priority list to identify important chemicals (on the grounds of human exposure levels and toxicity) for risk assessment is an important tool for governmental decision-making. A large number of governmental prioritisation schemes have been published. Some of these are introduced in Table 3.1. Throughout this review, many of these prioritisation methods are used as examples of different approaches to prioritising chemicals.

3 General Principles of Prioritisation

3.1 Introduction

Before prioritising environmental chemicals, it is important to identify the reasons why this is being done and the ultimate aim for which a priority list is being produced. Priority lists of environmental chemicals are most commonly produced for one or more of the following purposes:

- to establish research priorities by identifying data gaps that warrant investigation;
- to develop regulatory activity/set regulatory action priorities (e.g. governmental legislation concerned with chemicals of importance to human health);
- to target pollution prevention efforts (e.g. prioritise types of chemical emissions with greatest potential for human health risk);
- short-listing chemicals for specific assessment;
- review activity (i.e. prioritisation of chemicals to assess existing knowledge to obtain an overall view of current status);
- data gathering with the aim of producing chemical databases (e.g. IUCLID[a]); and
- risk assessment (helps justify using resources on the most important chemicals and justifies exclusion of other less important chemicals).

A large number of ranking schemes have been developed by European and US governmental agencies to prioritise environmental chemicals of concern (Table 3.1). Some are specialised methods (e.g. the method developed by the Ministry of Agriculture, Fisheries and Food (MAFF[b]) to screen organic chemicals for inclusion in a programme of surveillance of these chemicals in UK food; Wearne *et al.,* 1996) while other methodologies are more generic and aimed at prioritising large numbers of compounds, for example, the screening of new and/or existing substances for regulatory purposes (e.g. HSE, US-EPA/CHEMS-1 methods; Table 3.1). On the whole, published governmental prioritisation schemes do not follow a rigorous scientific approach on how to deal with data gaps and missing data and no international consensus has been established on how to deal with such problems (Pedersen *et al.,* 1995). In addition, the stated objectives for the prioritisation and the scoring methods used for chemical screening can vary quite considerably between governmental schemes. Such discrepancies can create serious problems for international bodies comparing priority listed chemicals derived by different governmental agencies, both within Europe and globally. A number of international workshops have been held to promote standardisation and consistency in prioritisation schemes, for example the Society for Environmental Toxicology and Chemistry's (SETAC) 'Chemical Ranking and Scoring' workshop (Swanson & Socha, 1997) and the US Environmental Protection Agency's (EPA) 'Workshop on Identifying a Framework for the Future of Human Health and Environmental Risk Ranking' (EPA, 1994).

A prioritisation scheme functions to identify a short list of chemicals that rank highest when scored according to a number of different screening criteria. To produce an overall ranking of chemicals, scores resulting from application of individual screening criteria are weighted and the chemicals are

[a] International Union Chemical Information Database; see http://ecb.jrc.it/existing-chemicals
[b] Now part of the Department for Environment, Food and Rural Affairs (Defra)

ranked in order of increasing total score. Prioritising environmental chemicals is an approach towards identifying the level of concern with which a chemical should be associated. Criteria that are commonly used to screen chemicals on the basis of their potential to cause human health effects include extent of environmental emissions, potential for human and environmental exposure and likely human toxicity. For each criterion, one or more different parameters are used to calculate/predict scores for chemicals. Physicochemical properties are most commonly used to predict environmental fate and behaviour of chemicals, and toxicity data (e.g. lethal concentration/dose causing 50% mortality; LC_{50}/LD_{50}), to predict human health effects. It could well be argued, however, that the results of acute lethality tests such as LC_{50}/LD_{50} are not particularly relevant to the effects of low-level environmental exposure.

Chemicals for which there are no data for a particular screening criterion, are usually assigned a default value. This value can be made high or low depending on the approach of the prioritisation scheme. Some approaches attach importance to chemicals for which there are no data in order to highlight the need for research, whereas others are only interested in chemicals for which there are adequate data available for screening. The process of classification/scoring chemicals can be pursued *ad infinitum*, culminating in a large number of groups and divisions. The extent to which this is taken depends on the purpose of the prioritisation scheme, the number of classification criteria available and the data available for ranking. It is essential, however, that a list of priority scores is not seen as a rigorous ordering of substances but rather as a means of highlighting individual substances, or groups of substances for further assessment. A representative conceptual model illustrating a typical sequence of screening in prioritisation schemes is presented in Figure 3.1.

Table 3.1 Examples of governmental schemes used to prioritise environmental chemicals according to their potential for human exposure and toxicity for regulatory purposes

Screening method	Prioritisation objective	Reference
HSE UK Health & Safety Executive	Prioritisation of EU new and existing substances for the 7th Amendment (92/32/EEC) to the Dangerous Substances Directive (67/548/EEC) for human exposure and potential associated health effects	Shillaker (1992)
MAFF[a] UK Ministry of Agriculture, Fisheries & Food Steering Group on Chemical Aspects of Food Surveillance	Prioritisation of manufactured organic chemicals on the basis of potential human exposure and health effects, for inclusion in a programme of surveillance of priority chemicals in food in the UK	Wearne *et al.* (1996)
US-EPA (CHEMS) US Environmental Protection Agency Chemicals Hazard Evaluation for Management Strategies	Prioritisation of hazardous chemicals for potential human health effects and environmental impact	Davis *et al.* (1994)
CHEMS-1 Chemicals Hazard Evaluation for Management Strategies	Update of US-EPA (CHEMS) method, to include a release weighting factor and new improved scoring algorithms	Swanson *et al*. (1997)
European Union Risk Ranking Method (EURAM)	Ranking of EU existing substances for risks to environment and human health using an exposure–effect model	Hansen *et al.* (1999)
German Method German Environmental Priority Setting System	Prioritisation of EU existing substances for potential to cause environmental and human hazards	Weiss *et al*. (1988)
CEPA Canadian Environmental Protection Agency Second Priority List	Prioritisation of substances for human exposure, human health effects and environmental hazards for the Minister's Expert Advisory Panel on Priority Substances	Koniecki *et al.* (1997)
DETR[a]**/WIR** Department of the Environment, Transport and the Regions/Water Industry Research	Prioritisation of organic chemicals for contamination of groundwater and human food chain uptake via crops and livestock	Duarte-Davidson and Jones (1996); Wilson *et al*. (1996)
CMR Critical Materials Register Michigan State Department of Natural Resources	Prioritisation of water pollutants for human uptake and potential associated health effects for regulatory purposes in the Great Lakes Region	EPA (1994)
Italian Method	Priority selection and risk assessment of EU existing substances	Sampaolo and Binetti (1989)
NCM Nordic Council of Ministers Guide to Environmental Hazard Classification	Prioritisation and classification of chemicals in the EU for environmental and potential ecotoxicological effects	Pedersen *et al*. (1995)

[a]Now part of the Department for Environment, Food and Rural Affairs (Defra)

Ideally, prioritisation methods should be flexible enough to incorporate new data and concerns and be able to serve a variety of purposes. To be practicable, they also need to be transparent and interactive. In order to be cost effective, prioritisation schemes must be simple, rapid and reasonably accurate. Some ranking systems attempt to condense all available data into a single score for each chemical for the purposes of quick referencing. However, overextensive simplification of data has limitations, since important information must be sacrificed to facilitate the scoring.

A representative example of a governmental prioritisation scheme is that developed by Koniecki *et al.* (1997) for the Canadian Environmental Protection Agency (CEPA). This particular scheme is tailored for screening substances in the Canadian environment and aims at identifying priority substances other than pesticides, drugs, food additives and flavouring substances. It has reduced the number of substances under consideration from an initial list of >600 substances down to 133.

Various techniques have been published and used for decision analysis in prioritisation. Each has different applications and varying degrees of success. In prioritising procedures for environmental issues associated with hazardous chemicals, provision can be made for the influence of socioeconomic and political factors in addition to the results of the technical assessment. A summary of these factors is given in Table 3.2 (Chicken & Hayns, 1989; EPA, 1994). Some of the more sophisticated ranking/prioritisation protocols therefore incorporate non-technical screening criteria, based on cost–benefit analysis, public perception of risk, considerations of practicability and concern for equity and/or sustainability concepts, to supplement the technical assessments of risks (HSE, 1997). Ranking systems with more than one selection criterion are termed Multi-Criteria Analysis (MCA) methods (HSE, 1997).

It is often necessary to modify ranking systems to meet specific needs. A large number of screening methods are available for prioritising chemicals, varying from broad generic methods for large groups of compounds (e.g. aromatic hydrocarbons) to highly specialised methods for screening closely related chemicals (e.g. polychlorinated biphenyls) for a specific purpose. In specialised methods, selection criteria are defined and tailored to meet the specific requirements of the scheme (e.g. DETR/WIR method; Duarte-Davidson & Jones, 1996; Wilson et al., 1996). Understandably, screening/selection criteria used in prioritisation schemes should always be dependent on the nature of the decision being addressed or the purpose of the prioritisation.

The two most important aspects of prioritising environmental chemicals on the basis of their potential effects in humans are the degree of exposure to a chemical and its toxicity. Chemicals reach environmental compartments indirectly (e.g. atmospheric deposition, leaching, etc.) or directly (chemical spills, industrial discharges, application of pesticides to soils and foliage). Compounds will only be of concern to human health in the first instance if they are ‘bioavailable’ via the skin, ingestion or inhalation after humans are exposed to the chemical from air, soil, water or foodstuffs. Various models have been developed to estimate the distribution and fate, and hence the likely exposure levels, of chemicals in different environmental media and compartments as a first step in identifying potentially hazardous chemicals. These models usually use physicochemical properties of chemicals to predict fate and behaviour in the environment.

Once a chemical has been identified as having the potential to be taken up by humans, the question then asked is whether the chemical is toxic to man at a specified environmental level and duration of exposure. This may be short or long-term exposure in the home (domestic), exposure at work (occupational) and/or regular exposure to ambient environmental levels in air, soil, food or water. The analysis of exposure parameters is often complicated by the generally low concentrations of chemicals in the environment, the large size of human populations and the diverse ecosystems involved.

Figure 3.1 Conceptual model of a representative prioritisation scheme

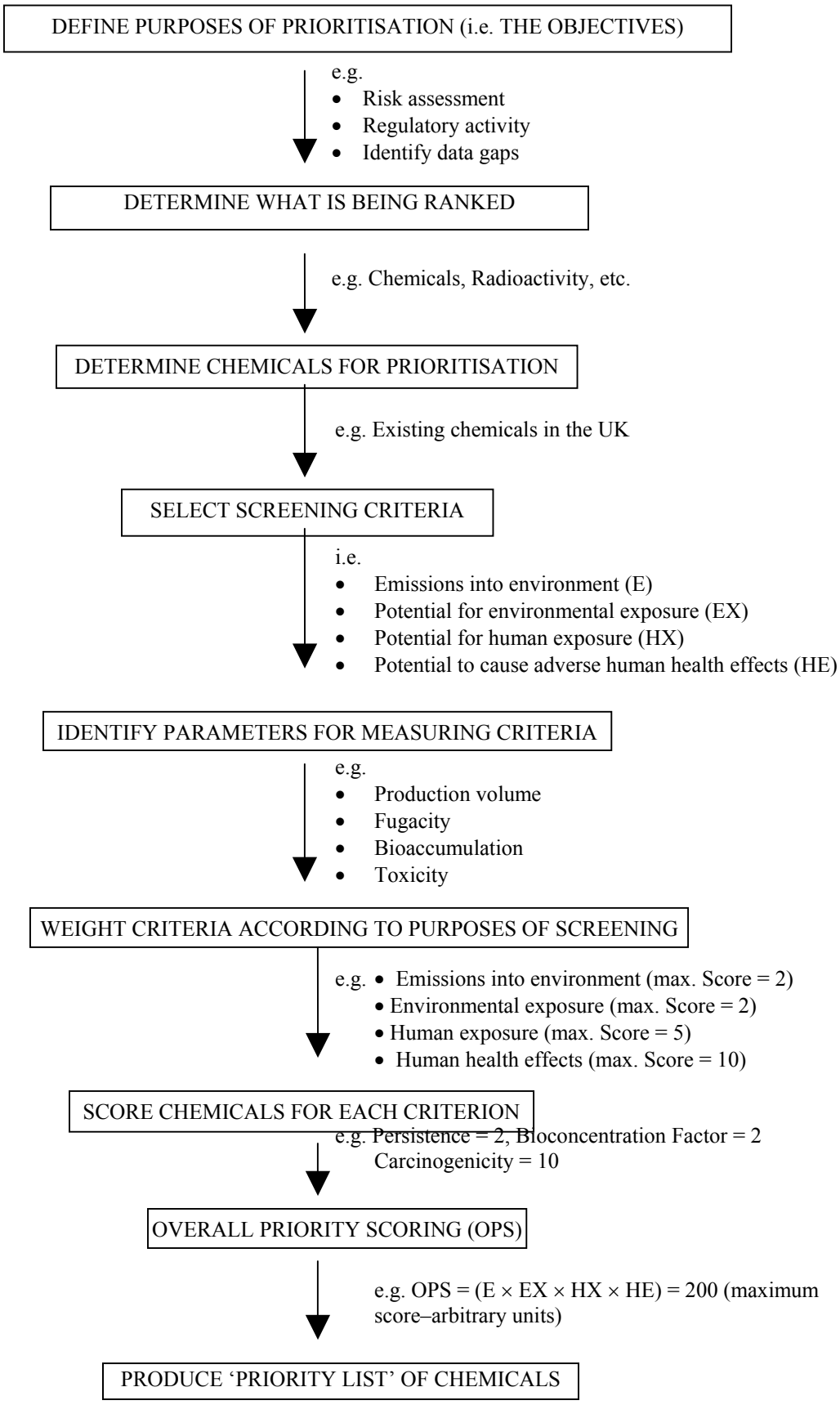


Table 3.2 Some factors considered in ranking systems for prioritising acceptability of risk

Factor	Nature of risk	Possible combination of factors
Economic	Less than optimum benefit from financial commitment	Marginal cost of saving life Payoffs Index of harm/benefit Cost–benefit analysis Supply and demand Value of life Cost of saving life
Sociopolitical	Public opposition	Results of public enquiry Public acceptability Political climate Views on current quality of life

From Chicken and Hayns (1989) and EPA (1994)

Human exposure to environmental chemicals is associated with a number of factors, such as: use in open-system applications and release into the environment (intentionally, incidentally or accidentally) in high production quantities; relative resistance to degradation; potential to move from one environmental compartment to another; and susceptibility to bioaccumulation through the food chain. Screening criteria, typically physicochemical properties, emissions data and pattern-of-use information, are used to identify which environmental chemicals are more likely than others to result in human exposure. Of these chemicals, the ones that are of greatest concern to human health are chemicals that cause chronic and/or acute toxic effects in animals. This provides a second stage of screening for chemicals, one based on potential human health effects.

Screening studies for acute and chronic toxicity in animals are widely used to predict a chemical's potential for causing adverse human health effects. However, it can be difficult to attribute an effect in humans to exposure to a specific environmental chemical, since individuals are usually exposed to complex mixtures of chemicals in the environment. The influence of antagonistic/synergistic effects between chemicals can impede attribution of particular toxic effects to specific chemicals. Animal studies on individual substances are therefore frequently used as predictors of effects in humans.

Prioritisation schemes aim to identify chemicals that are a risk to humans as a result of their presence in the environment by assessing their potential for human exposure and their potential to cause human health effects. The majority of published methods use a selection of widely accepted screening criteria including:

- emissions into the environment;
- fate and behaviour in the environment;
- potential for uptake by plants and animals from the environment;
- bioaccumulative potential in food/prey species;
- acute toxicity; and
- chronic toxicity.

The ways in which chemicals are screened using each of the above criteria can vary considerably between methods, depending on the group of environmental chemicals being examined, the environmental compartment in which they are found, and the routes and levels of human exposure. Scores assigned to chemicals during screening are combined using integrative algorithms to produce an overall priority score. The approaches to integrating scores can also vary widely between methods.

Consequently, for the purposes of this review, each of the above screening criteria will be discussed separately.

3.2 Exposure: Screening criteria and priority scoring

3.2.1 Emissions into the environment

Annual production or importation tonnage is of major importance in prioritising chemicals, particularly in governmental prioritisation schemes. The HSE method (Shillaker, 1992) for prioritising EU new and existing substances for human exposure and associated health effects under the 7th Amendment of the Dangerous Substances Directive (92/32/EEC) and the MAFF method (Wearne *et al.,* 1996) both use production volumes to rank chemicals for potential emission into the environment. Production volume provides an indication of the potential magnitude of environmental contamination by a chemical and the possible degree to which humans may be exposed to it. The HSE method, a simple model designed for prioritisation of high production volume chemicals (HPVCs), uses tonnage as an indicator of exposure, to prioritise chemicals in EINECS[a] whereby:

Tonnage Score = $\log_{10}$ (tonnage value) (1)

e.g. chemical produced at 10 000 tonnes per year scores a value of 4.0

It is also important to know the main patterns of chemical use in order to understand the potential of a chemical to contaminate air, soil, water, food and humans. A simple 'pattern of chemical use' classification scheme is used by a number of prioritisation schemes to screen chemicals according to the amounts emitted to the environment (e.g. HSE, EURAM methods; Table 3.1). The scheme is as follows:

- **Use in a closed system:** in these situations, chemical exposure is very limited because the chemical remains within a reactor or is transferred from vessel to vessel through closed pipework (including transportation), with the only losses being attributable to accidents/spills. However, some chemicals used in closed systems may eventually be released into the environment after use, potentially leading to human exposure. These chemicals are consequently classified as non-dispersive or of wide dispersive use.

- **Use resulting in inclusion into/on to a matrix:** in these cases, human and environmental exposure to a chemical is not possible because the chemical becomes permanently incorporated into or on to a non-degradable matrix (e.g. co-polymers in plastics) thereby preventing release under normal conditions. In exceptional circumstances, the chemical may be released during use or following disposal (e.g. release of textile impregnating agents after use) requiring re-classification of chemicals to non-dispersive or wide-dispersive use categories.

- **Non-dispersive use:** relates to chemicals used in the workplace by trained personnel. In these cases environmental and human exposure is limited due to protective measures employed during use, except when/if the chemical is released into the environment as a point source following use.

- **Wide dispersive use:** relates to chemicals that are released directly into the environment from a wide range of activities, leading to human exposure during use (e.g. household detergents and solvents).

