XA04N0315

General Approaches to the Risk Assessment of Chemicals

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Introduction

In the context of the UNCED 92 "Earth Summit" in Rio, the following definition of chemical risk assessment has been developed:

"Chemical risk assessment is a scientific process that identifies and quantifies the potential adverse effects on human health or ecosystems of defined exposures to chemical substances, to mixtures that include chemicals, or to chemically hazardous processes or situations. Risk itself is the probability of the occurrence of a defined adverse effect in a defined group and in defined circumstances."

I would not be so impertinent as to try and improve upon a definition that has the tacit endorsement of the majority of world-leaders. Furthermore, I consider that too many man-years have been spent discussing this topic. Thankfully the UNCED definition recognises chemical risk assessment as being a process and not some immutable physical law. In this presentation I will attempt to explain some of the details and mechanisms of that process but first of all it is worthwhile to spend a few moments putting chemical risk assessment in its proper context and asking the simple question: why do we want/need to assess the potential risk of chemicals?

In general terms, chemicals risk assessment is carried out in order to ensure that neither man (consumer/worker/general public) nor the environment are exposed to unacceptable risks arising from the production, use and disposal of chemicals. At a national and/or international level, risk assessments are performed by the regulatory authorities before they accept notification dossiers (e.g. new industrial chemicals) or grant authorizations (e.g. pharmaceuticals, pesticides, cosmetics, food additives). At the local level, plant-operators must carry out risk assessments to ensure that in the particular circumstances of their factory the workers are adequately protected and that satisfactory accident prevention and contingency plans are prepared. Similarly, local authorities must carry out risk assessments before deciding upon the granting of permits for landfill sites or the discharge of toxic chemicals to water or air and in doing so they must take into account the hydrology, geology and climate of the specific locality.

While the basic approach to chemical risk assessment will be the same, irrespective of the specific objective for which the assessment is carried out, the details will vary as a function of: the product type (pharmaceutical, pesticide, industrial chemical, etc), the target population of interest (patient, environment, consumer, worker, etc) and the exposure scenario (global, international, national, local).

Components of chemical risk assessment

While risk assessment is in practice an iterative process it is nevertheless possible to identify several, more or less, discrete components within that process (fig. 1).

Data input

All chemical risk assessment requires the collection of two types of data: those relating to the potential of the chemical to cause undesirable effects (effects data), and those relating to the environmental fate and behaviour of the chemical and which allow an assessment of the concentration to which the target population will be exposed (exposure data).

The quality of any risk assessment is dependent upon the quality and quantity of the input data driving the process. However, the extent and nature of the data to be collected will be dependent upon the precise objective of the assessment. Fig. 2 details the minimum pre-marketing data set (MDP) recommended by the OECD for the evaluation of new industrial chemicals before they are placed on the market. The data requirements specified are relatively modest but, nevertheless, this data package costs some 150,000 dollars to generate.

In contrast to industrial chemicals, registration procedures for new pharmaceuticals require far more extensive toxicological data although exposure, being regulated by controlled dose levels, is less problematic: furthermore, environmental concerns are generally of secondary importance. For pesticides, on the other hand, while extensive mammalian toxicological data is still required, information relating to effects on fish, birds and algae are equally important as are data allowing the estimation of exposure concentrations, for example, in the tractor cab, in food and in the environment.

If the extent of the data package is important, then so is the quality of that data. Given problems with inter-operator and inter-laboratory differences compounded, in tests on living organisms, by natural biological variability, the best way to ensure quality and comparability is to use standardised test methods. Methods, or guidelines, developed by organisations such as the OECD(1) constitute one of the essential pillars for developing harmonised international approaches to chemicals risk assessment. One further adjunct to the use of standardised test methods is the application of quality assurance control by means of good laboratory practice (GLP). Again, OECD(2) principles of GLP applied throughout the world are the assurance that tests allegedly carried out according to OECD test guidelines are in fact carried out according to best practice.

Hazard identification

Hazard identification was defined in the UNCED context as follows:

"Identifying the adverse effect which a specified chemical or mixture or process has an inherent capacity to cause. This is developed from determination of chemical and physical properties, epidemiological observations, animal experimentation, *in vitro* testing or structure activity relationships."

