# *Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances*

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# *Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances*

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## EXECUTIVE SUMMARY

In the absence of sound human exposure data, existing procedures for setting occupational exposure limits (OELs) for chemical substances are generally based on a no observed adverse effect level from repeated dose animal studies, with application of appropriate assessment factors to account for uncertainty and variability in the data set. These procedures are reviewed briefly in this report.

Contrary to these 'data-rich' substances, for which adequate data are available, no clear procedures exist for the derivation of OELs of 'data-poor' substances. In this report, six methods for setting OELs for such substances have been proposed and evaluated. Worked examples are provided.

- Hazard banding seems to be a promising method to set OELs for data-poor substances with EC risk phrases. These risk phrases are grouped following ECETOC criteria into four categories or hazard bands for gases/liquids and solids, each corresponding to a specific OEL range.
- The maximum tolerated dose in long-term studies can be used to derive an OEL. If not known, the maximum tolerated dose can be predicted from the acute oral toxicity (lethal dose in rats) and the octanol-water partition coefficient.
- Four-hour lethal concentrations from rat inhalation studies can be used directly for calculating OELs.
- Current (quantitative) structure-activity relationships for predicting toxicity are insufficiently reliable, and therefore of limited value for setting OELs. It is recommended to search for substances with similar structures and known toxicity, and then read the data across.
- If an OEL is to be based on sensory irritation, it can be predicted from the so-called respiratory dose, i.e. the concentration in air which reduces the breathing rate of mice by 50%. If not available, the respiratory dose can be calculated from the octanol-air partition for substances from a homologous series.
- Finally, the principle of threshold of toxicological concern (normally for food contaminants) can be used for deriving OELs if less conservative safety factors are applied.

For certain substances none of the proposed methods will be applicable. For others, one or more of the methods might be appropriate, but could lead to different results.

In conclusion, therefore, it is proposed that an integrated approach based on the six methods proposed can be used to set a provisional OEL for the data-poor substance concerned. However, for the value to be reliable, experienced toxicological expertise is required in the interpretation of the results.

# 1. SUMMARY

Occupational exposure limits (OELs) are maximum acceptable air concentrations that are used as reference parameters for the protection of workers from overexposure to chemical substances by inhalation. So far as can be predicted from the current state of knowledge, repeated exposure to concentrations below these levels during an entire working life does not cause any significant adverse effects on the health of exposed persons and/or their progeny. OELs are a useful basis for developing procedures for the safe handling of substances at the workplace.

There are well-established procedures for setting OELs. Where good quality human data exist, these should be taken into account. The amount of toxicological information available on a chemical substance varies significantly, but generally the OEL is based on the no observed or lowest observed adverse effect level (NOAEL or LOAEL) for the most critical effect seen in one or more repeated dose animal studies. Various default assessment factors are used by scientists and risk assessors for extrapolating from animal to human data (duration and route of exposure, variability between and within species); the derivation of risk assessment factors has been the subject of an ECETOC report (ECETOC, 2003a). So far these assessment factors have been applied only to single substances. In the present report, the derivation of OELs by a reciprocal calculation procedure, for substances such as the hydrocarbon solvents that are mixtures, has also been addressed.

No such OEL setting procedures currently exist for substances with limited or no toxicological or human data; for the purpose of this report these are designated 'data-poor' substances. Substances tested according to Annex V of the proposed EC regulation on the registration, evaluation and authorisation of chemicals (REACH) (volume up to 10 t/y) fall into this category. One possibility might be to use the derived no-effect level (DNEL), which is part of the output of a chemical safety assessment under the proposed REACH regulation (assuming that the DNEL is more or less equivalent to the OEL). However, REACH currently provides no guidance on deriving this value for data-poor substances.

In this report, several ways of addressing OELs for data-poor substances are explored, and six methods are proposed and evaluated. Worked examples are provided.

- Hazard banding can be used as follows, for estimating an OEL for a data-poor substance that has been assigned one or more risk phrases in accordance with Annex 1 of Directive 67/548/EEC. Substances with an UK OEL were divided into four hazard categories (bands) on the basis of their most severe risk phrase (risk-phrases in accordance with Annex 1 of Directive 67/548/EEC following criteria developed by ECETOC (2005). A distinction was made between gases and/or liquids, and solids, and the 10th percentile of the distribution of UK OELs in each category (band) determined. A substance without an OEL, but labelled

with risk phrases, was allocated to a hazard category on the basis of the most severe risk phrase, and assigned an estimated OEL equal to the 10th percentile of the OEL distribution of that hazard category.