The HSE system scores use in a closed system as 1, use resulting in inclusion into or on to a matrix as 2, non-dispersive use as 3 and wide dispersive use as 5 (Shillaker, 1992).

[a] European Inventory of Existing Commercial Chemical Substances (see http://ecb.jrc.it/existing-chemicals/)

The EURAM ranking method takes European production volume and main use data from IUCLID to derive a combined tonnage and pattern of use score, as follows (Hansen *et al.,* 1999):

Emission = $(0.01 \times T_I) + (0.1 \times T_{II}) + (0.2 \times T_{III}) + T_{IV}$ (2)

T_I, tonnes produced/imported of a chemical used in closed systems, or with no use or where there are no data (i.e. also a default score); T_{II}, tonnes produced/imported with use resulting in inclusion of chemical into or on to a matrix; T_{III}, tonnes produced/imported with non-dispersive chemical use; and T_{IV}, tonnes produced/imported with wide dispersive chemical use

The use of production volume and pattern of use scores is an over-simplified approach to exposure assessment as these scores do not take into consideration the environmental matrix into which HPVCs are released (e.g. air, water, landfill site). Another limitation of using these two parameters to prioritise chemicals is the paucity of reliable data for the UK in the open literature. Although production volume and production capacity data are available for some chemicals from commercial reports (Wearne *et al.,* 1996), these sources of information are often out of date and therefore may not reflect current emissions. In many cases, even though data are available, they cannot be used as they are contained in confidential industrial reports. Overall, prioritising chemicals on the basis of production volume and pattern of use serves as a useful pre-screen.

3.2.2 Fate and behaviour in the environment

Physicochemical properties may be used to predict a chemical's behaviour and its ultimate fate in the environment (air, water, soil/sediment, vegetation or food chain). Transfer of a chemical from one environmental compartment to another is dependent on the physicochemical properties of the chemical and the physical processes involved. Air–soil and air–water transfer of a chemical can be predicted using mathematical models incorporating physicochemical properties (ECETOC, 1992; Table 3.3). Dispersion models are also available for the estimation of background contamination levels associated with point source chemical release. The main routes of chemical transfer between environmental compartments are discussed below.

3.2.2.1 Behaviour in air

Chemicals can be emitted to air from point sources (e.g. car emissions, incinerators, cigarette smoke) and diffuse sources (e.g. by-products of industrial processes involving combustion, chemical reaction products, volatilisation from water or soil/sediment). Chemicals can also be transferred to air by mechanisms other than volatilisation from soil or water. The main mechanisms of chemical cross-transfer between air and other environmental compartments are summarised in Figure 3.2. Volatile chemicals may change physical state from a liquid or solid to a vapour or may become associated with particulates that become airborne (Figure 3.3). The tendency of a chemical subsequently to remain airborne is of great importance in predicting the environmental fate of chemicals in air. Particulate air pollutants can remain suspended in air for some time before being deposited onto soil (Philp, 1995). Dispersion of airborne chemicals, once released into the environment, is subject to the physical processes associated with the weather.

The environmental fate of airborne chemicals is dependent on physical processes associated with chemical persistence, such as resistance to degradation (mainly by photolysis), wet or dry deposition and re-volatilisation. Wet deposition is defined as the absorption of a chemical into aqueous droplets followed by precipitation, while dry deposition is defined as the adsorption or absorption of a chemical at the earth's surface to soil, water or vegetation (ECETOC, 1992). Deposition is the main route of transfer of atmospheric pollutants from air to other environmental compartments. It can lead to contamination of groundwater, soil and vegetation and hence lakes, rivers and the sea (Philp, 1995).

The environmental fate of airborne chemicals can be predicted using physicochemical properties. Atmospheric half-life ($T_{1/2}$) data can be used to estimate chemical persistence in air while the Henry's Law Constant (H_c) can be used to indicate volatility (Table 3.3). Half-lives ($T_{1/2}$) in air have been used

by Bunce and Schneider (1994) to screen persistent chlorinated aliphatic compounds in rural and urban atmospheres. The $T_{1/2}$ of compounds was estimated by using mathematical models that take into consideration photolysis and/or reaction with OH radicals. However, there tends to be a paucity of concentration measurements in rural and urban atmospheres, which gives rise to data gaps for methods using $T_{1/2}$ to screen persistent chemicals in air.

Table 3.3 Physicochemical properties employed to calculate cross-compartmental transfer

Physicochemical property	Model	Ranges	Reference
Water Solubility (S) (mg/l) indicates chemical's potential to stay in solution			a
Boiling Point (BP) and Vapour Pressure (V_p) (Pa) indicates chemical's potential to evaporate (at 25°C for V_p)			b
Henry's Law Constant (H_c) (Pa.m^3/mol or dimensionless) indicates a chemical's tendency to volatilise from solution. Can be determined experimentally or estimated	**H_c** = c_{air}/c_{water} Estimated $H_c = V_p/S$	High H_c, chemical likely to volatilise Low H_c, chemical likely to remain in solution	a
Octanol–Water Partition Coefficient (K_{ow} or log K_{ow}) indicates the tendency of a chemical to partition between water and lipid/organic matter (lipophilicity)	**K_{ow}** = c_{oct}/c_{water} Log K_{ow} = log (c_{oct}/c_{water})	High K_{ow}, lipophilic Low K_{ow}, hydrophilic	a, c
Organic Carbon–Water Partition Coefficient (K_{oc}) (cm^3/g) indicates chemical's tendency to adsorb onto organic carbon from solution	**K_{oc}** = c_{oc}/c_{water}	High K_{oc}, adsorbs onto organic carbon from solution Low K_{oc}, leaches from organic carbon into solution	a
Half-life ($T_{1/2}$) rate of loss of a chemical from a system by first-order kinetics due to biodegradation, volatilisation, abiotic degradation etc. Indicates chemical's persistence in the environment.		High $T_{1/2}$, persistent in environment Low $T_{1/2}$, short-lived in environment	a
Biochemical Oxygen Demand Half-life ($BODt_{1/2}$) indicates the rate of a chemical's degradation by microbial metabolism. Is a measure of the number of days required to reduce the BOD from a chemical in water by half due to biodegradation		High $BODt_{1/2}$, resistant to microbial metabolism Low $BODt_{1/2}$, readily metabolised	d
Water–Air transfer	$c_{air} = H_c \times c_{water}$		e
Soil–Air transfer	$c_{air} = (H_c/K_d) \times c_{sol}$		e

c, concentration (mol/m^3); c_{air}, air phase concentration (mol/m^3); c_{oc}, conc. of chemical in organic carbon; c_{oct}, conc. of chemical in octanol; c_{sol}, conc. of chemical in solid phase (mmol/kg); c_{water}, conc. of chemical in water phase (mol/m^3); K_d, adsorption coefficient between solid and water (l/kg)

[a] Wilson *et al.* (1996), [b] Shillaker (1992), [c] Isnard and Lambert (1988), [d] Davis *et al*. (1994), [e] ECETOC (1992)

Figure 3.2 Main mechanisms of chemical cross-transfer between air and other environmental compartments

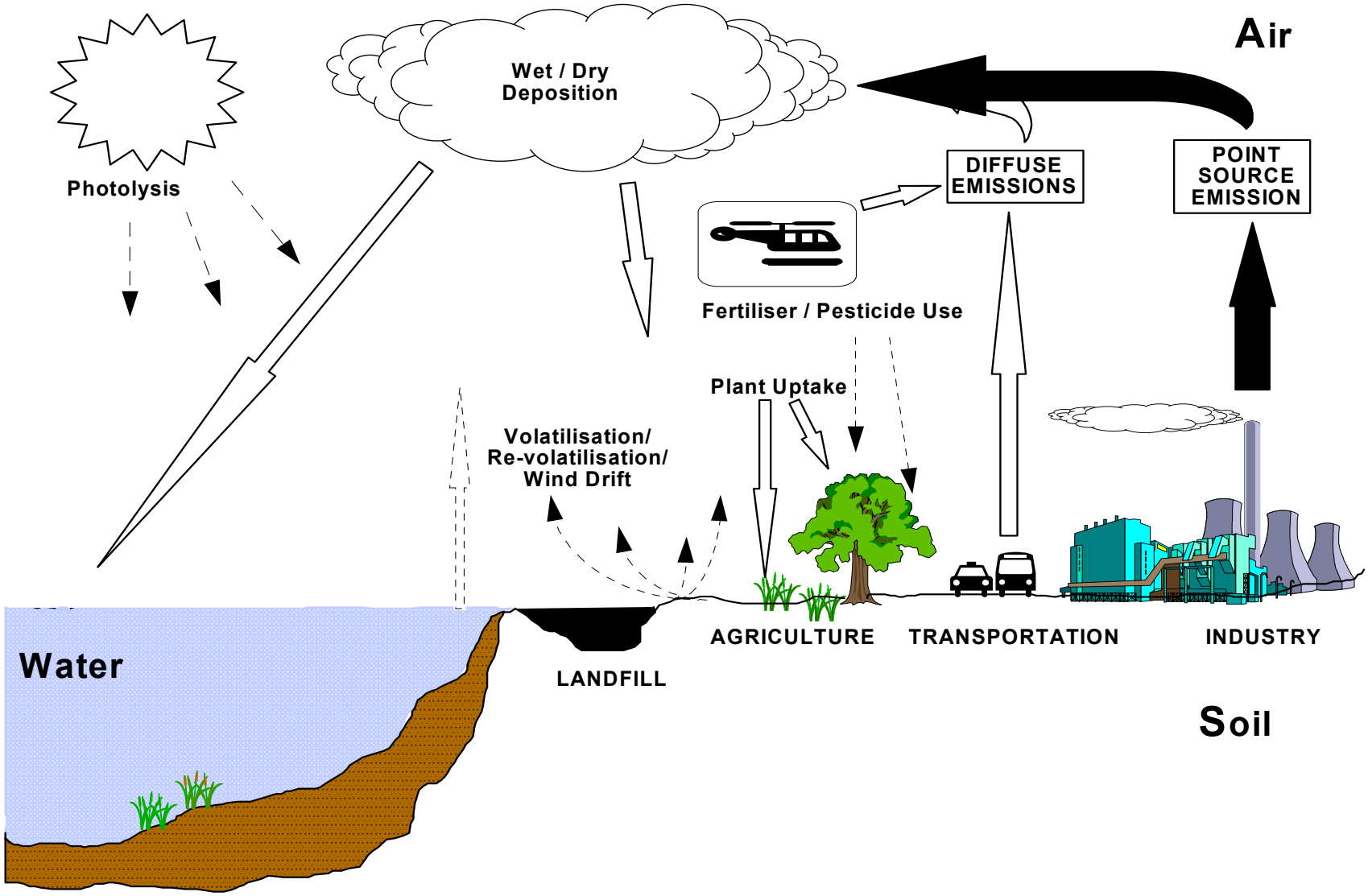
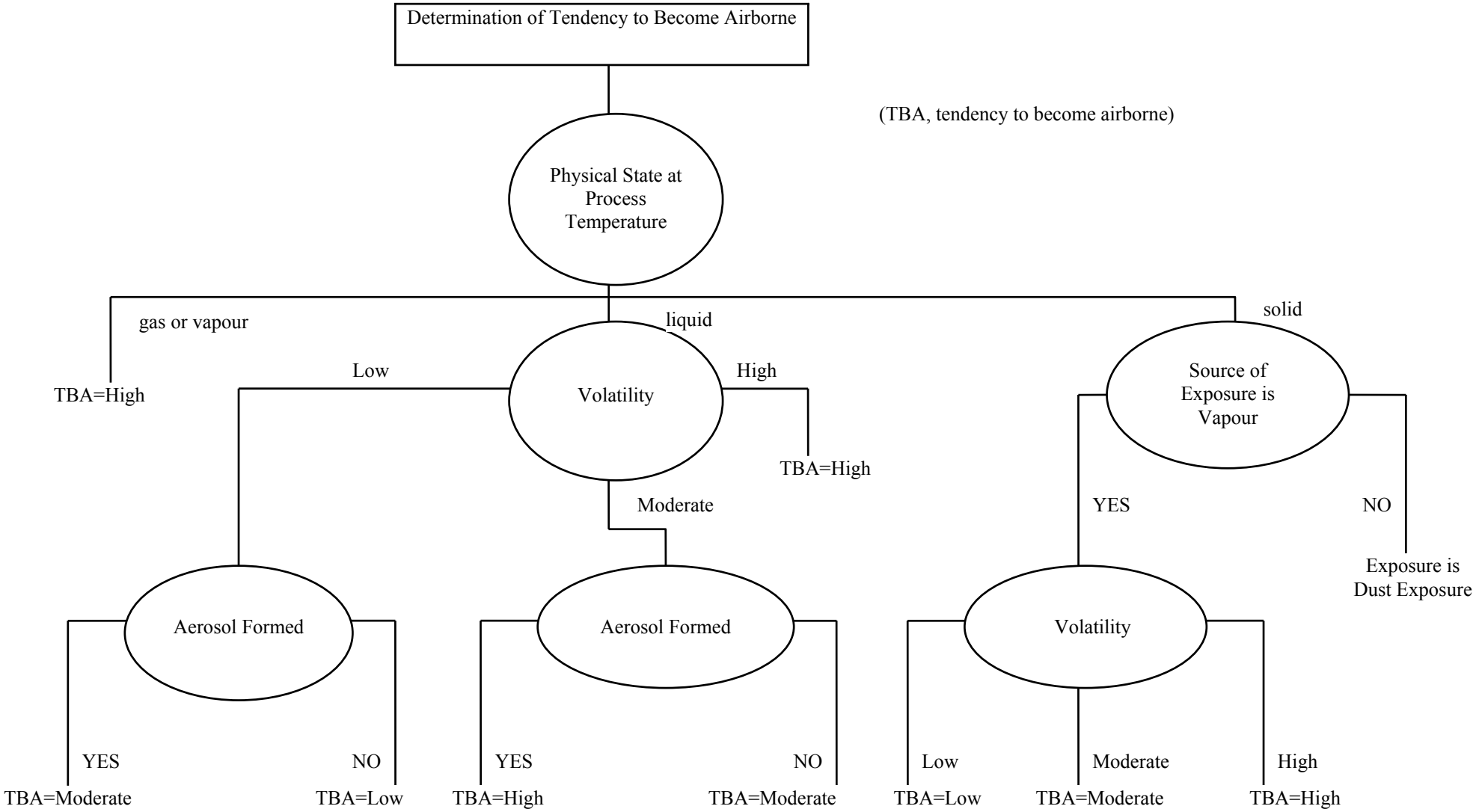


Figure 3.3 Determination of the tendency of a chemical to become airborne (from European Commission, 1996)



3.2.2.2 Behaviour in soil/sediments

The behaviour of environmental chemicals in soils and sediments is important to our understanding of their potential for contaminating water (e.g. groundwater), vegetation and the food chain (aquatic and terrestrial). Chemical emissions to soils and sediments can be from point sources (e.g. seepage from oil/petrol tanks) or diffuse sources (e.g. sedimentation of chemicals onto aquatic sediments from the water column). The loss of contaminants from soils is often biphasic: a preliminary phase of rapid dissipation is followed by a slower rate of loss. The processes responsible for loss of contaminants from soil include volatilisation, leaching to groundwater or run-off, biodegradation and chemical degradation (Beck *et al.,* 1995). When a chemical enters the sub-surface, it is subject to several chemical forces that influence its fate and the rate at which it is transported through the underlying soil and rock to groundwater, as defined in Table 3.4 (Kargbo, 1994). The primary factors limiting the loss of a contaminant from soil are sorption/desorption processes, although other chemical processes such as ionisation, cosolvation and chemical speciation will also influence the fate of a chemical in the soil. In addition, the overall loss of organic contaminants from soils is dependent on environmental factors such as organic content, soil type, temperature, pH, precipitation, cultivation and drainage.

Physical processes and the characteristics of the soil in the vicinity of a contaminant source will also affect the potential of chemicals to move from the soil to other environmental compartments, since both strongly influence the fate of the contaminant. The main mechanisms of chemical transfer between soil and other environmental compartments are presented schematically in Figure 3.4. The kinetics of sorption/desorption mechanisms, in particular, control the distribution of contaminants between the solid, aqueous and gaseous phases in the soil, and consequently the susceptibility of contaminants to dissipation processes (Beck *et al.,* 1995). Slow sorption can therefore be a serious impediment to biological or conventional remediation of contaminated soils and aquifers (Pignatello, 1993). Chemicals sorbed to soil particles are less available to air, water and uptake by plants, which therefore reduces environmental and food chain exposure from these sources.

Degradation or the volatilisation of chemicals to air are primarily responsible for removal of chemicals from soil (Beck *et al.,* 1995; Wilson *et al.,* 1996). Persistent chemicals will remain in soil and thus be available for compartmental transfer and/or food chain uptake. Persistence of a chemical is therefore an important factor for estimating human exposure and is widely used as a screening parameter for prioritising environmental chemicals. The main types of degradation are microbial metabolism (biological) and photodegradation (physical). Half-life data are typically used in prioritisation schemes to predict chemical persistence. Short half-lives ($T_{1/2}$) are indicative of extremely volatile, water soluble and/or easily degraded chemicals. Long half-lives ($T_{1/2}$) are indicative of non-volatile, relatively water insoluble, chemicals with a high affinity for the solid phase.