From the above definition the essential point to notice is that hazard identification concentrates on the intrinsic properties of the chemical and ignores the likelihood or extent of exposure to the

chemical. At first sight, hazard identification may therefore appear to be of limited interest in the risk assessment process because risk assessment requires that exposure is also taken into account. However, while effects data frequently allow an objective assessment of whether a chemical is explosive, flammable, very toxic, mutagenic, etc. exposure will frequently vary from person to person, ecosystem to ecosystem and country to country. It is therefore often easier to achieve agreement on hazard identification than on risk assessment and many countries and regional organisations use hazard identification as the starting point for their chemical control programmes. One example of such an international/regional programme is the system for the classification and labelling of dangerous substances and preparations established in the European Community. In this system the intrinsic properties of a chemical lead to a classification, a term synonymous with, hazard identification, which in turn results in the requirement to label the chemical in a certain way (see Fig. 3). Classification in certain categories may also lead to additional risk management measures being applied to the marketing of a chemical and or its use in the workplace.(3,4)

As indicated above, hazard identification (classification) is frequently the starting point in the risk assessment process. This has been recognised in Chapter 19 of Agenda 21 at the UNCED 92 meeting where it was agreed to develop an international system for the classification and labelling of dangerous substances.

Dose response assessment

UNCED defined this component in the process as:

"Estimating the relationship between dose, or level of exposure, and the incidence and or severity of any effect."

For ease of presentation it is convenient to differentiate between dose response assessment in relation to human health and dose response assessment related to the environment.

a) Human health — dose response assessment

The objective here is to define, on the basis of the available toxicological data, the highest acceptable exposure level in relation to the most sensitive end point. Toxicity data are therefore reviewed to identify the No Observed Adverse Effect Level (NOAEL). Then, in order to take account of the uncertainty in extrapolating across species, various assessment factors (usually in the range $1 \times 10^{-1} - 1 \times 10^{-4}$) are applied to this experimentally determined NOAEL in order to generate a) Maximum Acceptable Concentrations (M.A.C. values) for the workplace or b) Estimated Doses of Concern (EDC) or, with adjustments for normal dietary patterns, c) Acceptable Daily Intakes (ADI).

The above approach to dose response analysis is probably acceptable when dealing with chemicals and end points for which it is possible to establish a threshold level below which a chemical is expected to have no adverse effect e.g. general systemic toxicity, reproductive toxicity. This approach is based on the assumption that below a certain concentration, the organism's natural defence and de-toxification mechanisms will respond to, and cope with, toxicant challenge but that above this threshold these mechanisms are overwhelmed. However, when dealing with chemicals which are known, for example, to be genotoxic carcinogens, the concept of a threshold is probably meaningless and one has to assume that the chemical may exert an adverse effect at any concentration.

b) Environmental effects

Here again the objective is the definition of a no concern level, but in contrast to human health effects assessment, the no concern concentration normally applies to the entire ecosystem not to one target species. Natural ecosystems are highly complex and sometimes extremely fragile. Nevertheless, it is frequently the case that environmental effects data is limited to acute toxicity studies on one or two species of fish or aquatic invertebrates (frequently the water flea **Daphnia magna**). Chronic or long term toxicity studies are not usually available and tests on terrestrial organisms are extremely rare. Furthermore, studies involving multispecies test systems (mesocosms) or artificial ecosystems (e.g. artificial streams) are usually reserved for pesticides. Given the paucity of data the obvious problem is how to determine a realistic no-concern level. In practice, scientists have responded to the high degree of uncertainty by building-in very large safety or assessment factors when extrapolating from restricted data sets to the real environment. The general principle is: the smaller and weaker the data set, the greater the assessment factor. Fig. 4 shows the assessment factors agreed recently by the OECD Hazard Assessment Advisory Body and which have achieved a high degree of concensus in the international Community.

Pathway and exposure assessment

To this point I have concentrated on the evaluation of probable effects and the objective of defining a safe concentration of a chemical with respect to a given population or ecosystem. We now need to consider an evaluation of the concentration of the chemical to which the population or environment will be, or is, exposed. This is known as Pathway and Exposure Assessment.

In the UNCED context this element in the risk assessment jigsaw was defined as:

"Determining the pathways and rates of movement of a chemical in the environment, its transformation or degradation and its concentration, when possible, at critical points thereby estimating the doses to which various populations or ecosystems are actually exposed."