- Another possible method for setting an OEL makes use of the observed maximum tolerated dose (MTD) in rat 2-year toxicity studies. Based on 315 studies conducted by the US National Toxicology Program (NTP), a relationship was derived between the MTD and the acute oral median lethal dose ($LD_{50}$) in the rat, as modified by the octanol-water partition coefficient ($K_{ow}$). The combination of oral $LD_{50}$ and $K_{ow}$ appeared to be highly predictive of the MTD. If the MTD is not known, the relationship might be used to obtain the critical effect level needed to derive an OEL. This method cannot be used for chemicals suspected of being mutagenic, reprotoxic, carcinogenic or possessing other specific chronic effects.
- The possibility of deriving OELs from 4-hour median lethal concentration ($LC_{50}$) values from inhalation studies in the rat was also investigated. For 95 substances for which a reliable $LC_{50}$ was available, a direct relationship was derived between the OEL and the $LC_{50}$. The lower 90% confidence limit of the estimated OEL distribution could be taken as an OEL.
- Up till now (quantitative) structure-activity relationships [(Q)SARs] have not been considered sufficiently reliable for the qualitative and quantitative prediction of mammalian toxic endpoints (ECETOC, 2003b), or for setting OELs following the targeted risk assessment approach developed by ECETOC (2005). Towards predicting the toxicity of a substance with a given structure, the Task Force recommends searching for substances with similar structures and known toxicity. This read-across approach is facilitated, for example, by the use of the internet tool ChemIDplus.
- An OEL might be set on the basis of sensory irritation. In this context, the prediction of sensory irritation on the basis of the respiratory dose ($RD_{50}$) (concentration in air which reduces the breathing rate of mice by 50%) was addressed. For substances from a homologous series, it has been shown that the octanol-air partition coefficient ($K_{oa}$) is a predictor of the severity of the sensory irritation. Therefore, the Task Force derived a relationship to predict the $RD_{50}$ from the air-water partition coefficient ($K_{aw}$) and the $K_{ow}$.
- Finally, the principle of threshold of toxicological concern (TTC) was explored for setting OELs for data-poor substances. This principle, involving structure activity considerations, is used for assessing the public health risk from chemical food contaminants; the proposed daily limit doses are overly conservative for setting OELs. However, the TTC for a substance might be used if assessment factors were applied to adjust the TTC to the different circumstances at the workplace.

For certain substances none of the above-mentioned approaches may prove to be applicable. For others, one or more of the methods can be used, but may lead to different results.

No ranking is provided for the six methods described, as the information obtained from their evaluation was not considered convincing enough for such a ranking. In addition, no single method or sequence of methods could be recommended. Instead it is advised to evaluate on a case-by-case basis the extent to which the methods outlined provide a rationale for setting an OEL.

It is concluded that the integration of the above methods could be used to set provisional OELs for data-poor substances. However, for the provisional OELs to be reliable there is a need for experienced toxicological expertise in the interpretation of the results.

The term ‘provisional’ does not necessarily mean that these OELs are less reliable with respect to human health protection. Such OELs are based on a prudent interpretation of the limited toxicological information available, and in comparison with data-rich substances, the use of more conservative default assessment factors to compensate for the lack of data.

# 2. INTRODUCTION

## *2.1 Background*

Employers are legally obliged to provide a working environment that does not endanger the health of employees (e.g. Chemical Agent Directive 98/24/EC and Framework Directive 89/391/EEC). Occupational exposure limits (OELs) are a useful instrument for the prevention of health effects during the handling of chemical substances. OELs are defined as airborne concentrations (expressed as time-weighted average for a conventional 8-hour work day and a 40-hour work week) of a substance to which it is believed that nearly all workers may be repeatedly exposed (day after day, for a working lifetime) without adverse effect (ACGIH, 2006; DFG, 2005). Exposure concentrations are generally expressed in $mg/m^3$ ($ml/m^3$ or ppm for gases and vapours).

Within the EU, industry has a duty to comply with the regulations of the Member States wherein its activities are based. If no national OEL has been set, industry generally refers to the recommendations of, for example:

- Regulatory or advisory bodies, such as:
  - EC Scientific Committee for Occupational Exposure Limits (SCOEL);
  - National OEL committees, e.g. UK Health and Safety Executive (HSE) or German MAK Commission [a];
  - US Occupational Safety and Health Administration (OSHA);
  - American Conference on Governmental Industrial Hygienists (ACGIH);
  - American Industrial Hygiene Association (AIHA).
- Company internal OEL committees, typically consisting of toxicologists and industrial hygienists, physicians and epidemiologists. Company committees recommend internal OELs in similar ways as regulatory or authoritative bodies on the basis of toxicological data and professional judgement, and have exposure data and results of medical surveillance of the exposed workers.

European industry has also developed expertise and procedures for setting provisional internal hygiene standards even in cases where there is a relative lack of toxicity data.