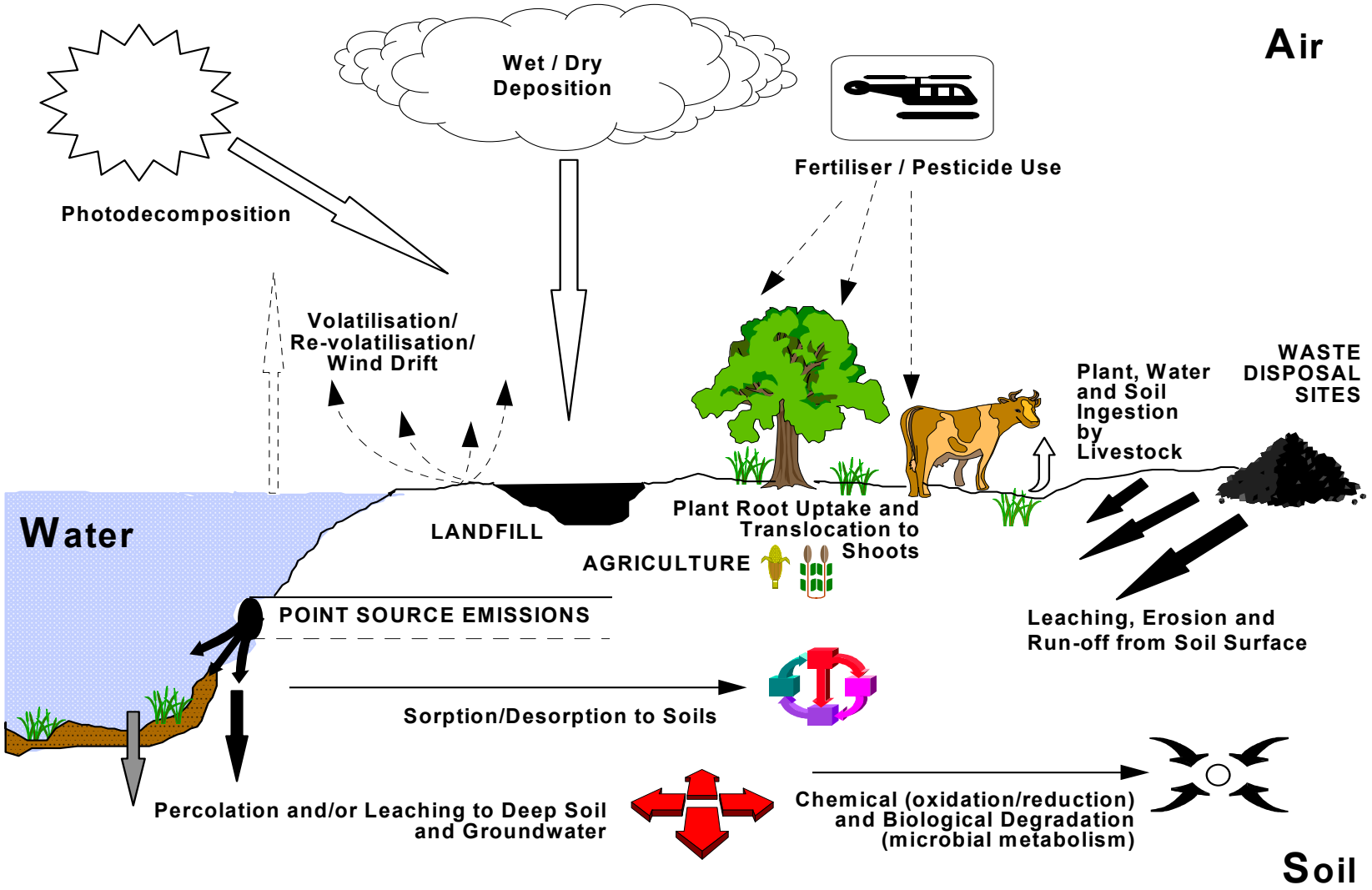
Table 3.4 Physicochemical forces influencing fate and behaviour of chemicals in soil and contamination of groundwater

Physicochemical force	Definition	Model
Adsorption/Desorption	Adsorption is the accumulation of a chemical at the liquid–solid interfaces and/or solid–gas interfaces (sorbent or solvent motivated)	$c_{s2} \leftrightarrow c_{s1} \leftrightarrow c_w$ $c_{s2} = K_{app}\, c_w$ $K_{app} = c_{s2}/c_w$
Ionisation	The mechanism involved in the interaction between contaminant and soil components depends, in part, on whether the chemical ionises or not; the ionisation potential of a chemical in soil is dictated by its polarity	$K_d = f_{oc}\, K_{oc}$
Cosolvation	This occurs when a mobile phase is formed from multiple solvents that are miscible with each other. The model is based on the assumption that sorption results from hydrophobic interactions	$\ln (K_d m) = \ln (K_d w) - (\alpha\, \sigma^c\, f^c)$
Chemical speciation (precipitation/dissolution)	This is a function of the redox potential of the soil solution, pH of soil and water, acid neutralising potential of soil, temperature, metal concentration in solids and soil solution, presence of complexing ligands and concentrations of exchangeable cations, Fe and Mn oxides and organic matter	

From Kargbo (1994)

α, empirical constant; c, concentration (mol/m^3); c_{s1}, sorbed phase conc. in equilibrium (mobile fluid) domain; c_{s2}, sorbed phase conc. in the mass-transfer constrained (stagnant fluid) domain; c_w, conc. in soil soln. phase; f^c, fraction of the co-solvent; f_{oc}, mass fraction organic carbon in phase; K_{app}, apparent distribution coefficient; K_d, chemical partitioning in soil; $K_d m$, partition coefficient from mixed solvents; $K_d w$, partition coefficient from water; K_{oc}, organic carbon partition coefficient (m^3/kg); σ^c, function of solute and solvents

Figure 3.4 Main mechanisms of chemical cross-transfer between soil/sediment and other environmental compartments



Screening methods are available for prioritising environmental chemicals on the basis of their potential to leach out of contaminated soil/sediment (e.g. from sewage-sludge application, landfills, chemical spills, etc.) and contaminate water, vegetation and grazing animals. These methods have been adapted and applied to examine specific environmental problems, such as examining the ability of organic contaminants to leach into groundwater from sludge-amended soils (e.g. DETR/WIR method; Duarte-Davidson & Jones, 1996; Wilson *et al.,* 1996).

Many of the physicochemical properties described in Table 3.3 have been used in models to predict movement of a chemical from soil to other environmental compartments. For example, a number of physicochemical properties are used to predict the potential of a chemical to move from soil to water ('leachability'), namely, chemical solubility (S) and vapour pressure (V_p), persistence and organic carbon–water partition coefficient (K_{oc}) (Table 3.4). Two popular methods for predicting leachability are the Leaching Potential Index (L_p; Laskowski *et al.,* 1982) and the Groundwater Ubiquity Score (GUS; Gustafson, 1989), which are described in Table 3.5.

Another physicochemical property used to predict chemical transfer from soil to water is chemical mobility. A chemical must have high convective mobility (t_C) to leach out of soil and enter water and low diffusive mobility (t_D) for minimal dissipation to the atmosphere (Jury *et al*., 1983, 1984, cited in Wilson *et al*., 1996) (Table 3.4). The DETR/WIR prioritisation method was developed to rank organic chemicals by their potential to leach from sewage-amended soil to groundwater and contaminate the human food chain via crops and livestock (Duarte-Davidson & Jones, 1996; Wilson *et al.,* 1996). This method integrates chemical mobility, leaching potential, the GUS index and persistence, to identify 'priority leachers': chemicals with high L_p, persistence, high t_C, low t_D and a high GUS index. The limitations of this method, as emphasised by the authors, are the variability of physicochemical property data and the lack of reliable data on UK sludge and soil compound concentrations in the aqueous phase.

Soil contaminants with high volatilisation potential (indicated by H_c and V_p, Table 3.3) can be important sources of air pollutants, under certain environmental conditions. Physical conditions that influence the degree of volatilisation are wind speed, soil temperature, and porosity (ECETOC, 1992). Mathematical models designed for predicting the partitioning of chemicals between soil and air recommended by ECETOC (1992) are given in Table 3.3.

Table 3.5 Physicochemical criteria for screening chemicals on the basis of their potential to leach from soil and contaminate water

Physicochemical criteria	Model	Range	Ref
Leaching Potential (L_p) chemical's tendency to leach from soil into water	$L_p = S/(V_p K_{oc})$	High L_p, leacher Low L_p, non-leacher	a
Half-life ($T_{1/2}$) Persistence in Soil rate of loss of a chemical from a system by first-order kinetics attributable to biodegradation, volatilisation, abiotic degradation etc. Indicates chemical's persistence in the environment		Class 1 (>100 d), highly persistent in soil Class 2 (30–100 d), moderately persistent in soil Class 3 (15–30 d), moderately short-lived in soil Class 4 (5–15 d), short-lived in soil Class 5 (<5 d), very short-lived in soil	b
Groundwater Ubiquity Score (GUS) chemical's tendency to leach from soil into groundwater	$GUS = \log_{10}(T_{1/2}) \times (4 - \log_{10} K_{oc})$	GUS >2.8, leacher GUS 1.8–2.8, intermediate GUS <1.8, non-leacher	c
Chemical Mobility time for a chemical to move through 10 cm of soil			
Convective Time (t_C)	$t_C = (s\, f_{oc}\, K_{oc} + q + a\, H_c)\, l/J_w$	Class 1, >300 d Class 2, 100–300 d Class 3, 30–100 d Class 4, 10–30 d Class 5, <10 d	b, d
Diffusive Time (t_D)	$t_D = l^2 ø^2 (s\, f_{oc}\, K_{oc} + q + a\, H_c)/D_{Gair}\, a^{10/3}\, H_c$	Class 1, >100 d Class 2, 20–100 d Class 3, <20 d	b, d

a, volumetric air content (m^3/m^3); D_{Gair}, gaseous diffusion coefficient (m^3/day); f_{oc}, mass fraction organic carbon in phase; H_c, Henry's constant (dimensionless); J_w, water flux (cm/day); K_{oc}, organic carbon partition coefficient (m^3/kg); *l*, distance travelled (cm); ø, porosity (m^3/m^3); q, volumetric water content (m^3/m^3); s, soil bulk density (kg/m^3); S, solubility in water (ppm at 25°C); $T_{1/2}$, half-life (days); V_p, vapour pressure (Pa)
[a] Laskowski *et al.* (1982); [b] Jury *et al.* (1983, 1984), cited in Wilson *et al.* (1996); [c] Gustafson (1989); [d] McCall *et al.* (1980)

3.2.2.3 Behaviour in water

Chemical emissions to water can occur from point sources (e.g. dumping at sea, industrial and sewage effluents) and diffuse sources (e.g. agricultural run-off, leaching from landfills, atmospheric deposition). Advection and dispersion transport processes affect the dilution and circulation of chemicals in water (ECETOC, 1992). Persistence of a chemical in water is dependent on physical and biological degradation processes. Physical degradation is usually by photolysis at depths with sufficient light penetration and biodegradation is mostly by microbial metabolism. The subsequent persistence of a chemical in water is highly dependent on conditions affecting biotic and abiotic degradation processes (e.g. water hardness, pH, oxygen content, temperature, light penetration, dissolved organic carbon).

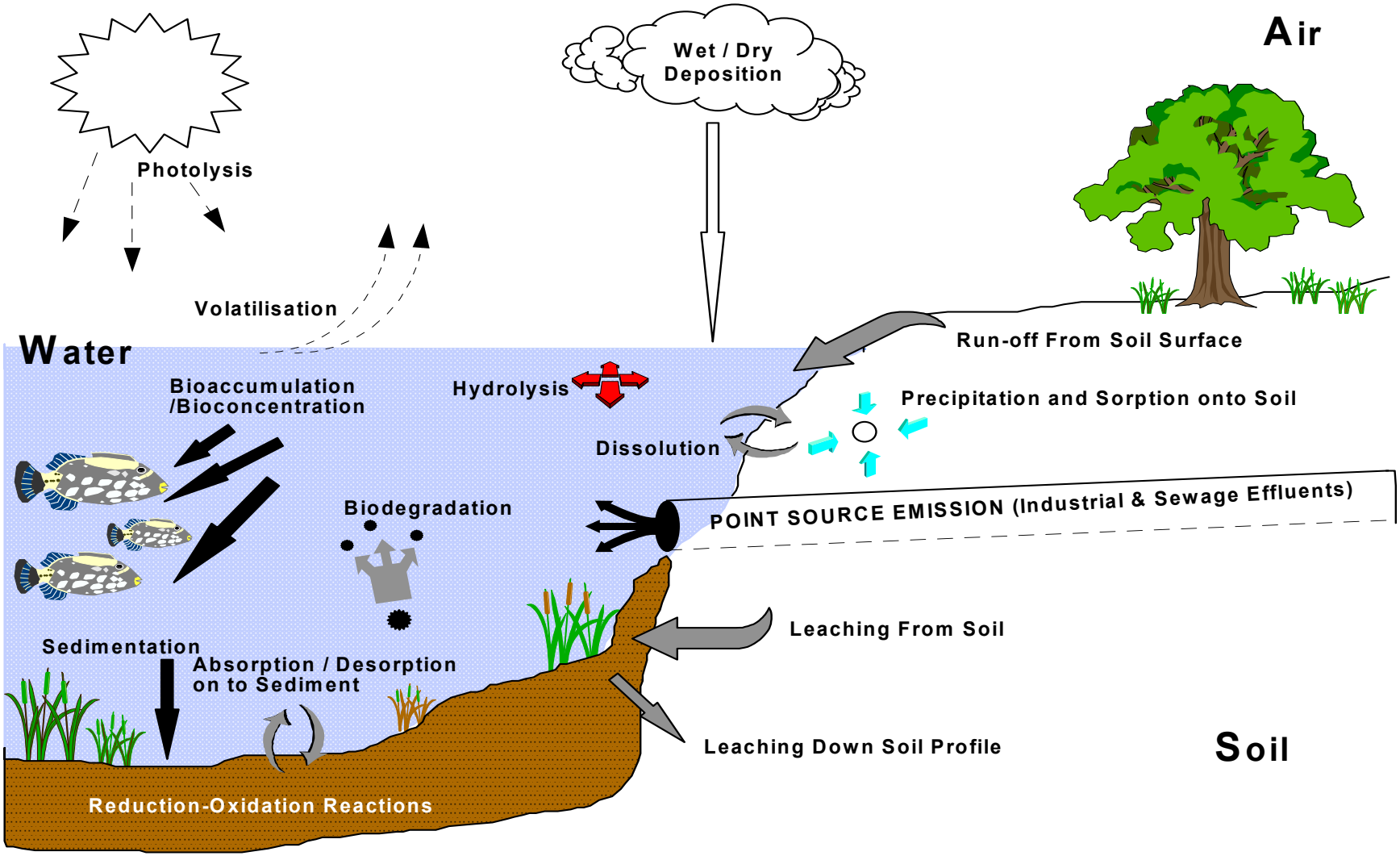
The sedimentation characteristics of a chemical in water are important for determining the potential of a chemical to deposit onto aquatic sediments, thereby facilitating cross-transfer between two environmental compartments, water and sediment. Chemicals sediment onto the 'active sediment' layer found at the water/sediment interface, which contains colloidal particles suspended in pore water (Philp, 1995). Lipophilic chemicals (chemicals with high K_{oc}), in particular (Table 3.3), tend to come out of solution and become strongly adsorbed on this part of the sediment, which act as a 'sink' for such chemicals. Lipophilic chemicals generally tend to accumulate in sediment so they are more available for uptake by benthic organisms (ECETOC, 1995).

Biological oxygen demand (BOD) half-life is widely used in prioritisation schemes to screen chemicals for persistence in water (e.g. Tabak *et al.,* 1981) and environmental exposure (e.g. NCM, US-EPA/CHEMS-1 methods; Table 3.1). The advantage of using BOD is that it can be determined experimentally using traditional microbial static-culture as developed by Bunch and Chambers (1967). In addition, BOD data can also be estimated for chemicals using quantitative structure–activity relationships (QSARs) or SARs (Niemi *et al.,* 1987). Metals and other inorganic compounds are by definition unbiodegradable; the CHEMS-1 method makes the assumption that metal compounds and certain other chemicals in highly oxidized states have infinite BOD and hydrolysis half-lives while zinc and aluminium dusts are assumed to have half-lives of 500 days based on the judgement that they would degrade (oxidize) eventually, although slowly (Swanson *et al.,* 1997).

Using BOD to indicate a chemical's potential for biodegradation has its limitations. For example, BOD data obtained from laboratory experiments may not accurately predict biodegradability of chemicals in a 'real' waste-water treatment situation, since the microbial culture-enrichment process employed may differ from standard conditions (e.g Bunch & Chambers, 1967) and these conditions may not be optimal for microbial activity. In addition, actual concentrations of chemicals in waste-water are usually much lower than those used in measurements of BOD. The use of BOD to screen chemical persistence in water, however, is still widely used for aquatic systems, particularly rivers and lakes.

In addition to persistence/degradability, a number of physicochemical properties are also used to predict the fate and behaviour of chemicals in water. These include: aqueous solubility (S), which indicates a chemical's potential to dissolve in water; K_{ow}, which indicates a chemical's potential to remain in water or partition to biological tissue/suspended organic matter or sediment; and $T_{1/2}$, which indicates a chemical's resistance to abiotic degradation in water (Table 3.3). Whenever these physicochemical properties are used, however, it must be clearly stated for which aquatic medium they apply (e.g. freshwater, sea-water or groundwater) since physicochemical property data can vary considerably between different media. The main mechanisms of chemical transfer between water and other environmental compartments are summarised in Figure 3.5.

Figure 3.5 Main mechanisms of chemical transfer between water and other environmental compartments



3.2.2.4 Transfer between environmental compartments

Predicting the final retaining compartment (e.g. air, soil, water) is particularly important for identifying which hazardous chemicals may contaminate the food chain and eventually cause human exposure via ingestion of food. Generally applied techniques for predicting the environmental fate of a chemical include the use of environmental partitioning or fugacity models (McKay *et al*., 1992a). The fugacity (*f*) of a chemical can be regarded as its tendency to escape from a specific environmental compartment when the concentration of the chemical is at a steady state between compartments. Fugacity models incorporate various physicochemical properties to predict the nature of the receiving environmental compartment and the behaviour of the chemical within it, and have the advantage of being easy to compile and manipulate. It is necessary, however, to calculate the retention or storage capacity (Z) of a compartment for a chemical before fugacity can be determined.

Fugacity models can be used to quantify the concentration of a chemical as it moves from a source through the environment to a target population. The physicochemical properties used to predict the behaviour of a chemical in the environment and their subsequent application to storage capacity and fugacity calculations are shown in Table 3.6. There are several multi-media fate and behaviour, and fugacity models available in the open literature, ranging from generic models applicable to all chemicals (MacKay *et al.,* 1991; Davis *et al.,* 1994; Kargbo, 1994; Schramm, 1994) to more dedicated models for use with specific groups of chemicals, for example unsubstituted monocyclic polyaromatic hydrocarbons (Gert-Jan de Maagd *et al.,* 1998).