Obviously, the most precise method for evaluating exposure concentrations is to measure them **in situ**. However, for chemicals about to be placed on the market this is clearly impossible and furthermore, for many existing chemicals such monitoring data do not exist. Therefore, in the absence of such information, models must be used to predict or estimate the likely exposure concentrations. There are a variety of such models, some addressing ecosystems others concerned with occupational or consumer exposure.

a) Consumer exposure

In our own homes we are exposed to a variety of chemicals: household cleaning products – detergents; emissions from paints and varnishes applied to walls and furnishings; pesticides applied to carpets and fabrics; flame retardants applied to fabrics, plastics and upholstery; dyes applied to furnishings and clothing. With the exception of the accidental ingestion of such products by children, the main routes of exposure to these chemicals are by inhalation and through the skin. Our exposure to these chemicals will be a function of their physical properties, their use pattern, whether we are passively or actively exposed, the amounts used, the amount of time we spend in the house, the time we spend in particular rooms and the pattern of our movements inside the house.

Obtaining accurate estimates of exposure to chemicals within the home is extremely difficult and can only be established on the basis of detailed market research, analysing how people spend their time within the house as well as how they use certain products. These sociological data are then combined with data on the physico-chemical properties of the substance e.g. physical form, vapour pressure and information on the quantities used, in order to generate estimates of exposure which are usually expressed as the annual dose or the lifetime dose.

b) Occupational exposure

Occupational exposure is determined as a function of the properties of the chemical, the quantities used, the industrial process used and the personal protective equipment which is worn by the operator. Again, as with consumers, exposure is usually by inhalation or through the skin rather than by ingestion. In the absence of monitoring data, occupational exposure is usually determined on the basis of anology with similar chemicals used in similar industrial processes. Many agencies charged with ensuring occupational safety have, on the basis of experience, developed generic models relating to specific industrial processes and product types e.g. paint spraying in the automobile industry.

c) Environmental exposure assessment

In a few, rare, cases monitoring data will be available with real, measured, concentration in the environment but for the most part, environmental exposure concentrations must be predicted using models. Such models will be dependent, among other factors, upon:

1) the stage in the life-cycle of the chemical which is of interest (production/use/disposal);
2) the tonnages of the chemical which are produced or placed on the market;
3) the type of production process or the type of product concerned;
4) the properties of the substance including: solubility, volatility, potential to degrade (physical/chemical/biological) absorptive capacity, etc.

The end product of such models will be a predicted environmental concentration or PEC.

Risk characterisation

The following definition is to be found in the UNCED documentation:

"Estimating the incidence and severity of the adverse effects which are liable to occur in a population or an ecosystem due to actual or predicted exposures. It brings together the results of the dose-response and exposure assessments. The term risk estimation is used when the estimated probability of an effect is precisely stated: risk characterisation is also used to cover less precisely quantified assessments."

As made clear in the above definition this last step in the process involves a comparison of the (predicted) exposure concentration and the maximum acceptable concentration. Where the margin of safety between these two values is sufficiently wide then risk reduction or risk management actions will not be required. Where the two values overlap or where the margin of safety is too narrow, risk management initiatives should be considered.

For human health protection, this means in practice, that MAC values, or EDC values or ADIs are compared to the concentrations or doses to which consumers/workers will be exposed in the workplace, in the home or through the diet. If the margins of safety are too narrow then restrictions on marketing and use may be required. An example of such a risk characterisation process is given for the chemical methylene chloride in Fig. 5.

For substances suspected of being genotoxic, carcinogens and for which a threshold or cut off value does not exist the situation is less clear. If it is assumed that any exposure to such substances will carry some risk the objective must be to set an acceptable dose. Some authorities use a value of between 10^{-5} and 10^{-7} for such a safe-dose; meaning that the daily exposure of a population to that dose for a lifetime would be expected to increase the incidence of cancer by between 1 person in 100,000 to one person in 10,000,000. In Western Europe the risk of dying of cancer is approximately 1 in 4 i.e. 25%, therefore an additional risk of 10^{-5} would equate to an additional 0.01% i.e. the total risk of dying from cancer would increase to 25.01%. The use of the concept of a safe dose is an essentially political decision which gives rise to heated debate.