The data necessary for setting an OEL has been outlined in a number of guidance documents from regulatory or advisory bodies (e.g. SCOEL, German MAK Commission and ACGIH) and from scientific working groups including ECETOC (1994). Substances that satisfy these

[a] Deutsche Forschungsgemeinschaft (DFG), Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe (Senate Commission on the Investigation of Health Hazards of Chemical Compounds in the Work Area)

requirements have been designated 'data-rich' substances for the purpose of this report. Following an analysis of all known potential health effects, OELs for such substances can be based on sound scientific data, and OEL setting organisations world-wide should ideally come to similar conclusions. However, apart from differences in scientific opinion about the critical health effect and/or most relevant route of exposure, methodological differences exist in the application of the adjustment factors used, and this may sometimes lead to different standards being set by the various regulatory bodies.

The new REACH proposal will include a requirement to submit a chemical safety report, in which the producer has to demonstrate that production and use of a substance do not present a significant risk for man and the environment. Moreover, the existing and new legislation requires that available and newly generated data are appropriately applied in health risk management at those workplaces where these chemicals are handled. These requirements will apply to chemicals with low production volumes (< 10 t/y). According to Annex V of REACH, the testing requirements for these substances are: *in vitro* skin irritation or corrosivity and eye irritation tests, skin sensitisation test and *in vitro* mutagenicity test (EC, 2003a) (Appendix A). In many cases these low production volumes chemicals will lack toxicity data. For the purpose of this report, such chemicals are considered to be 'data-poor'. (It is worth noting that an acute oral, dermal or inhalation toxicity test is not part of the Annex V requirements.)

### *2.2 Purpose*

In the case of data-poor substances, the most important data gap in relation to setting OELs is the lack of a repeated dose study of effects in animals; the latter often serves as the key study for the derivation of the NOAEL. In the absence of such data, it is not possible to apply the established procedures available for 'data-rich' substances. Therefore, other approaches for setting 'provisional' OELs are required. The term 'provisional' does not necessarily mean that these OELs are less reliable with regard to human health protection. These provisional OELs are based on a prudent interpretation of limited toxicological information. In comparison with data-rich substances, more conservative default assessment factors are used to compensate for the lack of data.

This report highlights procedures for the derivation of OELs dependent on the extent of available data. For this purpose substances have been divided into two categories:

- 'Data-rich' substances, i.e. those with sufficient toxicological and other data to comply with established procedures for developing OELs (EC, 1999) and those covered by the REACH proposal, Annex VI to VIII (Appendix A);

- 'Data-poor' substances, i.e. those with limited or no toxicological data and those covered by REACH proposal, Annex V (Appendix A).

The Task Force has focused on formulating appropriate guidance for data-poor substances, for which a threshold type dose-response relationship is expected on the basis of available information. Substances with structures similar to known mutagens, genotoxic carcinogens or reproductive toxicants (category 1 and 2) were not considered; under the REACH proposal these structural alerts will trigger extensive information requirements.

### *2.3 Scope*

Several approaches for deriving OELs for data-poor substances are discussed. Each approach can be applied meaningfully only to a limited number of substances. For some chemicals, none of the approaches will lead to useful results; for others, several approaches may be applicable. In any case, expert judgement will always be necessary to interpret the results of such simplified hazard assessments and to arrive at a provisional OEL. No single approach is preferred, but the order of the listing below reflects an increasing level of sophistication/complexity.

The approaches discussed in this report are as follows:

- Hazard banding, making use of existing classification and labelling requirements. The OELs of substances with similar risk phrases might be of value in developing a provisional OEL for a data-poor substance. Risk phrases may be based on short/long-term toxicity data or on experience from handling (e.g. irritation of skin or mucous membranes) (Directive 67/548/EEC, Annex VI).
- Acute toxicity data (oral $LD_{50}$ or inhalation $LC_{50}$, or equivalent, in the rat) are available for many more substances than the NOAELs from repeated dose toxicity studies. This report explores to what extent the $LD_{50}$ and $LC_{50}$ can be used in OEL setting. [It is recognised that the $LD_{50}$-test is no longer carried out and that an acute toxicity test will not be required according to Annex V of REACH (Appendix A)].
- The usefulness of (quantitative) structure-activity relationships [(Q)SARs] and read-across for relevant mammalian toxicological endpoints is discussed in terms of reliability and accuracy. In the read-across approach, substances are searched for that are structurally similar to the substance of interest, but which are toxicologically well-characterised. Recent developments in internet technology, facilitating a search for substances on the basis of structural similarity might make this a promising approach in the future.

- The concept of TTC has received wide attention in the scope of food contaminants and additives. The possible relevance for the derivation of an OEL is explored. The TTC approach includes elements of structure-activity considerations and thus excludes substances of particular concern.

For many data-poor substances it may not be possible to propose a satisfactory rationale without resorting to excessive assessment factors. In such circumstances it may be unwise to set a provisional OEL. In these instances, pragmatic approaches will play an important role in the management of health risks arising from the handling of hazardous substances.