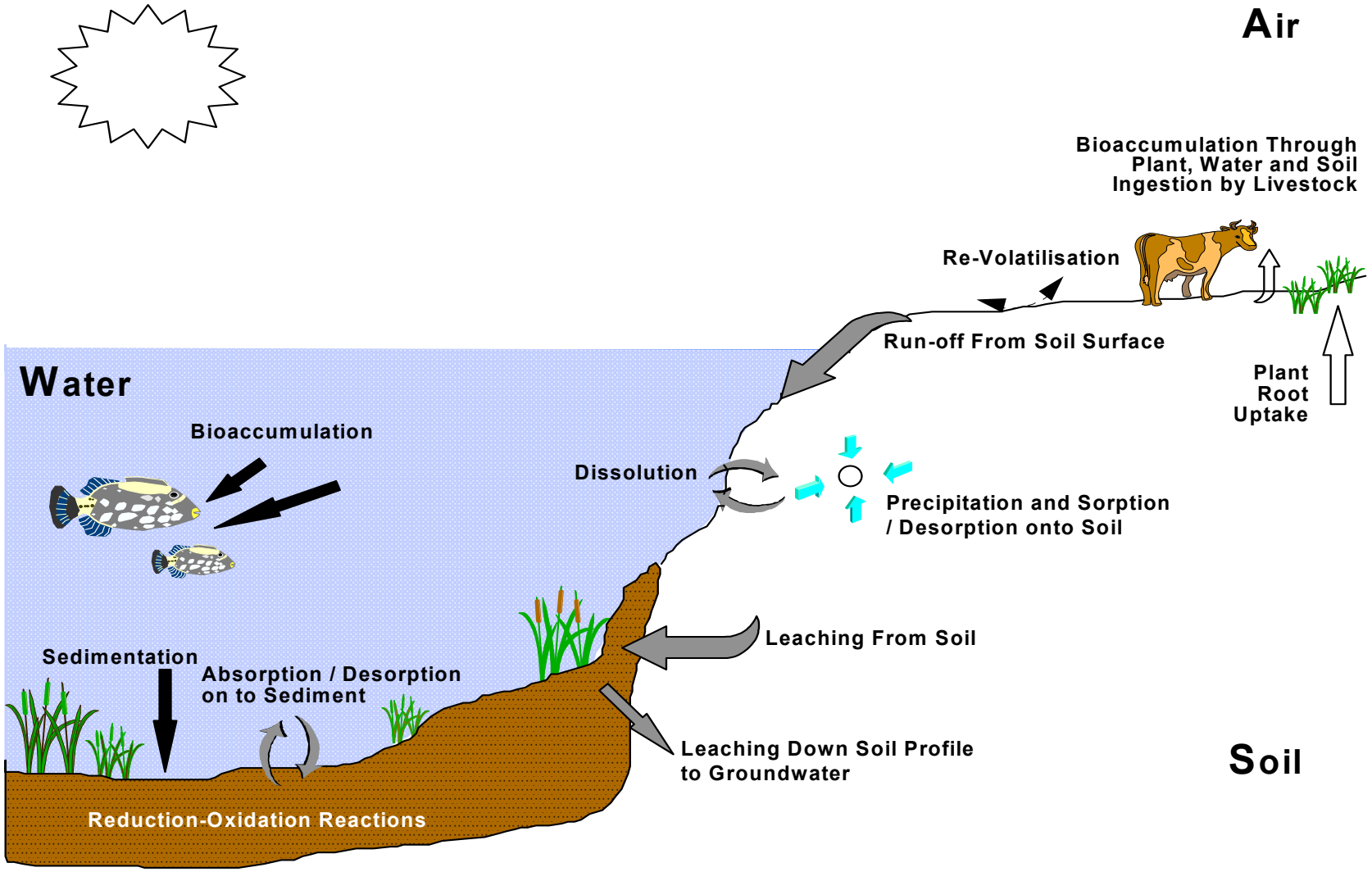
Table 3.6 Calculation of the storage capacity and fugacity of a chemical in the environment

	Model
Storage/Fugacity Capacity (*Z*) (mol/m^3 Pa) indicates the potential of an environmental compartment to retain a chemical and therefore its capacity for fugacity	$Z_{air} = 1/RT$ $Z_{water} = S/V_p$ $Z_{soil} = (Z_{water}\ \rho\ f_{oc}\ K_{oc})/1000$ $Z_{sediment} = (Z_{water}\ \rho\ f_{oc}\ K_{oc})/1000$ $Z_{susp.solids} = (Z_{water}\ \rho\ f_{oc}\ K_{oc})/1000$ $Z_{fish} = (Z_{water}\ \rho\ L\ K_{ow})/1000$
Fugacity (*f*) (Pa) indicates the tendency of a chemical to escape from a specific compartment	$f_i = c_i/Z_i$

From MacKay *et al.* (1991)
c, concentration (mol/m^3); f_{oc}, mass fraction organic carbon in phase; i, specific environmental compartment (air/soil/water/sediment/fish); K_{oc}, organic carbon partition coefficient (m^3/kg); L, lipid content (fraction of total mass); R, gas constant (Pa m^3/mol/Kelvin); ρ, density of phase (kg/m^3); S, solubility; T, temperature (°C)

A number of hypothetical fate and behaviour paradigms exist that present possible routes of chemical transfer from environmental compartments to plants and animals leading to human exposure (MacKay *et al.,* 1991; Philp, 1995) (Figure 3.6). Models such as these are useful for understanding the fate and behaviour of a chemical in an integrated fashion since physicochemical processes at the inter-compartment interface are inherently related and inter-dependent. Fate and behaviour models are also used in risk assessment because it is necessary to know the type and levels of environmental exposure to a specific chemical.

Figure 3.6 Main pathways of chemical transfer between environmental compartments



3.2.3 Potential for chemical uptake via the food chain

Uptake of chemicals by plants from the environment is mainly from the soil (uptake and translocation, soil splashing on to plant surface; Figures 3.4, 3.6), but can also occur from water (e.g. root uptake; Figures 3.5, 3.6) and air (e.g. deposition onto foliage; Figures 3.2, 3.6). Animals may be exposed to chemicals through the ingestion of contaminated food and water, inhalation of airborne pollutants and direct contact of chemicals with skin. Fate and behaviour paradigms are useful for demonstrating the possible routes of uptake of environmental chemicals via the food chain. They provide information on the sources of chemical exposure, the main pathways of chemical transfer between compartments and may help identify the final retaining compartment of a chemical. From this information, it is possible to predict the potential main sources of human exposure.

Figure 3.7 shows a model for uptake of chemicals by humans. Humans are exposed to chemicals via the ingestion of food, drinking water (surface or groundwater), inhalation of air and from dermal contact. The model highlights the importance of human exposure from chemicals accumulated in the food chain, which should therefore be considered together with direct exposure to chemicals from air, soil and water. Although the figure shows the possible pathways of exposure, the significance of each pathway as a source of chemical uptake can vary depending on the circumstances of exposure.

3.2.3.1 Plant uptake of chemicals from the terrestrial environment

The uptake of chemicals by plants is affected by temperature, air disturbance, soil organic matter content and the plant's characteristics (leaf shape, type of root system, lipid and cuticle characteristics). The amount of an organic compound found in a plant reflects the combined uptake via all pathways minus metabolism and volatilisation (Duarte-Davidson & Jones, 1996). Mechanisms of organic contaminant uptake and transfer by plants include:

- root uptake from soil solution and subsequent translocation to the shoots;
- absorption of volatilised organic compounds by roots/shoots from surrounding air;
- uptake by external contamination of shoots by soil and dust;
- retention by cuticle/penetration through cuticle; and
- uptake and transport in oil channels in oil-containing plants (e.g. carrots).

The general principles outlined in the DETR/WIR prioritisation method are also applicable to agricultural soils that have not been amended with sludge (Duarte-Davidson & Jones, 1996; Wilson *et al.,* 1996). The models used are presented in Table 3.7. Chemicals were screened on the basis of their potential for foliar uptake (cuticular accumulation and uptake through stomata), potential for root surface retention (chemical partitioning from soil particles and sorption to root surface) and potential for root uptake and translocation in xylem (active uptake from root into transpiration stream, transporting persistent chemicals to shoots and leaves).

Figure 3.7 Main sources and routes of non-occupational chemical uptake by humans

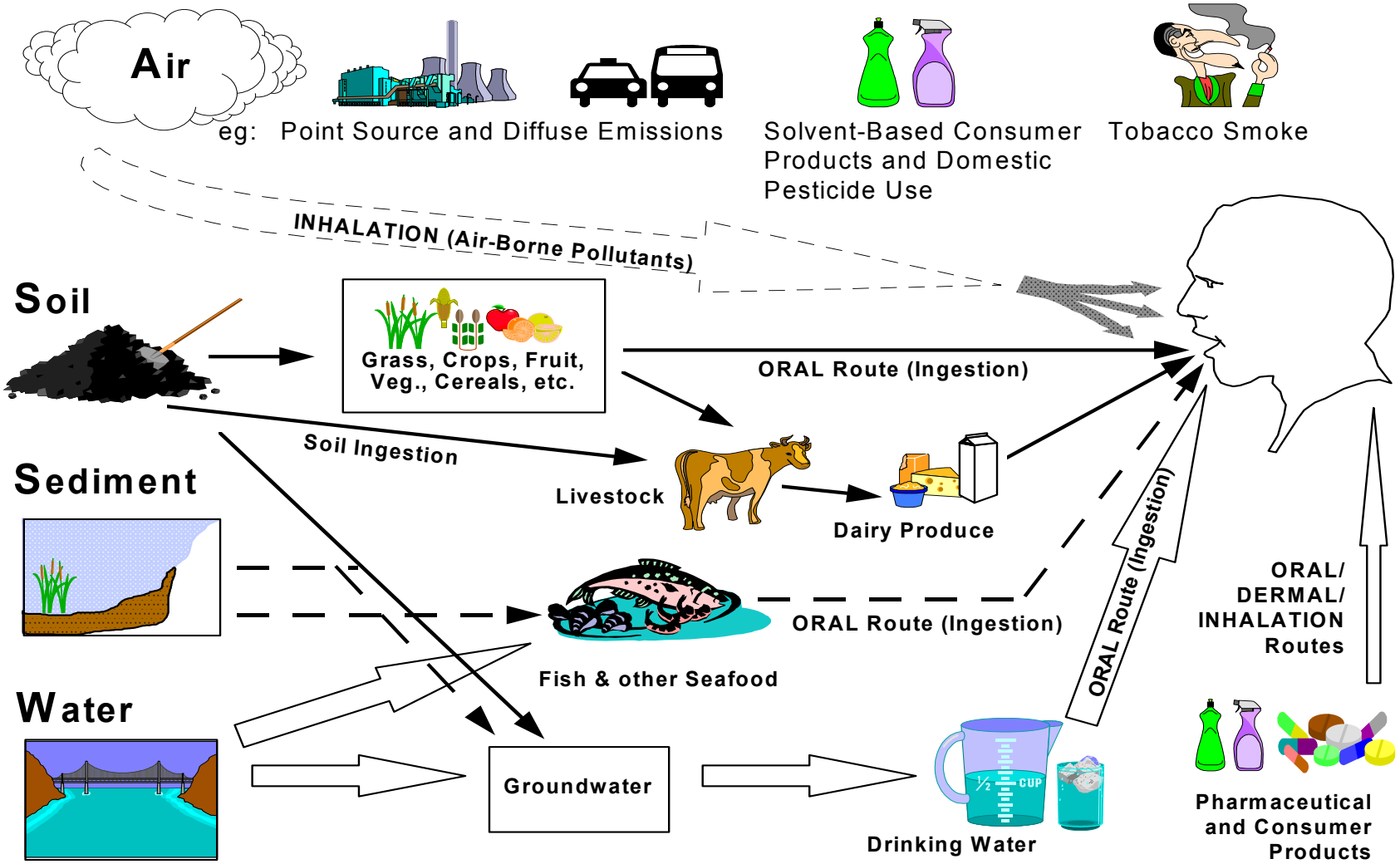


Table 3.7 Screening for transfer of organic compounds from soils to plants

Screening parameter	Physicochemical property	Range
Potential for Foliar Uptake, defined as:		
Susceptibility to volatilisation (Henry's Law constant);	Log H_c	Class 1 = log H_c >1 × 10^{-4}, high volatilisation Class 2 = log H_c ~1 × 10^{-4}, medium Class 3 = log H_c <1 × 10^{-4}, low volatilisation
Potential of chemical to dissolve in waxy cuticle of leaves (lipophilicity) (octanol–water partition coefficient); and	Log K_{ow}	Log K_{ow} >4.0, high cuticular accumulation 4.0 > log K_{ow} > 2.5, medium Log K_{ow} <2.5, low cuticular accumulation
Potential to volatilise and be taken up by leaves or remain adsorbed on root surface (air–octanol partition coefficient).	K_{ao}	K_{ao} >1 × 10^{-9}, high uptake of air-borne chemicals K_{ao} <1 × 10^{-9}, low uptake of air-borne chemicals
Potential for Root Surface Retention, defined as:		
A chemical's potential to adsorb to the root surface from soil solution, which is proportional to the organic carbon–water partition coefficient (K_{ow})[a].	Log K_{ow}	Class 1 = log K_{ow} > 4.0, high root retention Class 2 = 4.0 > log K_{ow} > 2.5, medium retention Class 3 = log K_{ow} < 2.5, low (does not enter root system)
Potential for Root Uptake and Translocation, defined as:		
Potential of chemical to enter xylem;	Log K_{ow}	Range for maximum translocation: log K_{ow} = 1.5–1.8
Resistance to plant metabolism (persistence[b]); and	$T_{1/2}$	Class 1 = $T_{1/2}$ >100 days, low degradability Class 2 = 100 > $T_{1/2}$ > 15 days, medium Class 3 = $T_{1/2}$ <15 days, high degradability
Potential for transport in the transpiration stream to shoots and leaves.	Log K_{ow}	Class 1 = 1 < log K_{ow} < 2.5 Class 2 = 2.5 < log K_{ow} < 3.0 or 0.5 < log K_{ow} < 1.0 Class 3 = log K_{ow} < 0.5 or log K_{ow} > 3.0

From Duarte-Davidson and Jones (1996)

[a]Root surface retention is affected not only by the K_{ow} of a chemical, but also to some extent by soil particulate size and organic content

[b]Data on degradability in plants are sparse so data on degradability in soils were incorporated into the screening process

3.2.3.2 Animal uptake of chemicals from the terrestrial environment

Of particular concern for human exposure to environmental chemicals are the characteristics of chemical uptake from soil, water, vegetation and air, directly or indirectly, by animals (e.g. cattle, pigs, sheep, or fish and other seafood) as this may ultimately lead to bioaccumulation in the human food chain. The main sources of chemical intake by animals are through the ingestion of contaminated soil, water and vegetation (Figure 3.7). After ingestion chemicals may pass through the gastrointestinal membrane, enter the blood stream or lymph system and become incorporated into tissues and organs (Duarte-Davidson & Jones, 1996). Absorption efficiency is determined by a chemical's log K_{ow}, which is used to identify and prioritise environmental chemicals with the highest absorption potential. Generally, absorption efficiencies increase proportionally with K_{ow} values up to a log K_{ow} of 6 or 7; beyond this, increases in absorption efficiency level off.

Persistent lipophilic organic compounds ingested by cattle can become deposited in adipose tissue and (in lactating females) milk. This may lead to significant contamination of humans consuming large amounts of dairy products and beef. It is therefore important that prioritisation schemes include screening for chemicals that are most likely to contaminate the human food chain on the basis of their uptake by animals, absorption efficiency, resistance to metabolism and lipophilicity. In the case of livestock, the uptake of organic compounds from sewage sludge applied to farmland is particularly important. Rate of transfer is dependent on several factors including the livestock species, type/form of sludge addition, season, grazing habits and diet. Ingestion of organic contaminants associated with vegetation or soil will increase the uptake of these compounds by the animal (Duarte-Davidson & Jones, 1996). Soil ingestion is an important route of exposure; sheep for example may ingest 1–2% soil in their diet, reaching 26% in extreme cases (Chaney, 1985, cited in Duarte-Davidson & Jones, 1996).

The DETR/WIR prioritisation method also includes screening for uptake of organic compounds by grazing animals after plant ingestion. Potential transfer of organic compounds from soils to animal tissues (livestock) via herbage requires that the compounds have been successfully incorporated from the soil into the foliar portion of the herbage (Duarte-Davidson & Jones, 1996; Wilson *et al.,* 1996). This transfer is dependent on chemical persistence, potential for translocation and foliar uptake (Table 3.8).

Table 3.8 Screening chemicals for potential for animal intake via plant ingestion

Category	$T_{1/2}$ (days)		Translocation potential		Foliar uptake	Animal intake potential
I	>36	and	High	and/or	High	High
II	>36	and	Medium	and	Medium	Medium
III	>36	and	Medium	and	Low	Medium
IV	>36	and	Low	and	Medium	Medium
V	<36	and/or	Low	and	Low	Low

From Duarte-Davidson and Jones (1996)

3.2.3.3 Plant and animal uptake of chemicals from the aquatic environment

Human chemical uptake from aquatic environments tends to be centred around exposure from ingestion of food (fish and other seafood) and drinking water, and this is reflected in the fate and behaviour models currently used in prioritisation schemes.

In the aquatic environment, uptake of environmental chemicals by phytoplankton occurs directly from the water column via diffusion across the cell wall. Uptake processes are dependent on the physicochemical processes that affect diffusion forces and phytoplankton growth, including temperature, light and oxygen availability. The uptake of lipophilic environmental chemicals by phytoplankton is particularly important in human food chains where planktivorous fish and/or fish

feeding on planktivorous fish form a large proportion of the daily diet. Direct uptake of environmental chemicals from the benthos by aquatic animals, is via benthic foraging, filter-feeding, diffusion across the cell membrane of zooplankton and the gill surface of fish (ECETOC, 1995). Indirect uptake of environmental chemicals by aquatic animals is via the ingestion of contaminated prey items.

Specific models dedicated to predicting the fate and behaviour and uptake routes for chemicals in the aquatic environment (e.g. ECETOC, 1995) are not widely used in prioritisation schemes. This is because the majority of prioritisation methods are designed specifically for predicting sources of human exposure to hazardous chemicals. However, as the purpose of this review is to prioritise compounds relevant to human exposure, uptake via the ingestion of fish is of concern here.

In aquatic food chains, biomagnification is significant for chemicals with a log K_{ow} >6 (Davis *et al.,* 1994). The direct bioconcentration of a chemical is often lower than that predicted from K_{ow} and tends to decrease with log K_{ow} > 6 due to increasing molecular size (Bintein *et al.,* 1993). The use of K_{ow} alone as an estimation of bioconcentration potential is limited to non-polar organic chemicals, as water-soluble (polar) chemicals have been estimated to bioconcentrate to a lesser extent than that predicted by K_{ow} (Niimi, 1987; Isnard & Lambert, 1988; Davis *et al.,* 1994).