With regard to the environment, a comparison of the predicted environmental concentration with the environmental concern level will yield a hazard quotient. If this quotient exceeds unity then there will be a need to refine the hazard assessment either by further testing or by generating further exposure data. If further refinement still indicates a high level of concern then restrictive measures may be appropriate. Fig. 6 gives an environmental risk characterisation for the substance, Linear Alkyl Benzene Sulphonate which has been used as a component in household washing powders for many years.

Discussion

Chemicals risk assessment is a relatively new discipline and there are many improvements which need to be made. In particular, the degree of uncertainty regarding exposure concentrations must be reduced. For the most part, regulators will, in the absence of better data, base their exposure predictions on worst case scenarios, which may, or may not be realistic. This is quite understandable, their responsibility is to protect the population and the environment from unacceptable risks and they will always err on the side of safety. Nevertheless, industry, as producers of the chemicals in question, must have more detailed knowledge on likely exposure scenarios. Without such information, it would not be possible for them to place chemicals on the market. Certainly, concepts such as Product Stewardship and Responsible Care, if they are to be more than rhetoric, must require companies to carry out their own detailed risk assessments before marketing a chemical. Therefore, if industry has such data, it should share it with the regulatory community and consumers alike. If industry cannot respond to this challenge then regulators will continue to be "overly" protective.

Our knowledge concerning the possible environmental effects of chemicals is deplorable. For many end-points of concern, (e.g. soil functioning, soil chemistry, photodegradation in water and air and anaerobic degradation), we have no agreed standard test methods. For other end points, our methodologies are crude, and unreliable: and our knowledge about inter-species differences and the ability to extrapolate from the laboratory to the real world is totally insufficient.

We make a considerable mistake if we continue to invest significant resources in improving the sophistication of testing methods designed to pick out possible human toxicants, but do not make similar efforts in relation to potential effects on ecosystems: are we content that one acute

toxicity test on a water flea is sufficient to satisfy environmental concerns? The link between general environmental quality and human health is universally accepted and if we allow our environment to deteriorate then the quality of our own lives will also diminish. Far more research effort should be devoted to understanding the mechanisms by which chemicals impact upon our environment and in developing test methods which will detect and predict such effects.

One issue which I have not addressed so far is the communication of information on chemicals risk assessment to the general public and their involvement in the risk assessment debate. With such a complex subject there is a real danger of Regulators and Regulated forming a charmed circle from which the uninitiated are excluded by means of impenetrable jargon. Other speakers in this Conference will discuss this issue in more detail; my personal view is that resolution of this problem would be facilitated if we could identify and separate those aspects which are of an essentially political nature e.g. the desired level of protection (acceptable level of risk); the economic and social costs of achieving or not achieving a given level of protection, from those aspects which are essentially scientific/technical e.g. how to calculate/determine a predicted environmental concentration or a no effect concentration.

References

1. Organisation for Economic Co-operation and Development: Guidelines for the Testing of Chemicals.
2. Organisation for Economic Co-operation and Development, Council Decision of 12th May 1981 on the mutual acceptance of data in the assessment of chemicals, Annex 2, Principles of Good Laboratory Practice.
3. Directive 90/394/EEC on the protection of workers from the risks related to exposure to carcinogens at work (Sixth Individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC), Official Journal of the European Communities, Series L, Number 196, pp 1-7, 26th July 1990.
4. Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. Official Journal of the European Communities, Series L, Number 262, pp 201-203, 27th September 1976.
5. Organisation for Economic Co-operation and Development, Draft Report on the OECD Workshop on the extrapolation of laboratory aquatic toxicity data to the real environment held in Washington (USA) on 11-12 December 1990 – OECD 1991.
6. Directive 67/548/EEC as amended for the sixth time by Directive 79/831/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official Journal of the European Community, Series L, number 259, pp 10-28 of 15th October 1979.