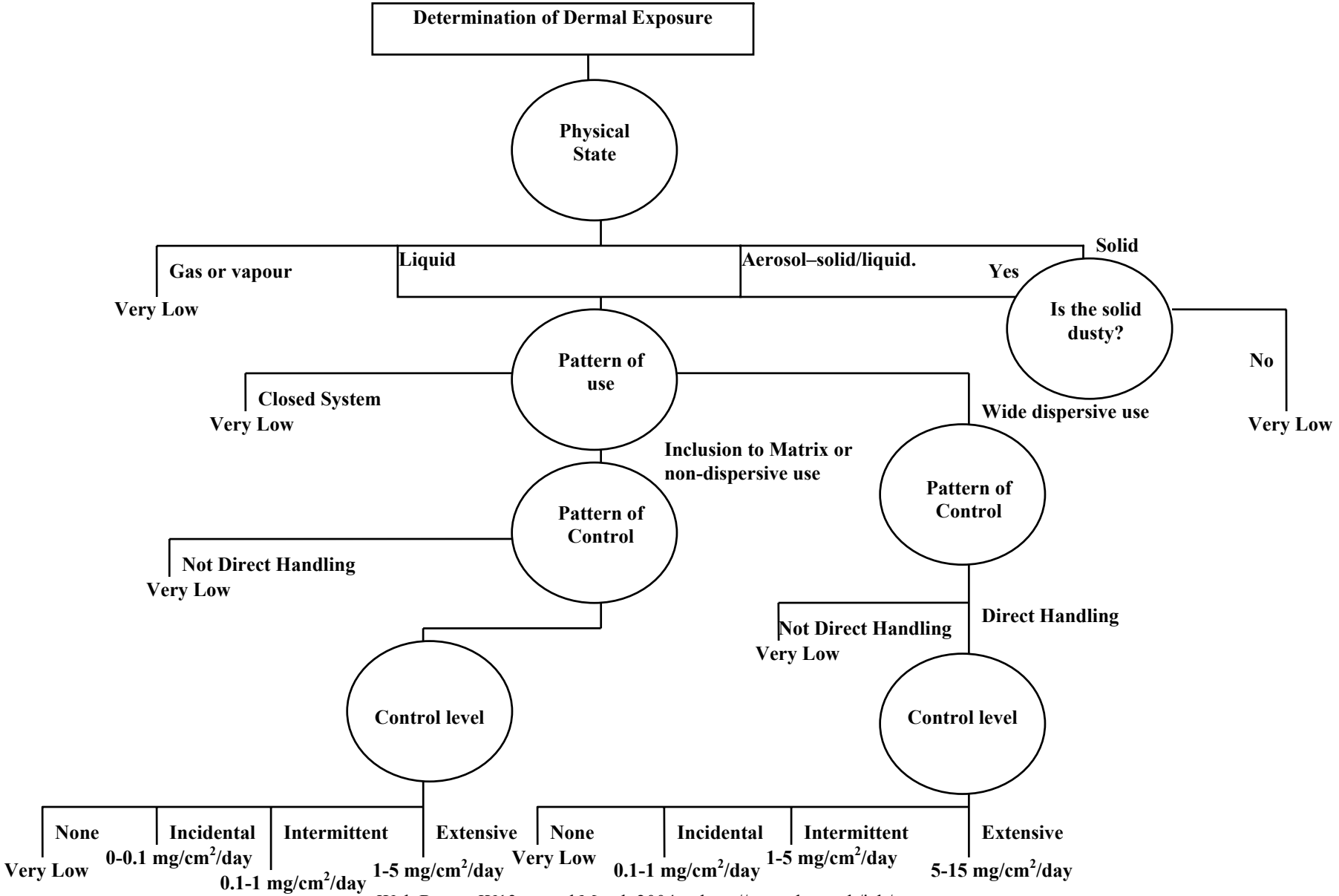
3.2.3.4 Human uptake of chemicals from the environment

The main sources of uptake by humans are via the consumption of contaminated food and water, inhalation and direct contact with the skin, eyes and respiratory tract. Of particular concern in this review is the prioritisation of non-occupational human exposure to environmental levels of chemicals from these sources. Humans are exposed to airborne chemicals outdoors, in the workplace and also in non-workplace environments. The main sources of chemical uptake by humans are highlighted in Figure 3.7.

While there is often reasonable knowledge of human exposure to airborne pollutants in the outdoor environment and the workplace (occupational exposure), there is little information on indoor levels of airborne pollutants and levels of human exposure in the home. Chemical volatility can be used to identify chemicals more likely to be airborne (Figure 3.3) and therefore taken up by inhalation. Physicochemical properties that can be used to prioritise chemicals for potential human exposure from air include H_c and V_p (Table 3.3).

To predict levels of dermal exposure to air- and waterborne chemicals in humans, the physical state (gas, liquid, solid) of the chemical, its pattern of use and contact level require consideration. Physical characteristics predisposing to dermal contact with chemicals are their volatility (tendency to become airborne) and aqueous solubility (soluble in water). Pattern of use influences dermal exposure to chemicals, particularly since chemicals used dispersively in open systems are more likely to contaminate air and/or water and come into contact with the skin. Contact level between humans and chemicals influences dermal exposure, particularly in the occupational environment, where routine inhalation and/or handling of chemicals can occur. The European Commission's Technical Guidance Document (European Commission, 1996) takes these inter-dependent factors into consideration when assessing dermal exposure potential as part of its risk assessment guidelines. A flow chart demonstrating how potential for dermal exposure is determined in the Technical Guidance Document is presented in Figure 3.8.

Figure 3.8 Method for determination of dermal exposure (from European Commission, 1996)



3.2.4 Bioaccumulative potential

Bioaccumulation is defined as the process by which a chemical is taken up by an organism to a concentration greater than in the surrounding environment (Davis *et al*., 1994). Biomagnification is the increase in a chemical's concentration from one organism to the next in a food chain following various pathways along different trophic levels. In general, chemicals with high log K_{ow} values and low water solubilities have the greatest potential to bioaccumulate in animal tissues, that is bioconcentration and bioaccumulation potential increases with lipophilicity.

Dietary exposure only becomes relevant at log K_{ow} >4.5–5, helping to reduce the number of chemicals that require screening (ECETOC, 1995). It is only necessary to conduct dedicated bioaccumulation studies of chemicals once they have been identified as priority chemicals from aquatic exposure levels, by their bioconcentration factors (BCFs) and if bioaccumulation through ingestion of food is relevant (i.e. chemicals with log K_{ow} >5).

Bioconcentration factors are a measure of the 'bioaccumulative potential' of a chemical. They can and have been used as a screening criterion to prioritise environmental chemicals on the basis of their potential to bioaccumulate in animal tissues. A BCF is defined as the ratio between the concentration of a chemical in an organism and its concentration in the environment at a steady-state concentration (when the rate of ingestion equals rate of excretion) (Davis *et al.,* 1994) and can be calculated/estimated via a variety of mathematical models, some of which are summarised in Table 3.9. BCFs have been most widely studied and applied in fish and are used to relate concentrations of a chemical in the diet to concentrations in the animal.

Objectives and guidelines are available on the measurement of bioconcentration and bioaccumulation in fish, such as the OECD (1996) test guidelines and the ASTM (1993) standard guide on bioconcentration. According to the OECD, bioconcentration tests must be conducted under strictly standardised experimental conditions (e.g. temperature variation ± 2°C, pH variation ± 0.5) with the concentration of the chemical, the amount of organic carbon in water and dissolved oxygen content maintained relatively constant to ensure valid results and facilitate inter-laboratory data comparison (OECD, 1996).

Bioconcentration factor measurements have limitations, however. Reliable determinations are only possible at steady state concentrations of a chemical, for example persistent organic chemicals that take extended periods of time to be metabolised and excreted. BCF estimations are therefore less accurate in the case of organisms where significant metabolism occurs (Davis *et al.,* 1994). When estimating/calculating BCF ratios, it is assumed that they are independent of exposure level, ambient temperature, time of exposure and fish species, such that the BCFs derived result from the intrinsic properties of the chemicals in isolation (Isnard & Lambert, 1988). There is also no consideration of source (air, water, soil) and type of exposure (ECETOC, 1995). In the US-EPA method, BCF values for chemicals determined in the field take precedence over data acquired under controlled laboratory conditions, because they provide BCF values that are more realistic for normal environmental conditions (Davis *et al.,* 1994).

Due to the difficulty and expense of conducting experiments to determine BCFs directly, physicochemical property information for environmental chemicals, particularly log K_{ow}, aqueous solubility (S) and half-life ($T_{1/2}$), has been used to calculate BCFs (Table 3.9). Also log K_{ow} data can be predicted from linear regression analyses and/or QSARs (ECETOC, 1995) where these have not been determined experimentally. Three different methods are available for these calculations: the Fragment Constant Method (Hansch & Leo, 1979, cited in ECETOC, 1995), a method for deriving log K_{ow} using Activity Coefficients (Banerjee & Howard, 1988) and the Parachor (P) method (Briggs, 1981) (Table 3.10).

Table 3.9 Models used for calculating/estimating bioconcentration factors (BCFs) and biological half-lives ($T_{1/2}$)

Model	Reference
$BCF = c_f/c_w$	Isnard and Lambert (1988)
$BCF = 0.048 \times K_{ow}$	MacKay (1982)
$BCF = (0.79 \times \log K_{ow}) - 0.4$	Veith and Kosian (1983)
$\log BCF = 2.02 - (0.47 \log S)$	Isnard and Lambert (1988)
$T_{1/2} = 0.693/(K_e + \lambda)$	Niimi (1987)

c_f, conc. of chemical in fish (g/g or mg/l); c_w, conc. of chemical in water (g/g or mg/l); K_e, clearance coefficient; λ, growth weight coefficient; S, aqueous solubility (mol/m^3)

Table 3.10 Mathematical models used to calculate bioconcentration factors from QSAR data

	Model	Reference
Fragment Constant Method	$\log K_{ow} = \Sigma_{i,j} (f_i + F_j)$	Hansch and Leo (1979), cited in ECETOC (1995)
Log K_{ow} derived from Activity Coefficients (γ)	$\log K_{ow} = -0.40 + (0.73 \log \gamma_w) - (0.39 \log \gamma_w)$	Banerjee and Howard (1988)
Parachor (P) method	$\log K_{ow} = 0.011P - 1.2n - 0.18$	Briggs (1981)

f_i, fragment factors; F_j, structural factors; γ_o, activity coefficient in octanol; γ_w, activity coefficient in water calculated using UNIFAC (Fredenslund *et al.,* 1975, cited in Banerjee and Howard, 1988); *n*, correction value for each hetero-atom or functional group present in chemical

The biological half-life of a chemical is the time required for its concentration in an organism to decline by 50% (Niimi, 1987). BCFs can be estimated from $T_{1/2}$ data, such as change in chemical concentration or change in chemical content (body burden) per unit time, using the models of Niimi (1987) (Table 3.9). Ambient temperature, salinity, body weight, sampling strategy, internal distribution/partitioning of a chemical, growth dilution and concentration effects on chemical concentrations all influence $T_{1/2}$ data (Niimi, 1987). The $T_{1/2}$ of organic chemicals acquired through the diet (e.g. prey), can be longer than those from waterborne exposure, since a chemical must resist metabolism in prey/food item to persist and contaminate the predator/consumer.

3.2.5 Integrating and scoring exposure

3.2.5.1 Environmental exposure

In the EURAM ranking method exposure is scored using the Environmental Exposure Value (EEXV), which integrates emissions, biodegradation/persistence ($T_{1/2}$) and MacKay's fugacity scores (see Tables 3.3, 3.6) (Hansen *et al.,* 1999). The EEXV is subsequently used to derive an overall score for environmental exposure called the Environmental Exposure Score (EEX). This score is useful for identifying chemicals that will persist in the environment and that will be likely to be taken up by plants and animals via the food chain. It can also be useful for ranking and prioritising contaminants of concern regarding human exposure via the ingestion of contaminated food (e.g. fish). The EEXV and EEX are calculated as follows:

$$\mathbf{EEXV_{(air/soil/water/etc.)}} = \text{Emission} \times \text{Dist.}_{(air/soil/water/etc.)} \times \text{Degradation Score} \quad (3)$$

$$\mathbf{EEX_{(air/soil/water/etc.)}} = 1.37\,(\log (EEXV_{(air/soil/water/etc.)} + 1.301) \text{ normalised to range 0–10} \quad (4)$$

where $\text{Dist.}_{(air/soil/water/etc.)}$ = fraction of a chemical that partitions at equilibrium into a specified environmental compartment

However, in practice EEX can be difficult to calculate owing to the lack of reliable data. For example, production volume data for calculating the emission score are not easily obtainable for the UK.

Similarly, data on chemical concentrations in different environmental compartments are also difficult to obtain for most chemicals.

3.2.5.2 Human exposure

Individual scores for different physicochemical properties for a chemical can be integrated into dedicated mathematical models to provide overall scores of human exposure. For example, EURAM integrates an emission and distribution score (defined as the fraction of emitted chemical to which humans are exposed based on BP, V_p and log K_{ow}), to derive a Human Exposure Value (HEXV) as follows (Hansen *et al.,* 1999):

$$\textbf{HEXV} = \text{Emission} \times \text{Dist.}_{(\text{humans})} \quad (5)$$

The human exposure score is given by:

$$\textbf{HEX} = 1.785\ (\log \text{HEXV} - 0.398) \quad \text{normalised to range 0–10} \quad (6)$$

Where $\text{Dist.}_{(\text{humans})}$ = fraction of a chemical to which humans are potentially exposed (Table 3.11).

The HEX score obtained is then used to prioritise chemicals for potential human exposure and is also a pre-requisite for the calculation of human health effects scores (HEFs). In this prioritisation scheme (see Section 3.3.4), the widely accepted indicators of chemical volatilisation and bioaccumulation potential, BP, V_p and log K_{ow}, are used to assign $\text{Dist.}_{(\text{humans})}$ scores (Hansen *et al.,* 1999). The highest BP or V_p value score is added to the log K_{ow} score to calculate the final $\text{Dist.}_{(\text{humans})}$ score (Table 3.11). The HEX model can be useful for prioritisation schemes concerned with screening chemicals for potential human exposure, provided all the necessary data can be obtained. In practice, though physicochemical property data are quite widely available, there is a considerable shortage of the production volume data necessary for calculating the emission scores required by this model.

Table 3.11 EURAM human exposure score index

Physicochemical property	Value	Distribution Score
Boiling Point (BP)	≤60	0.75
(°C at 950–1050 hPa)	60–200	0.50
	200–1500	0.25
	>1500	0.05
	Default	0.50
Vapour Pressure (V_P)	≥200	0.75
(hPa at 20–30 °C)	0.5–200	0.50
	<0.5	0.25
	Default	0.50
Log K_{ow}	>3	0.25
	≤3	0.00
	Default	0.25

From Hansen *et al.* (1999)

Another method that uses the same physicochemical properties as EURAM to score and prioritise the potential of chemicals for human exposure is that developed by HSE (Shillaker, 1992; Hansen *et al.,* 1999) (Table 3.12). A total physicochemical property score is used to prioritise chemicals for potential human exposure. The total physicochemical property score is subsequently used in an overall multi-factorial priority scoring model (the Overall Priority Score) described in Section 3.4 (Equation 8). However, insufficient information is provided in this method on how the physicochemical properties are scored to rank potential for human exposure.

Table 3.12 Physicochemical properties score index used in the priority setting method for UK dangerous substances

Physicochemical property[a]	Value range	Score[b]
BP	<60°C	
V_p	>10 hPa	3
BP	60–200°C	
V_p	1–10 hPa	2
BP	>200°C	
V_p	<1 hPa	1
Log K_{ow}	>3	1
	<3	0

From Shillaker (1992)
[a]BP, Boiling Point at 933–1067 hPa; V_p, Vapour Pressure at 25°C
[b]If no BP or V_P data available, default score applied to chemical = 2; if no log K_{ow} data, default score applied to chemical = 1

3.3 Effects on human health

3.3.1 Introduction

Human health effects of chemicals are quantified on the basis of a defined toxicological end-point or a suite of toxicological end-points, depending on the purposes of the prioritisation method. The health effects of a chemical can be assessed by the following methods: studies of *in vitro* test systems, animal studies, case reports and epidemiological studies in humans. In the absence of data, structure–activity relationships may be used but this entails a high degree of uncertainty. Predictive testing may include information on physicochemical properties, quantitative assessments of acute oral, inhalation and dermal toxicity, screens for subchronic and chronic toxicity, carcinogenicity and effects on reproduction (including teratogenic effects) and studies aimed at identifying specific neurotoxic and other effects. However, many chemicals have few toxicity data and these are often only from the cheap and quick toxicity tests that are conducted, for example LD_{50} or mutagenicity tests. The extent to which predictive testing is undertaken varies widely and depends, in part, on the intended use. Prioritisation schemes usually take into account information on acute toxicity, carcinogenicity and/or other specific effects (e.g. mutagenicity, teratogenicity, reproductive, neurotoxic, respiratory and skin sensitisation) to screen chemicals for overall toxicity. It must be recognised that any attempt to generate a single score to quantify a range of health effects is extremely crude.

3.3.2 Prioritisation of chemicals for their potential to cause acute health effects

In vivo toxicity tests are the most common predictive tests used to determine potential toxic effects in humans. These tests employ laboratory species and, because physiological processes are well known, the quantification of toxic responses in these animals is well studied. Acute toxicity end-points are used as a crude measure of chemical toxicity to help screen chemicals for potential human health effects. However, as discussed in Section 3.1, these may not be the most appropriate for low-level environmental exposure but are often used in prioritisation schemes because they are the only toxicity data available. The most commonly used acute toxicity end-points are rodent lethality following inhalation (LC_{50}), dermal exposure (LD_{50}) and oral ingestion (LD_{50}). These may provide an indication of the overall serious health effects that can result from human uptake via inhalation, contact exposure or ingestion. The US-EPA/CHEMS-1 method (Davis *et al.,* 1994; Swanson *et al.,* 1997) uses rodent oral LD_{50} (lethal dose for 50% mortality of test animals) and inhalation LC_{50} (lethal concentration for 50% mortality of test animals) as representative toxicological end-points to screen chemicals for

potential health effects, while the HSE, EURAM and CEPA methods use all three (oral, dermal and inhalation) acute toxicity end-points (Table 3.13; Koniecki *et al*., 1997).

Risk phases (R-phrases) are used as a method of labelling commercial substances after they have been classified toxicologically by the possible hazards to humans resulting from their use. Guidance for the classification and labelling of chemicals is provided under the Chemicals (Hazard Information and Packaging for Supply) CHIP) Regulations 1997 (HSC, 1997). This guide uses R-phrases to classify chemicals. Wherever R-phrases are applied, the wording used must comply with that laid down in the guide (HSC, 1997). R-phrase definitions cover most health effects resulting from exposure via ingestion, skin contact and inhalation. R-phrases are usually only applied when evidence for an effect has been adduced and evaluated, with some exceptions. For example, isocyanates are automatically assigned R48 unless there is evidence that the isocyanate does not cause respiratory hypersensitivity (see Annex). Some caution needs to be exercised when using R-phrases as a basis for prioritisation, partly because of the uncertainty in their derivation, but mainly because many substances have no R-phrase owing to lack of data.

Table 3.13 R-phrases used to describe the acute human health effects of chemicals

Acute toxicity	R-phrase[a]	Examples of prioritisation schemes using these R-phrases
Very toxic		
Oral	R28	UK Dangerous Substances[b], MAFF[c], EURAM[d]
Dermal	R27	UK Dangerous Substances[b], MAFF[c], EURAM[d]
Inhalation	R26	UK Dangerous Substances[b], MAFF[c], EURAM[d]
Toxic		
Oral	R25	UK Dangerous Substances[b], EURAM[d]
Dermal	R24	UK Dangerous Substances[b], EURAM[d]
Inhalation	R23	UK Dangerous Substances[b], EURAM[d]
Harmful		
Oral	R22	UK Dangerous Substances[b], MAFF[c], EURAM[d]
Dermal	R21	UK Dangerous Substances[b], MAFF[c], EURAM[d]
Inhalation	R20	UK Dangerous Substances[b], MAFF[c], EURAM[d]

[a]According to HSC (1997); [b]Shillaker (1992); [c]Wearne *et al.* (1996); [d]Hansen *et al.* (1999)

A number of prioritisation schemes use R-phrases to rank environmental chemicals for acute human health effects (e.g. HSE, EURAM and MAFF methods; Table 3.1). R-phrases are used as toxicity screening parameters because they cover a wide range of toxic effects in humans for a large number of new and existing substances. R-phrase data for European Commission new and existing substances can easily be obtained from a number of chemical databases (e.g. IUCLID; Pedersen *et al.,* 1995) and directories (e.g. Commission of the European Communities, 1993; Tomlin, 1994). R-phrases that have been used in prioritisation schemes to classify chemicals for acute health effects in humans are presented in Table 3.13. A full list of R-phrases and their definitions is given in the Annex.

3.3.3 Prioritisation of chemicals for their potential to cause chronic and other health effects

Carcinogenicity and mutagenicity are the most frequently, and sometimes the only, chronic health effects used to screen environmental chemicals in prioritisation schemes. Chronic and other health effects that are also used in prioritisation schemes include reproductive toxicity, teratogenicity, irritancy, neurotoxicity, respiratory and skin sensitisation.

3.3.3.1 Mutagens

Mutagenic effects are the result of alterations in the genetic material of the germ and/or somatic cells induced by chemical exposure. These alterations may take the form of a point mutation or a clastogenic event. The US-EPA/CHEMS-1, EURAM and HSE prioritisation methods use mutagenicity to prioritise environmental chemicals. Despite the fact that positive data for

mutagenicity tend to suggest carcinogenicity via a genotoxic mechanism, chemical mutagenicity is considered separately from carcinogenicity in these prioritisation methods. The HSE method, for example, includes a score for mutagenicity in calculating Total Toxicity Scores for environmental chemicals (see Table 3.14; Section 3.4).

Table 3.14 Mutagenicity score index for UK dangerous substances

Score	Mutagenic effect
9	Labelled for carcinogenicity or mutagenicity, or positive in an *in vivo* somatic or germ cell test
9 (default)	No test for gene mutation (*in vitro*) and no test for chromosome aberrations in somatic cells (*in vitro/vivo*) conducted
9	Positive in one *in vitro* test but no *in vivo* somatic cell test conducted
6	Positive in one *in vitro* test and negative in one *in vivo* somatic cell test
3 (default)	Negative test(s) (*in vitro*) for gene mutation, or negative test(s) (*in vitro/vivo*) for chromosome aberrations in somatic cells
0	Positive in one *in vitro* test but two or more *in vivo* somatic cell tests which were negative
0	Test(s) (*in vitro*) for gene mutations and chromosome aberrations in somatic cells (*in vitro/vivo*) — all tested negative

From Shillaker (1992)

3.3.3.2 Carcinogens

Carcinogenic effects are usually observed as tumours (i.e. neoplasms) induced in an organism (usually rodents) by exposure to a chemical via a genotoxic or epigenetic mechanism (Davis *et al.,* 1994).

A commonly used ranking system for assessing the quality of evidence for chemical carcinogenicity is the weight-of-evidence (WOE) classification scheme developed by the International Agency for Research on Cancer (IARC, 1987) (Table 3.15). The US-EPA/CHEMS-1 method makes use of the IARC WOE classification system to prioritise environmental chemicals for human health effects (Davis *et al.,* 1994; Swanson *et al.,* 1997). The IARC system is widely used and has been modified in certain prioritisation schemes to suit specific purposes. For example, the MAFF method emphasises the need for a consistent and objective scheme for classifying food chemicals to prioritise chemicals for risk assessment (McDonald *et al.,* 1996). McDonald and co-workers (1996) adapted and augmented the IARC system to 'assess the carcinogenic hazard' posed to humans by food chemicals in the UK by including additional categories to differentiate between genotoxic and non-genotoxic chemicals.

Table 3.15 IARC carcinogen classification system

Group	Definition of carcinogenic effect
4	Probably not carcinogenic. Evidence suggests *lack* of carcinogenic effects
3	Not classifiable as carcinogenic to humans. This classification is used when chemicals *cannot be placed into any other group*
2B	Possibly carcinogenic to humans. *Limited/inadequate* evidence in humans in the absence of *sufficient* evidence in laboratory animals Or, *limited* evidence in laboratory animals combined with *supporting* evidence from other relevant data
2A	Probably carcinogenic to humans. *Limited* evidence in humans and *sufficient* evidence in laboratory animals
1	Carcinogenic to humans. Sufficient evidence in humans

From IARC (1987)

When a large number of chemicals have to be prioritised, the WOE approach is useful for formalising qualitative classification. The principal limitation of WOE systems is that they relate to quantity of

evidence and give no information on 'carcinogenic potency'. In addition, they often do not take proper account of toxic mechanisms, pharmacokinetic considerations or mutagenic potential. This can influence the extrapolation of evidence from laboratory animals to humans (Woodward *et al.,* 1991). However, where reliable data for ranking carcinogens are lacking, WOE can be the only means of prioritising chemicals. The IARC system has also been adapted to rank the carcinogenicity of comparatively well-studied potent carcinogens (e.g. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) since good evidence of carcinogenicity for these is relatively easily acquired.

Another parameter that can be used to prioritise environmental chemicals on the basis of their carcinogenic potency is the TD_{50} in rodents (the toxic dose required to cause a tumour in 50% of the animals) (Nesnow, 1990; Glass *et al.,* 1991; Woodward *et al.,* 1991; McDonald *et al.,* 1996). Carcinogenicity ranking should aim to take genotoxicity studies, bioassay results, epidemiological data, mechanistic information and pharmacokinetic data into consideration, in addition to TD_{50} data, to provide an overall understanding of the health risks posed by exposure to chemicals.

More recently, a simplified approach to assessing carcinogenic potency has been developed using T_{25} to provide a Carcinogenic Potency Index. T_{25} is defined as 'the chronic dose rate in mg per kg body-weight per day which will give 25% of treated animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life time of that species' (Dybing *et al.,* 1997). An evaluation comparing T_{25} with TD_{50} values for a set of 110 chemicals gave an excellent correlation value ($r = 0.96$, $p < 0.0001$; Dybing *et al.,* 1997). The use of T_{25} values has shown that common trans-species, multiple-site carcinogens, as a group, are 10-fold more potent than single-site carcinogens. No such significant differentiation has been demonstrated using TD_{50} values. This is of particular relevance to prioritising carcinogenic potency in humans as multiple-site carcinogens represent a higher relative hazard in animals than single-site carcinogens (Tennant, 1993).

The proportion of new and existing chemicals on which extensive rodent testing has been performed is relatively small (Omenn *et al.,* 1995). Testing can therefore become very expensive when chemicals are being screened for their carcinogenic potency. In practice, the actual cumulative costs and time expenditure necessary to conduct toxicity testing on all chemicals for which there are no data available are too high. Therefore, some prioritisation schemes take advantage of predictive models based on chemical QSARs to predict the likelihood of the chemical's toxicity. Full toxicity testing can be conducted on the short-listed chemicals, which can help to minimise cost and time expenditure.

QSARs and SARs are models that predict a chemical's toxicity by extrapolation of data available from chemicals with a similar molecular structure. Recognisable chemical moieties and predictable physicochemical properties are central to accurate predictions of chemical carcinogenicity using SARs. In general, high molecular weight, high aqueous solubility, being a good substrate for conjugation and high general reactivity correlate with lower carcinogenic potential (Omenn *et al.,* 1995).

QSARs can be calculated using specially written computer software that enables a comparative analysis of chemical molecular structure and toxic properties (Woo *et al.,* 1994; Omenn *et al.,* 1995). The CHEMS-1 method uses SARs to assign a carcinogenicity rating to a chemical if the chemical contains one or more molecular substructures that have been related to carcinogenicity (e.g. a polyaromatic hydrocarbon) (Swanson *et al.,* 1997). Many prioritisation schemes and risk assessment guidelines derive QSARs from available toxicity data to compensate for missing data in WOE judgements (e.g. Davis *et al.,* 1994; European Commission, 1996). For example, in the US-EPA method, IARC WOE classifications were available for only 48 of the chemicals investigated (Davis *et al.,* 1994). QSARs were used to assign carcinogenic effect scores for those chemicals where data were unavailable.

There are many published methods for predicting chemical carcinogenicity. The most powerful are integrated computerised methodologies combining a number of tests (mutagenicity, clastogenicity, organ toxicity, physicochemical properties and SARs) to produce predictions of carcinogenicity for

untested chemicals. A critical review of a number of the methods available using SARs was published by Omenn *et al.* (1995). From their evaluation, the method of Ashby and Tennant (1994) was found to be the most reliable predictive method using SARs for estimating carcinogenicity. This method combines available experimental mutagenicity and toxicity data, with electrophilicity and structural information for predictions of chemical carcinogenicity. Omenn *et al.* (1995) concluded that this method was a good model for empowering risk-management decisions and prioritisation of chemicals as it could reduce the need for routine rodent lifetime bioassays, thereby limiting testing to very unusual or valuable chemicals.

3.3.3.3 Other health effects

Some prioritisation schemes accommodate any available toxicological information on the compound being prioritised and assign default values when information is lacking. The information could include toxicity data obtained from repeat dose sub-chronic and chronic studies, which might include evidence of neurotoxicity or immunotoxicity, as well as data from more specialised studies investigating potential reproductive toxicity (which includes potential developmental effects), sensitisation studies, etc. In most cases there are likely to be few data available and so any scheme needs to make provision for lack of data. In the HSE method (see Table 3.16), a high score is awarded if there are reproductive toxicity tests indicating adverse results or if there are no reproductive toxicity data.

Table 3.16 Reproductive toxicity score index for screening UK Dangerous Substances

Score	Reproductive effect
9	Labelled repro-toxic or, positive in a reproductive toxicity test
9 (default)	No test for reproductive toxicity conducted
3 (default)	No fertility test conducted but negative in a teratogenicity test
2 (default)	No teratogenicity test conducted but negative in fertility test
0	Negative in fertility and teratogenicity tests

From Shillaker (1992)

Developmental effects (e.g. teratogenic and other embryotoxic effects) may also be induced by chemical exposure. Embryotoxic effects include malformation, death and growth retardation. These are good indicators of potential for human developmental toxicity that have been used as end-points to screen chemicals for human health effects in a number of prioritisation schemes, including the US-EPA/CHEMS-1, EURAM and MAFF methods (Table 3.18).

Also of considerable toxicological importance to chemical prioritisation and risk assessment are chemicals that are potentially corrosive or irritant in contact with the skin or eyes and those causing adverse effects on the immune system (e.g. immunosuppression and allergenic sensitisation). The HSE method uses R-phrases to score for these types of health effects (Tables 3.17, 3.18) (Shillaker, 1992). R-phrases cover a wide range of effects including acute toxicity, repeat exposure toxicity, carcinogenicity, mutagenicity, reproductive toxicity, teratogenicity, irritancy and sensitisation for a large number of new and existing chemicals. They are therefore compatible with prioritisation schemes aiming to screen chemicals for a range of chronic health effects, particularly as R-phrase information is available for large numbers of chemicals from various chemical databases (e.g. IUCLID). For chemicals with no R-phrase data, it is necessary to conduct an assessment of available toxicity data (e.g. from rodent testing) to assign a toxicity score or apply a default score for the chemical.

The HSE method gives different weighting to a number of toxic end-points by assigning scores between 0 and 9 for each of the following: mutagenicity, reproductive toxicity, irritation/corrosion potential, sensitisation effects and acute toxic effects (see Tables 3.14, 3.16, 3.17, 3.18 for individual scoring; Shillaker, 1992). These scores aim to reflect the severity of individual health effects following exposure to individual chemicals. The choice of the most appropriate ranking scheme (i.e.

whether different health effects are given equal weighting or whether some types of effects are given greater importance than others) will vary to reflect the purposes of the prioritisation scheme. However, carcinogenicity, DNA damage and reproductive toxicity are generally given a higher score relative to other health effects.

Respiratory sensitisers are of particular concern as they can be potentially life-threatening to sensitised individuals at relatively low concentrations in the environment. As a consequence, the HSE method gives a high default score to this type of health effect (Table 3.17; Shillaker, 1992). Neurotoxic chemicals can cause alterations in human motor function and behaviour and impair learning ability. Neurotoxicity is a parameter used by the US-EPA/CHEMS-1 prioritisation method to screen chemicals for human health effects (Davis *et al.,* 1994; Swanson *et al.,* 1997). However, in practice neither immunosuppression nor neurotoxicity is included routinely as a parameter to screen chemicals for toxicity in prioritisation schemes, owing to the paucity of reliable data for these toxic effects.

Table 3.17 Toxicity score index for sensitisation and irritancy health effects

Toxic effect	R-phrase[a]	Score
Sensitisation effects		
Respiratory sensitiser	R42	9
Skin sensitiser	R43	2
No skin test conducted		1 (default)
Skin test conducted, no R-phrase needed		0
Irritation/Corrosion effects		
Corrosive	R34, R35	2
Serious damage to the eye	R41	2
Eye irritant	R36	1
Skin irritant	R38	1
Respiratory irritant	R37	1
No test conducted		1 (default)
Test conducted, no R-phrase needed		0

From Shillaker (1992)
[a]R-phrase — when toxicity data are available, scoring is based on the proposed/agreed R-phrases applied to a substance.
Many prioritisation schemes screen chemicals for different health effects using the relevant R-phrases in one ranking system.

3.3.4 Integrating and scoring human health effects

Crucial to any successful prioritisation scheme is the way in which scores for different types of toxicity are combined to ensure that the ranking system is compatible with the objectives of the scheme. Methods that use total or overall toxicity scores for a final prioritisation of chemicals for human health effects include the EURAM and US-EPA/CHEMS-1 methods (Table 3.18).

If multi-stranded prioritisation processes are used, then the strands must be condensed to produce a final priority list. For example, both the MAFF and EURAM prioritisation schemes use R-phrases to rank chemicals for acute and chronic health effects on a scale of 1 (low priority) to 10 (high priority) to produce their Toxicity Score (T) and Human Health Effects Score (HEF) (Table 3.18; Wearne *et al.,* 1996; Hansen *et al.,* 1999). The basis upon which a chemical can be assigned one of the R-phrases presented in Table 3.18 is provided in the Annex. Both methods assign a higher priority to carcinogenic, mutagenic and reproductive effects relative to other health effects. However, the two methods differ in their approach to dealing with missing R-phrase data and the way in which they score chronic health effects. The different purposes or concerns of the prioritisation scheme and the approach used to handle data gaps tend to be the main reasons for differences in health effect scores between these two schemes.

The EURAM method assigns a value of 0 to missing data, while the MAFF method uses a default value of 5 (Wearne *et al.,* 1996; Hansen *et al.,* 1999). The reasons for choosing a higher or lower

default value are not discussed. Similarly, the MAFF method assigns a much lower score to chemicals that can cause burns (R34/35) or serious damage to the eyes (R41) and ignores those that cause eye, skin and respiratory irritation (R36–38), while the EURAM method assigns a higher priority to all of these health effects since it is concerned with exposure from several environmental compartments (Table 3.18). An explanation for this may be that MAFF is more concerned with health effects resulting from ingestion of contaminated foodstuffs than those resulting from inhalation or dermal/eye contact, although this is not discussed (Wearne *et al.,* 1996). Most prioritisation schemes use expert/professional judgement to decide the weighting of data gaps and different health effects, and this process can differ widely between different expert groups to reflect scientific judgement.

The HSE method uses an algorithm that integrates the toxicity scores derived from the five different health effect scores represented earlier (Tables 3.14, 3.16, 3.17) called the Total Toxicity Score (Equation 7; Shillaker, 1992). For substances where all the required toxicity data score 0, there is a 'no effects of concern' category. The drawback associated with this model is that a score for carcinogenicity is not included. However, carcinogenicity is often the consequence of a mutagenic event (in a somatic cell) and a score for mutagenicity is included in the model. The Total Toxicity Score is calculated as follows:

Total Toxicity Score = Acute Toxicity Score + Irritation Score + Sensitisation Score + Repeated Exposure Effects Score + Mutagenicity Score + Reproductive Toxicity Score (7)

The US-EPA prioritisation method uses a Human Health Effects score algorithm to integrate its different health effects scores. It is virtually identical to the HSE Total Toxicity Score (Shillaker, 1992), incorporating several health effects (mutagenicity, reproductive toxicity, irritation and sensitisation potential) (Davis *et al.,* 1994).