Figure 1

General Overview of Risk Assessment

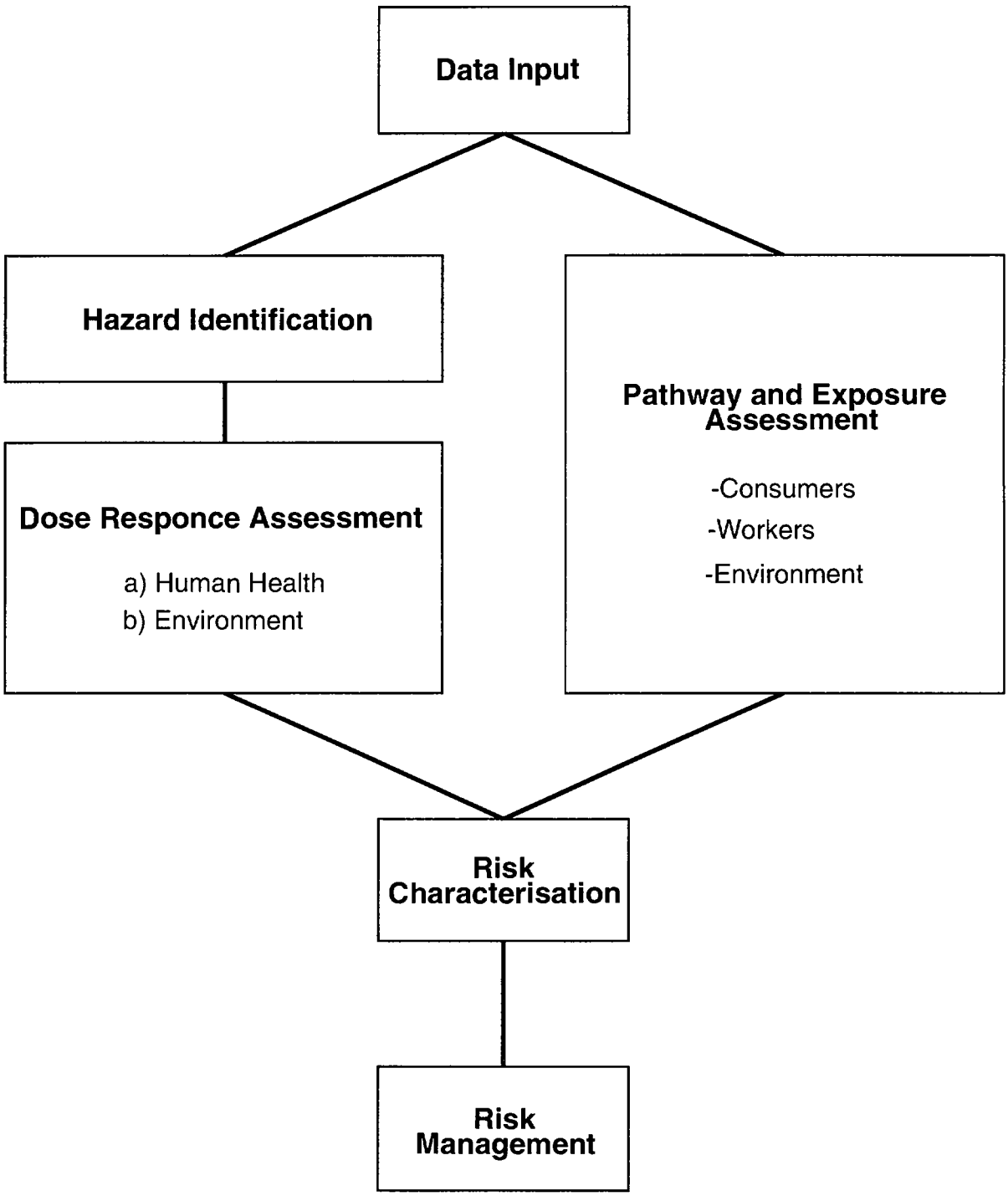


Figure 2

Data Components for the OECD Minimum Pre-marketing Set of Data

Chemical identification data

Name according to agreed international nomenclature, e.g. IUPAC
Other names
Structural formula
CAS-number
Spectra ("finger-print spectra" from purified and technical grade product)
Known impurities, and their percentage by weight
Essential (for the purposes of marketing) additives and stabilisers and their percentage by weight

Ecotoxicity data

Fish LC50 – at least 96 hours exposure
Daphnia – reproduction 14 days
Alga – growth inhibition 4 days

Degradation/Accumulation data

Biodegradation:

Screening phase biodegradability data

Bioaccumulation:

Screening-phase bioaccumulation data (partitioning coef., n-octanol/water, fat solubility, water solubility, biodegradability

Production/use/disposal data

Estimated production, tons/year
Intended uses
Suggested disposal methods
Expected mode of transportation

Recommended precautions and emergency measures

Analytical methods

Physical/chemical data

Melting point
Boiling point
Density
Vapour pressure
Water solubility
Partition coefficient
Hydrolysis*
Spectra
Adsorption-Desorption*
Dissociation constant
Particle size*

Acute toxicity data

Acute oral toxicity
Acute dermal toxicity
Acute inhalation toxicity
Skin irritation
Skin sensitisation
Eye irritation

Repeated dose toxicity data

14-28 days, repeated dose

Mutagenicity data

*only the screening part to be done for base set

Figure 3

Classification and labelling of dangerous substances on the basis of their acute toxicity according to Annex VI of Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances(6)

Category

	Very Toxic	Toxic	Harmful
LD50 Oral rat $mgkg^{-1}$	≤ 25	25-200	200-2000
LD50 Dermal rat $mgkg^{-1}$	≤ 50	50-400	400-2000
LC50 Inhalation mg/L/4 H	≤ 0.25	0.25-1	1-5

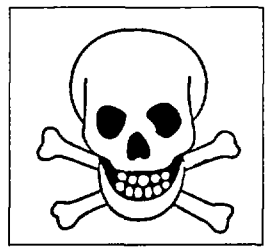
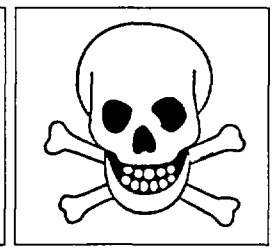
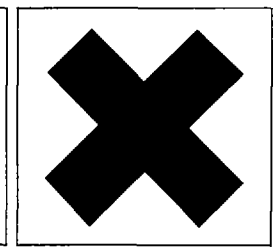
	Very Toxic	Toxic	Harmful
	T+	T	Xn
Symbols to be used on packaging			
	Very Toxic	Toxic	Harmful

Figure 4

Assessment factors for Aquatic Toxicity Data to derive Environmental Concern Levels (OECD, 1991)

Available information	Assessment factor applied to the lowest value
NOEC-value[c] or QSAR[d] estimate for chronic toxicity derived from a set of data at least consisting of algae, crustaceans and fish	10[a]
acute L(E)C50[e] or QSAR estimate drived from a set of data at least consisting of algae, crustaceans and fish	100[b]
acute L(E)C50 or QSAR estimate for acute toxicity	1000

a), b): the lowest value of the two (a) or (b) may be preferred.
c): No observed effect concentration
d): Qualitative structure activity relationship – estimate of toxic effect based upon knowledge of the chemical structure
e): Median lethal or effective concentration usually determined by experimentation.

If NOECs are not available for each of the three taxonomic groups mentioned in the table (algae, crustaceans and fish), an assessment factor of 10 may be applied to the lowest NOEC. This calculated ECL is compared to the concern level calculated from the L(E)C50 values and the lowest value should be selected as the Environmental Concern Level.

Figure 5

Outline Risk-Assessment for Methylene Chloride

Substance: Methylene Chloride
Synonyms: Dichloromethane
Methane dichloride
Methylene dichloride
Formula: CH_2Cl_2
World Production (estimate) 570,000 tonnes per annum

Types of Use	%
Aerosols	20-25
Paint Remover	25
Process Solvent	35-40
Misc	10-15

Product types

- Paint strippers
- Household cleaners
- Lubricants
- Degreasers

Exposure Concentrations (Measured, ppm)	
Manufacturing Industry	50-485
Occupational Paint Stripping	up to 500 (Exceptionally 1000-2000)
Non occupational Paint Stripping	up to 500 (Occasionally 1000s)

Neurotoxicity

200-300 ppm, psychomotor and audiovigilance impaired, mild headaches and mild nausea

500 ppm alterations in visual evoked response

Above 500 ppm, neuro-depressant effects become more pronounced headaches, nausea, fatigue, reduced ability to concentrate

Carcinogenicity

Classified by IARC as a carcinogen category 2B (Animal data but human data lacking)

IARC also considers there to be evidence of genotoxicity

Physiological effects

Exposure to 100 ppm for 8 hours results in blood carboxy-haemoglobin levels in non smokers, of 5%

Assessment indicates the need to reduce exposure. This can be done by local control measures. Wider restrictions on use constrained by doubts as to the safety and efficacy of possible substitutes.

Figure 6

Outline Risk Assessment for a Detergent

Substance: Linear Alkyl Benzene Sulphonate (L.A.S) C16-H25-SO3Na - C19-H31-SO3Na
Mixture of alykl homologues C10-C13 average carbon chain length = 12