Table 3.18 Health effects scores used by EURAM and MAFF prioritisation schemes

Health effect (Type of exposure)[a]	R-phrase	Health effect score	
		EURAM[b]	MAFF[c]
Acute toxicity			
Very toxic (Oral)	R28	3	2/3
Very toxic (Dermal)	R27	3	2/3
Very toxic (Inhalation)	R26	3	2/3
Toxic (Oral)	R25	2	Not used
Toxic (Dermal)	R24	2	Not used
Toxic (Inhalation)	R23	2	Not used
Harmful (Oral)	R22	1	1
Harmful (Dermal)	R21	1	1
Harmful (Inhalation)	R20	1	1
Chronic toxicity			
Causes severe burns	R35	6	2
Causes burns	R34	6	2
Irritancy			
Irritating to skin	R38	5	Not used
Risk of serious damage to eyes	R41	6	2
Irritating to eyes	R36	5	Not used
Irritating to respiratory system	R37	5	Not used
Sensitisation			
May cause sensitisation by inhalation	R42	7	7
May cause sensitisation by skin contact	R43	6	6
Carcinogenicity			
May cause cancer in humans	R45	10	10
May cause cancer in humans (inhalation)	R49	10	10
Possible risk of irreversible effects	R40[d]	9	9
Mutagenicity			
May cause heritable genetic damage	R46	10	10
Possible risk of irreversible effects	R40[d]	9	Not used
Reproductive toxicity			
May impair fertility	R60	10	10
Possible risk of impaired fertility	R62	9	9
May cause harm to unborn child	R61	10	10
Possible risk of harm to the unborn child	R63	9	9
May cause harm to breast-fed babies	R64	9	9
Other health effects			
Danger of cumulative effects on health (Repeat Dose)	R33	5	5
Toxic to health (Prolonged)	R48	7	7
Harmful to health (Prolonged)	R48	6	6

Default categories = 5 (MAFF) or 0 (EURAM)
[a]Definitions from HSC (1997); [b]Hansen *et al.* (1999); [c]Wearne *et al.* (1996)
[d] R40 has been redefined as 'Limited evidence of a carcinogenic effect'; see http://www.hse.gov.uk/chip/phrases.htm [accessed 10/03/04]

3.4 Overall total priority scoring

To produce a reliable short list of priority chemicals, it is important that the final ranking takes into consideration both the toxicological effects and potential for human exposure of the chemicals. A chemical should only receive high priority if the levels to which humans are exposed may potentially lead to adverse health effects. A number of prioritisation schemes use a score for environmental exposure incorporating, for example, production volume, pattern of use, persistence in the environment, bioaccumulative potential and a score for toxicity to humans (representing total acute and chronic toxic health effects). The overall priority scoring systems developed by the HSE,

EURAM, US-EPA/CHEMS-1, MAFF and Italian prioritisation schemes (Table 3.1) are described below.

The HSE method uses a model that integrates scores from four score indices to produce an Overall Priority Score (OPS) as follows (Shillaker, 1992):

Overall Priority Score (OPS) = Total Toxicity Score × Physicochemical Property Score × Use Pattern Score × Tonnage Score (8)

Where Total Toxicity Score is calculated as shown in Equation (7), Physicochemical Property Score as shown in Table 3.12, Use Pattern and Tonnage Score (= amount of the substance emitted annually into the EU environment) as in Section 3.2.1

Although this appears to be a comprehensive model, the scores included to represent human and environmental exposure (tonnage, use pattern and physicochemical property scores) do not account specifically for personal human exposure and may therefore not be suitable for prioritisation of environmental chemicals following non-occupational human exposure. However, by incorporating an additional score for human exposure into the model, it could then be more appropriately used for this prioritisation scheme. The model used by EURAM derives a Human Health Priority Score (HPS) as follows (Hansen *et al.,* 1999):

Human Health Priority Score (HPS) = HEX × HEF normalised to range 0–100 (9)

Where human exposure value (HEX) = Equation 6 (see Section 3.2.5.2) and health effects score (HEF) is given in Table 3.18

The HPS can be used in prioritisation schemes concerned especially with prioritising chemicals in the environment for human exposure and potential human health effects. However, in practice, it may not be possible to derive HPS from HEX due to the considerable lack of the emissions data for the UK that is required to calculate HEX in the first instance (Equation 5). It should also be highlighted that although the EURAM method does derive a score for environmental exposure (EEX) (Equation 4, Section 3.2.5.1), this score is not taken into account when deriving the HPS. Chemicals with a high potential for environmental exposure (i.e. a high EEX score) may be taken up by aquatic and terrestrial food chains, ultimately leading to human exposure via consumption of fish, other seafood, meat, dairy products and water.

The US-EPA method provides a comparably simple model to derive a Total Hazard Value (THV) for prioritising chemicals (Davis *et al.,* 1994). This model takes environmental exposure (bioconcentration and persistence) into account and identifies chemicals for potential to bioaccumulate in the food chain. There are no scores in the model for production volume and use pattern, so it may be used for prioritising chemicals for which there are no adequate databases available for scoring these parameters. The THV is calculated as follows:

Total Hazard Value = (Human Health Effects Score + Environmental Effects Score) × Exposure Potential (10)

Where exposure potential = biodegradability score + hydrolysis score + bioconcentration factor score

The MAFF prioritisation scheme uses an overall scoring algorithm to produce a final list of priority chemicals that incorporates all the major chemical screening parameters (production volume, pattern of chemical use, environmental fate and behaviour, bioaccumulation, persistence, food chain uptake and toxicity; Wearne *et al.,* 1996) called the Total Score (TS), which is calculated as follows:

Total Score (TS) = $P \times U \times R \times M \times E \times B \times T$ (11)

Where P = total score for production volume, U = total score for pattern of chemical use, R = total score for possible fate in the environment, M = total score for mechanism of entry into the food chain, E = total score for likelihood of chemical entering the food chain, B = total score for persistence and accumulation in the food chain and T = total score for toxicity (as shown in Table 3.18)

The Italian method was developed by Sampaolo and Binetti (1989) to prioritise European Commission existing substances for environmental and human exposure and potential associated hazards. This method presents a number of multi-factorial algorithms incorporating all of the major

screening parameters, with the exception of chemical pattern of use and persistence. The algorithms produce a value for Priority Direct Personal Exposure (DPE) and a DPE Risk Index as follows:

DPE Priority = $(PCP + TP) \times R' \times Q \times PDE \times BC \times RP$ (12)

DPE Risk Index = $(PCP + TP) \times Q \times PDE \times BC \times RP$ (13)

Where PCP = total score ascribed for physicochemical properties (molecular weight, melting point, BP, relative density, V_p, surface tension, water solubility, fat solubility, flammability, explosivity and oxidising properties); TP = total score ascribed for toxicological properties (rabbit dermal LD_{50}, rat oral LD_{50} and inhalation LC_{50}, irritation, sensitisation, long-term toxicity, mutagenicity, carcinogenicity and teratogenicity); R' = coefficient of priority for direct personal exposure, Q = score for quantity of chemical on the open market (tonnes/yr); PDE = score for plurality of direct exposure (sum of scores for personal, domestic and occupational exposures); BC = score for bioconcentration; and RP = score for size of risk population (partial population sectors).

These models can provide meaningful integrated overall total scores for chemicals since they take many important chemical parameters into consideration. Priority lists of chemicals produced on the basis of scores calculated with these models are more likely to represent a 'realistic' prioritisation of chemical exposure and toxicity to humans than other models. The Italian method is most suited to schemes concerned with prioritising chemicals for hazards to human health following exposure in domestic and workplace environments (Sampaolo & Binetti, 1989). In practice, however, despite the availability of chemical concentration data for occupational environments, there is a considerable paucity of data on ambient chemical concentrations in the UK environment, creating problems for any prioritisation scheme concerned with screening chemicals at low-level environmental human exposure.

Due to the simplicity of most of the models described above, it is possible to add or subtract scores for different parameters to suit the objectives of the prioritisation scheme, assuming all scores are equally weighted in the model. The Italian method in particular is easily augmented by, for example, the inclusion of scores for persistence and pattern of use (using appropriate existing scoring indices, such as those of the HSE method; Shillaker, 1992) because all parameters are scored as percentages by dividing individual score values by 100 (Sampaolo & Binetti, 1989). Similarly, if there are insufficient data to derive a score for a particular parameter in a model, the score for this parameter can be removed or assigned a default value. For example, in the Italian method, a 'priority coefficient' (R) is used and is defined as the ratio of the sum of the scores for parameters for which there are no data by the sum of the scores ascribed to all parameters (including scores for parameters where, in the absence of data, alternative criteria have been used). Values for R range from 0 (all data available) to 1 (no data available).

4 Limitations of Prioritisation Schemes

The production of a priority list of chemicals is only the first step in environmental management and it is important to emphasise it is not a conclusive list of chemicals of concern but a short-list of chemicals warranting individual full risk assessment, according to established guidelines (e.g. European Commission, 1996), before conclusions regarding any risks to humans can be established. There is no perfect, wholly scientific approach to weighting different selection criteria in prioritisation processes due to the number of assumptions and diversity of confounding factors that are incorporated into such schemes.

The majority of existing prioritisation schemes are developed for specific groups of chemicals and cannot be extrapolated to screen other groups. For example, inorganic chemicals and heavy metals behave in a different manner to organic compounds and are ubiquitous in the environment in different forms; they are largely ignored by most prioritisation schemes. The majority of the published screening methodologies do not deal with chemical mixtures owing to the different behaviour of the constituent chemicals in a mixture once they enter the environment and the difficulties of obtaining toxicity data for such mixtures. Traditional quantitative structure–activity relationships (QSARs) can assist in the estimation of the toxicity of individual chemicals in a mixture but provide no information on the possible interactions between them. However, recently efforts have been made to overcome the problems associated with ranking the carcinogenicity of chemical mixtures. For example, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) has developed a mathematical model to classify the carcinogenicity of chemical mixtures at hazardous waste sites (Reuter *et al.,* 1997). The classification is based on toxicity testing of the mixture itself or on the sum of toxicity data from the individual component chemicals of the mixture.

Although some refinement of selection criteria is afforded when ranking systems are designed for a specific purpose such as the determination of (i) human hazards, (ii) wildlife effects, (iii) key chemicals in specific environmental compartments (air, soil or water) or (iv) key groups of chemicals (e.g. organohalogens, heavy metals), there is still the problem of obtaining data for compounds for which little or no research on environmental exposure or likely fate and behaviour or toxicity has been conducted. This is highlighted by the fact that the European Council Regulation on Existing Substances (Council of the European Communities, 1993) requires manufacturers to provide data for chemicals only if data are currently available. This inevitably results in frequent data gaps and subsequent problems in priority setting (van der Zandt & van Leeuwen, 1992, cited in Hansen *et al*., 1999). With respect to the purposes of this review, it is anticipated that, in practice, reliable data on ambient levels of chemicals in air, soil and water in the UK and associated chronic health effects may be difficult to obtain for most chemicals.

4.1 Data gaps and data estimation

Errors may be introduced into a prioritisation scheme owing to the problem of data gaps. This may be exacerbated where there is no pre-defined procedure in place to deal with them in a scientific manner. Approaches to missing data vary widely across different systems. The worst-case scenario is the unavoidable omission of certain chemicals from prioritisation schemes on the grounds of insufficient data. Some prioritisation methods compensate for missing data by taking the most sensitive indicator to determine impact, while others provide alternative indicators of impact from which the user selects or defaults to an arbitrary pre-determined indicator designated for use in the absence of appropriate data (EPA, 1994). Methods that assign high scores to chemicals owing to uncertainty (e.g. when following the ‘precautionary principle’) can produce ‘false positives’, potentially creating a barrier

against new, possibly more environmentally sound chemicals (Siljeholm, 1997). Examples of methods providing default categories for chemicals with no data include the EURAM, HSE, MAFF and Italian methods (Table 3.1).

In some ranking systems data are estimated to fill gaps. Provided it can be estimated within an acceptable degree of accuracy this is useful. Other systems make *ad hoc* expert judgements to predict missing data. A number of prioritisation methods rely heavily on expert estimation techniques throughout priority setting. An example is the case by case expert judgement used to evaluate data on existing chemicals in IUCLID (Heidorn *et al*., 1996; Hansen *et al*., 1999), leading to a priority list based on potential for human exposure and hazard.

In many prioritisation schemes, quantitative predictive methodologies are used to estimate data gaps in an attempt to base predictions on a more scientific footing. A popular approach is to use structure–activity relationship(s) between chemicals, that is quantitative/qualitative SARs. This approach involves determining the likely toxicity of a chemical, based on its molecular structure, using models and some expert judgement (EPA, 1994). SARs have been used to fill data gaps in a number of prioritisation schemes, for example schemes for screening chemicals for cutaneous contact allergenicity, mutagenicity and skin carcinogenicity (Ashby *et al.,* 1993). SARs can also be used to predict general human and ecological toxicity of chemicals in prioritisation schemes with data paucity problems (Tennant *et al.,* 1990; Walker, 1991; Pedersen *et al.,* 1995; European Commission, 1996).

The general approach used by most prioritisation schemes is to 'ignore' irreconcilable data gaps, although some methods assign default values or resort to 'expert/professional judgement' (e.g. EURAM; Hansen *et al.,* 1999) based on weight of available scientific evidence such as the IARC WOE carcinogen classification system (Table 3.15; IARC, 1987). The US-EPA method, for example, uses SARs to estimate missing toxicity data and where no reliable QSAR/SARs exist to estimate these, they are left as 'missing data' (Davis *et al.,* 1994).

There is an unavoidable and variable margin of error associated with toxicity predicted using SARs, since there are generally no real data from an *in vitro*/*in vivo* toxicity test or bioassay of the chemical in question. Although SARs are calculated from chemicals with highly similar structures, small differences between chemicals in chemical–receptor molecular interactions may cause significant differences in the resultant toxic response at a higher level. Another example of a quantitative mechanistic method for use in estimating data is the Binary Chemical Interaction Methodology developed and applied to predict the carcinogenic hazard of chemicals by Woo *et al.* (1994).

The problem of data gaps was addressed at a SETAC workshop on chemical ranking and scoring (Swanson & Socha, 1997). The following possible approaches to handling data gaps and data estimation were proposed by the group:

- Use of alternative surrogate end-point for scoring purposes;
- The application of QSARs/SARs where possible and appropriate;
- Assignment of an empirically derived default value for the score (e.g. the median or geometric mean of the scores assigned to other substances for the same end-point);
- Postponing evaluation or scoring of a chemical until data are developed/acquired;
- Conduct sensitivity analysis to determine the impact of the data gap on the overall score and rank if no measured data are readily available and there is no acceptable QSAR estimate which may be applied;
- Use expert evaluation of the chemicals (e.g. scoring systems assigning scores based on expert evaluation for the various biological effects).

5 Recommendations for Future Improvements to Prioritisation Methodologies

There have been a number of workshops and steering committees concerned with producing prioritisation methodologies and their application. Examples are the SETAC workshop on chemical ranking and scoring and the US-EPA workshop on identifying a framework for the future of human health and environmental risk ranking, with the purpose of promoting a standardised and consistent approach to future prioritisation schemes (Swanson & Socha, 1997; EPA, 1994). A report by the UK Inter-departmental Liaison Group on Risk Assessment (ILGRA) highlighted the following shortcomings in current risk assessment techniques: inter- and intra-governmental prioritisation criteria should be standardised when comparing risk (both real and perceived); the ranking of risks should be done in more wide-ranging categories; common strategies should be developed for assessing high priority risks in an attempt to standardise data; and assessments should be repeated periodically to take account of new information, changes in public attitudes and available technology (ILGRA, 1996).

There are further limitations in priority ranking of environmental chemicals, mainly due to the lack of coordination and standardisation of definitions, procedures and applications adopted internationally. Some examples were presented at the US-EPA workshop (EPA, 1994).

- How can users be instructed to apply priority ranking systems properly and avoid misuse?
- Must a minimum, mutually available database be developed before a ranking system can be employed?
- A single technical framework needs to be developed that is scientifically sound and is consistent across EPA offices and state, federal and international boundaries.
- Approaches to missing data (data gaps) should be standardised.

6 Evaluation of Prioritisation Schemes

This section discusses the key parameters used to screen chemicals in prioritisation schemes for scoring chemical exposure (emissions to the environment; environmental exposure; human exposure) and adverse health effects for the purpose of developing a prioritisation scheme for the Department of Health (DH). The main objective of the DH scheme is to identify and prioritise environmental chemicals that might cause adverse human health effects following low-level exposure (from air, soil, water and food) in the UK with a view to conducting further work on these chemicals. This might include obtaining better exposure data and/or conducting a more thorough toxicological assessment that might entail further toxicological testing or other research work. The different approaches available for selecting criteria to estimate exposure and adverse health effects are evaluated, taking into consideration the likelihood of obtaining adequate data. The physicochemical properties that are used to prioritise chemicals for DH are summarised. Full details of the proposed screening method are discussed in a separate report (IEH, 2004). The criteria used by a number of existing prioritisation schemes to score the exposure and health effects parameters are compared in Table 6.1.

Table 6.1 Summary of the emission, physicochemical properties and health effect end-points used by several prioritisation schemes

Scoring of:	Criteria used to derive score:							
	EURAM[a]	**US-EPA[b]**	**CHEMS-1[c]**	**CEPA[d]**	**HSE[e]**	**Italian[f]**	**MAFF[g]**	**DETR/WIR[h]**
1 Emissions into the environment:								
Prod. Volume?	√	√	√	√	√	√	√	√
Pattern of Use?	√				√		√	
2 Environmental exposure:								
Environmental Diffusion?								
Soil Mobility (t_C,t_D)						√		√
Persistence?								
Photolysis $T_{1/2}$				√		√		
Hydrolysis $T_{1/2}$		√	√	√				
Volatilisation $T_{1/2}$	√			√				√
Metabolism/BOD		√	√	√				
Fugacity?	√							
3 Human exposure:								
Physicochemical Properties?								
Henry's Constant								√
Molecular Weight					√	√		
Boiling Point	√					√		
Melting Point					√	√		
Vapour Pressure	√					√	√	
Water Solubility						√	√	
Surface Tension						√		
Lipid Solubility						√	√	
Phase Density							√	
K_{oc}						√		
Log K_{ow}	√							
Bioaccumulation?								
Log K_{ow}	√		√	√	√		√	√
BCF (fish)		√	√	√		√	√	√
Persistence?								
$T_{1/2}$ in Fish	√							
4 Human health effects:								
Acute?								
Oral LD_{50}	√	√	√	√	√	√	√	
Dermal LD_{50}	√			√	√	√	√	
Inhalation LC_{50}	√	√	√	√	√	√	√	
Chronic & other?								
Carcinogenicity	√	√	√	√	√	√	√	
Mutagenicity	√			√	√	√	√	
Reproductive Tox.	√		√		√		√	
Teratogenicity	√	√	√	√	√	√	√	
Irritancy	√				√	√	√	
Sensitisation	√				√	√	√	
Neurotoxicity		√	√					
Repeat Exposure	√				√	√	√	
Other				√				

BCF, bioconcentration factor; BOD, biological oxygen demand during microbial metabolism; log K_{ow}, log octanol–water partition coefficient; LC/D_{50}, lethal concentration/dose for 50% mortality of test animals; $T_{1/2}$, half-life; t_C, convective mobility; t_D, diffusive mobility
[a] Hansen *et al.* (1999); [b] Davis *et al.* (1994); [c] Swanson *et al*. (1997); [d] Koniecki *et al.* (1997); [e] Shillaker (1992); [f] Sampaolo and Binetti. (1989); [g] Wearne *et al*. (1996); [h] Duarte-Davidson and Jones (1996), Wilson *et al*. (1996)

6.1 Scoring exposure

6.1.1 Environmental exposure

6.1.1.1 Emissions to the environment

Production volumes and patterns of use are widely used by different prioritisation schemes to estimate annual emissions to the environment (see Table 6.1). For example, humans are more likely to be exposed to chemicals that are used in a dispersive manner and emitted into the environment in large quantities than those used in closed systems. It should be noted that compounds that are (i) emitted into the environment in small/negligible amounts (e.g. <10 tonnes/annum), (ii) produced unintentionally or (iii) produced as by-products may not be accounted for when annual production volume and pattern of use data are used as estimates of exposure. For example, tobacco smoke has been identified as a major source of exposure to benzene in the general population, despite the fact that this source accounts for only 0.007% of the total benzene emitted annually (IEH, 1996). Similarly, despite the fact that dioxins are produced unintentionally and are present in the environment in very low concentrations (i.e. production volumes are negligible), they have often been prioritised due to their bioaccumulative potential and adverse heath effects (e.g. Duarte-Davidson & Jones, 1996).

Data on production volumes and pattern of use are currently available for the EU as a whole in databases such as IUCLID. However, it is more difficult to obtain this sort of information for the UK as it is only available by contacting the main UK producers/manufacturers directly; since there is no statutory obligation requiring companies to disclose production volume data, these are only provided on a voluntary basis. In addition, details of the amounts of a substance that are imported/exported from/to the UK annually are also necessary to determine the total amounts of a chemical emitted to the UK environment. Contacting companies to obtain this type of information is a time consuming exercise that goes beyond the scope of this prioritisation scheme.

The MAFF method uses production volume data to prioritise organic contaminants in foodstuffs for possible adverse health effects (Wearne *et al.,* 1996). However, production volume data were often found to be unavailable. To compensate for missing data, two default values were introduced into the emission score index: a higher default value for chemicals with no production volume data (i.e. no UK or EU data) and a lower default value for those where EU production volume data were available but there were no UK data. Other ranking systems have used EU data in other ways to estimate production volumes for individual countries. However, these different approaches do not provide realistic estimates of emissions into the UK environment, since production volumes and import volumes vary considerably between EU countries according to their level of industrialisation, economy, and so on.

In view of the difficulties of obtaining accurate emission data for the UK and due to the probability that, in using an emission score, a large proportion of chemicals will be assigned 'missing data' or 'default' scores, this parameter was not incorporated into the DH prioritisation scheme. It is plausible, however, that an emission score could be incorporated into the scheme in the future once production volume data for the UK become more widely available.

6.1.1.2 Physicochemical properties

A number of physicochemical properties have been selected to determine the environmental exposure of chemicals. These are molecular weight, water solubility (S), vapour pressure (V_p), the octanol–water partition coefficient (K_{ow}), the organic carbon–water partition coefficient (K_{oc}), Henry's Law Constant (H_c), bioconcentration factors in fish (BCF) and persistence (half-life in soil, water and air; $T_{1/2}$). Data for all of these physicochemical properties can be obtained from a number of databases (e.g. IUCLID; Howard, 1989, 1990, 1991; MacKay *et al.,* 1991, 1992, 1993; Tomlin, 1994) or can be calculated relatively easily from the other physicochemical properties. These physicochemical

properties were concluded to be the most appropriate for screening environmental exposure in the DH prioritisation scheme because they have been used successfully in other schemes (e.g. EURAM, US-EPA/CHEMS, DETR/WIR) and are generally widely available. Although additional physicochemical properties would provide a more accurate picture of environmental fate, the number of physicochemical properties included in the model has been balanced with the difficulty of obtaining data for these. For example, BCF data for fish were selected to predict the potential of a chemical to bioaccumulate in the food chain, rather than BCF data from other species (e.g. BCFs from soils, crops, livestock or milk) as there tend to be more data available for fish.

6.1.1.3 Environmental fate

MacKay's fugacity model was used as the first step in the DH scheme to predict the environmental fate of a chemical, that is the amount of a chemical likely to partition to air, soil, water and fish following its release into the environment (MacKay *et al.,* 1991; Table 3.6). This was then used to weight the contribution of each medium to the total population exposure (i.e. to weight the different exposure routes, see Section 6.1.2).

The physicochemical properties needed to calculate fugacity (*f*) are S, V_p, H_c, K_{ow}, K_{oc}, temperature (T), phase density (ρ), lipid content (L) and mass fraction of organic carbon (f_{oc}). As with all models, assumptions have to be made on a number of variables (e.g. T, ρ, L and f_{oc}).

6.1.2 Human exposure

The parameters used to score human exposure depend on the environmental compartment in which the chemical is found. The main environmental sources of chemicals for human exposure are (i) air (i.e. inhalation), (ii) drinking water/groundwater (i.e. ingestion), (iii) soil (root uptake by plants in the human food chain, e.g. vegetables) and (iv) foodstuffs (contaminants bioaccumulated from the food chain) (Figure 3.7). In the DH prioritisation scheme, fugacity and physicochemical properties are used in simple algorithms to determine scores for potential for human exposure from air, water, soil and food. Equal weight is given to each environmental compartment of interest as the purpose of the DH scheme is to highlight compounds of interest in each of these media rather than to find out the importance of these relative to each other. The physicochemical properties used to estimate chemical exposure from each medium are summarised below.

6.1.2.1 Exposure via air inhalation

The potential of chemical exposure via inhalation is estimated from f_{air} (proportion of the chemical retained in air), H_c (tendency of a chemical to volatilise) and $T_{1/2}$ in air (residence time/persistence of the chemical in air).

6.1.2.2 Exposure via water ingestion

The potential of chemical exposure via water ingestion is estimated from f_{water} (proportion of the chemical retained in water), $T_{1/2}$ in water (persistence of a chemical in water) and H_c and/or K_{ow} (tendency of the chemical to remain in solution).

6.1.2.3 Exposure from soil

The potential of chemical exposure from soil is estimated from f_{soil} (proportion of the chemical retained in soil), $T_{1/2}$ in soil (persistence of the chemical in soil) and K_{ow} (potential of the chemical to remain in soil via adsorption to organic matter). K_{ow} also provides an estimate of the tendency of a chemical to adsorb to plant roots. Also strong soil adsorption may lead to food chain bioaccumulation following the route soil–animal ingestion–beef/milk/dairy products.

6.1.2.4 Exposure from food/food chain

The potential of chemical exposure from fish is estimated from f_{fish} (proportion of the chemical likely to partition to fish) and BCF in fish (potential of the chemical to bioaccumulate in fish) or log K_{ow} (general indication of bioaccumulation potential). BCF values are more widely available for fish and can be calculated from K_{ow} to compensate for missing data.

6.2 Scoring health effects

R-phrases for a number of acute and chronic toxic end-points are used to score chemicals for human health effects. However, it should be stressed that R-phrases have their limitations, not only in their scientific definition, but mainly because not all chemicals have R-phrases, either because of a lack of data or because they have not been through the EU classification or Labelling Working Group in DGXI. R-phrase data were developed with relevance to humans. They also cover a wide variety of health effects and have been used successfully by the EURAM, HSE and MAFF methods to produce health effects scores. The weighting of different health effects is dependent on the purposes of the prioritisation scheme. For the DH scheme, health effects following human exposure from UK environmental levels of chemicals in air, water, soil and food are of greatest concern. From low-level exposure, chronic health effects tend to be more commonly observed than acute effects, so they are therefore a higher priority for a DH health effects score. The method followed here is that of EURAM (Table 3.18) although missing data are given a value of 5 (instead of 0) to ensure that data gaps for R-phrases are accounted for.

6.3 Overall priority scores

It is generally accepted that prioritisation schemes that are concerned with screening environmental chemicals for adverse human health effects must identify a chemical's propensity for environmental and human exposure in order to determine whether it can pose a risk to human health. Considering this, some prioritisation schemes weigh scores for exposure and toxicity equally, while others may be concerned with one aspect more than the other. Consequently, the way in which an overall priority score is derived from exposure and toxicity scores depends on the purposes of the prioritisation scheme.

In the DH scheme, exposure and health effects scores are weighted equally using an appropriate algorithm. The highest scoring chemicals are identified as a 'priority' to human health following exposure to environmental levels in the UK. Chemicals are given an overall score that accounts for all exposure routes and health effects as well as for individual exposure routes (i.e. air, soil, water, food chain) and health effects.

7 Conclusion

A number of dedicated workshops have been held on the improvement, use and interpretation of prioritisation methodology. These provide considerable insight for environmental managers faced with the task of prioritising hazardous environmental chemicals. Some good examples of proceedings from specialist workshops, dedicated guidance notes and reviews on prioritisation methodology include:

- Data Collection and Interpretation Guide for Environmental Hazard Classification (Pedersen *et al.,* 1995);
- Proceedings from the US-EPA 'Workshop on Identifying a Framework for the Future of Human Health and Environmental Risk Ranking' (EPA, 1994);
- HSE Research Strategy Unit 'Risk Ranking' Report (HSE, 1997);
- EURAM method (Hansen *et al.,* 1999).

An arbitrary score is assigned to a chemical for each of the criteria (e.g. between 0 and 10 or 100) on the basis of its comparative importance or priority (e.g. bioaccumulative potential or carcinogenicity). Scores from each of the criteria are then weighted according to the importance of each criterion and integrated using a specially formulated mathematical model to produce a final overall priority score. Prioritisation is a process of elimination, so it is imperative that environmental managers have clear objectives for prioritisation, othewise important chemicals may be omitted by the screening process owing to a low score being assigned for a comparatively unimportant parameter.

It is also very important to identify clearly the role and boundaries of professional judgement in cases where data are missing or estimated in chemical screening. A set response procedure on what action should be taken where data gaps appear should be agreed prior to screening. For example, should professional judgement be used in combination with or instead of quantitative structure–activity relationships (QSARs) and computerised prediction models? The approach that should be used in the valuation of scores and weighting of data from different parameters should also be researched with the aims and purposes of the prioritisation method in mind. The flexibility and transparency of the method adopted are also important in order to allow new data or unforeseen modifications in methodology to be incorporated as and when necessary. The method used should also be compatible with existing methodology, to facilitate comparison and cross-referencing of data in cases of data gaps and/or professional judgement.

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Annex

R-phrase definitions and the grounds upon which chemicals are assigned R-phrases

R-phrase	Health effect (Exposure type)	Basis for classification under corresponding R-phrase
	Acute toxicity	
R28	Very toxic (Oral)	LD_{50} (rat): ≤ 25 mg/kg Less than 100% survival at 5 mg/kg oral (rat) by the fixed dose procedure
R27	Very toxic (Dermal)	LD_{50} (rat or rabbit): ≤ 50 mg/kg
R26	Very toxic (Inhalation)	LC_{50} (rat) for aerosols or particulates: ≤ 0.25 mg/l/4 hr LC_{50} (rat) for gases and vapours: ≤0.5 mg/l/4 hr
R25	Toxic (Oral)	LD_{50} (rat): 25 < LD_{50} ≤ 200 mg/kg Discriminating dose, oral (rat) 5 mg/kg: 100% survival but evident toxicity
R24	Toxic (Dermal)	LD_{50} (rat or rabbit): 50 < LD_{50} ≤ 400 mg/kg
R23	Toxic (Inhalation)	LC_{50} (rat) for aerosols or particulates: 0.25 < LC_{50} ≤ 1 mg/l/4 hr LC_{50} (rat) for gases and vapours: 0.5 < LC_{50} ≤ 2 mg/l/4 hr
R22	Harmful (Oral)	LD_{50} (rat): 200 < LD_{50} ≤ 2000 mg/kg Discriminating dose, oral (rat) 50 mg/kg: 100% survival but evident toxicity
R21	Harmful (Dermal)	LD_{50} (rat or rabbit): 400 < LD_{50} ≤ 2000 mg/kg
R20	Harmful (Inhalation)	LC_{50} (rat) for aerosols or particulates: 1 < LC_{50} ≤ 5 mg/l/4 hr LC_{50} (rat) for gases and vapours: 2 < LC_{50} ≤ 20 mg/l/4 hr
	Chronic toxicity	
R35	Causes severe burns	If, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of <3 min exposure or if result can be predicted
R34	Causes burns	If, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of <4 hr exposure or if result can be predicted
	Irritancy	
R38	Irritating to skin	If the chemical causes significant inflammation of the skin which persists for ≥24 h after an exposure period of <4 hr determined on rabbit according to the cutaneous irritation test method
R41	Risk of serious damage to eyes	If when applied to the eye of an animal severe ocular lesions are caused which occur in <72 hr exposure and which are present ≥24 hr from testing
R36	Irritating to eyes	If when applied to the eye of an animal significant ocular lesions are caused which occur in <72 hr exposure and persist for ≥24 hr from testing
R37	Irritating to respiratory system	For substances which cause serious irritation to the respiratory system based on practical observation in humans and positive results from appropriate animal tests
	Sensitisation	
R42	May cause sensitisation by inhalation	If there is evidence that the substance can induce specific respiratory hypersensitivity. Where there are positive results from appropriate animal tests. If substance is an isocyanate, unless there is evidence that it does not cause respiratory hypersensitivity.
R43	May cause sensitisation by skin contact	If practical experience shows that the chemical is capable of inducing a sensitisation reaction in a substantial number of people. Where there are positive results from an appropriate animal test.

R-phrase	Health effect (Exposure type)	Basis for classification under corresponding R-phrase
	Carcinogenicity	
R45	May cause cancer in humans	For chemicals which present a carcinogenic risk following ingestion, inhalation and skin contact.
R49	May cause cancer in humans (inhalation)	For chemicals which present a carcinogenic risk only when inhaled, e.g. dust vapour or fumes, and for which other routes of exposure (e.g. ingestion, skin contact) do not present any carcinogenic risk.
R40[a]	Possible risk of irreversible effects	Carcinogenic irreversible effects following exposure according to information from epidemiological data, appropriate animals tests for genotoxicity, metabolic or biochemical studies, induction of spontaneous tumour formation, SARs relative to similar carcinogens.
	Mutagenicity	
R46	May cause heritable genetic damage	Mutagenic irreversible effects of heritable genetic damage following exposure according to *Category 1* human epidemiological data, *Category 2* animal testing showing mutagenic effects, other
R40[a]	Possible risk of irreversible effects	cellular interactions relevant to mutagenicity in germ cells of mammals *in vivo* or mutagenic effects in mammalian somatic cells *in vivo* in combination with clear evidence that substance or its metabolite reaches the germ cells (e.g. specific locus mutation test; heritable translocation test; dominant lethal mutation test; test for sister chromatid exchanges; unscheduled DNA synthesis; assay of covalent binding of mutagen to germ cell DNA; assaying other kinds of DNA damage; toxicokinetic models) or *Category 3* data from *in vivo* somatic cell mutagenicity assays or in vivo somatic cell DNA interaction assays.
	Reproductive toxicity	
R60	May impair fertility	Substances which impair fertility in humans; e.g. impair reproductive function, adverse effects on libido, sexual behaviour, spermatogenesis/oogenesis, hormonal responses relevant to physiological responses relating to fertilisation, ovum development and implantation.
R62	Possible risk of impaired fertility	Substances which cause concern for human fertility; e.g. impair reproductive function, adverse effects on libido, sexual behaviour, spermatogenesis/oogenesis, hormonal responses relevant to physiological responses relating to fertilisation, ovum development and implantation.
R61	May cause harm to unborn child	Substances which cause developmental toxicity; e.g. non-heritable harmful effects on progeny, interference with development *pre* and *post partum*, reduced body weight, growth and developmental retardation, organ toxicity, abortion, structural defects (teratogenic effects), death, impaired postnatal mental/physical development up to age of puberty,
R63	Possible risk of harm to the unborn child	Substances which cause concern for humans owing to possible developmental toxic effects
R64	May cause harm to breast-fed babies	For substances which are absorbed by women and may interfere with lactation or which may be present in breast milk in amounts sufficient to cause concern for the health of a breast-fed child, on the basis of data from; toxicokinetic studies which indicate likelihood that the substance would be present in potentially toxic levels in breast milk; and/or that according to two generation studies in animals the presence of adverse effects on offspring occurs due to lactational transfer; and/or evidence in humans which indicates a risk to babies during lactation.
	Other Health Effects	
R33	Danger of cumulative effects on health (Repeat dose)	For substances when accumulation in human body is likely and may cause some concern which, however, is not sufficient to justify use of R48.

[a] R40 has been redefined as 'Limited evidence of a carcinogenic effect'; see http://www.hse.gov.uk/chip/phrases.htm [accessed 10/03/04]

R-phrase	Health effect (Exposure type)	Basis for classification under corresponding R-phrase
R48	Danger of serious damage to health (Prolonged or repeated)	Serious damage (clear functional disturbance or morphological change which has toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route. Substances are classified at least Toxic with R48 when these effects are observed at levels of the order of : oral (rat) ≤5 mg/kg (body weight)/day dermal (rat or rabbit) ≤10 mg/kg (body weight)/day inhalation (rat) ≤0.025 mg/l, 6 hr/day

From HSC (1997)