The terms of reference of the Task Force are given in Appendix B.

# 3. GENERAL CONSIDERATIONS ON WORKPLACE EXPOSURE TO CHEMICAL SUBSTANCES

In workplace exposure to chemical substances having a systemic (toxicological) mode of action, absorption can occur via the alveoli of the lungs, via secondary ingestion or by absorption through the skin. The absorption of a chemical by a given route of exposure is related to its physical state (gas, liquid or solid) at the relevant temperature (during handling, processing, storage or transport) and properties (such as lipophilicity, molecular weight and toxicokinetics). Absorption into the body also depends on the way the chemical is used and handled.

Gases are absorbed primarily by inhalation.

Liquids can be absorbed via inhalation of vapour or of aerosol droplets of the liquid, and by direct skin contact with the liquid or skin absorption of the vapour.

Solids can be absorbed via inhalation of aerosols of solid particles. Particle size is an important parameter for substances that are insoluble in physiological body fluids. The major fraction of inhaled aerosols enters the body within hours by secondary ingestion (CIIT, 1999). Up to a maximum of 30% are deposited in the pulmonary region, the amount depending on whether the material contains a high proportion of particles in the respirable range. Insoluble respirable particles may be retained in the lungs for months or even years. Certain solids may also be absorbed via direct skin contact (e.g. 4,4'-methylenedianiline). Solubility characteristics play an important role in this context.

Absorption via the skin is a diffusion-controlled process and parameters, such as the octanol-water partition coefficient, molecular weight and water solubility, play a major role.

Substances that are sensitising to the skin and the respiratory tract need to be absorbed, at least locally, for an immune response to occur. In deriving an OEL for a sensitising substance, consideration must be given to whether the substance is a dermal or a respiratory sensitiser (or both), and its sensitising potency taken into account. Unfortunately there are currently no standardised tests for the induction and potency of respiratory sensitisation. In practice, reliance has to be placed on structural similarities with well known respiratory sensitisers, such as acid anhydrides, isocyanates, enzymes (e.g. proteinases and amylases), azodicarbonamide, piperazine, peroxydisulphates, ethylenediamine and glutaraldehyde. Reducing exposure levels to below the (airborne) OEL may not always be sufficient to protect against the risk of skin sensitisation. Skin contact takes place mainly via surfaces contaminated by spills or by deposition of the substance from the workroom air. Experience has shown that to avoid sensitisation induced by dust deposited from contaminated workroom air, airborne dust levels should not exceed 1 $mg/m^3$ for weak, and should be below 1 $\mu g/m^3$ for strong skin sensitisers (Naumann *et al*, 1996).

For locally acting agents (e.g. substances corrosive or irritant to the upper respiratory tract) the OEL has to be low, so that respiratory irritation and irritation of the eyes do not exceed the level of slight (i.e. not annoying) irritation. The threshold of irritation for the upper respiratory tract can be explored by means of the mouse $RD_{50}$-test (Alarie, 1973).

In the absence of any systemic effects at the irritant level, occupational experience and volunteer studies are useful in setting an OEL. If, due to its limited water solubility, the irritant or corrosive substance can reach the alveoli to a considerable extent or is inhaled as particles of critical size distribution ('respirable dust'), the OEL has to be based on the prevention of damage to the lung epithelium in the short term and on prevention of chronic obstructive pulmonary disease, emphysema or fibrosis of the lung after long-term exposure.

The direct applicability of an OEL (8-hour TWA) is obvious in frequent (daily) handling of substances. However, the pattern of exposure may differ from the internationally agreed definition of an OEL (8 h/d, 5 d/wk, 40 working years). If, for example, exposure occurs only sporadically or only briefly during the work shift, the OEL expressed as an 8-hour TWA is likely to be overly protective. The degree to which the 8-hour TWA can be temporarily exceeded is related to the mode of toxicological action of the substance in the short and long term. The ACGIH provides guidance on Excursion Limits, or short periods of time that the TWA may be exceeded. In the case of acute effects, respiratory irritants, or strongly dose-rate dependent systemic toxicity, there is often little margin to tolerate a higher exposure, even during short periods of time. Typically, in such cases, a short-term exposure limit (STEL, e.g. 15- or 30-min TWA) is set. The STEL is a concentration, to which it is believed that workers can be exposed for a short period of time without suffering from irritation, chronic or irreversible tissue damage, dose-rate dependent toxic effects, narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency (ACGIH, 2006).

# 4. DERIVATION OF OCCUPATIONAL EXPOSURE LIMITS FOR DATA-RICH SUBSTANCES

The objective of developing an OEL is to protect workers against potential harmful effects of chemicals under typical workplace exposure conditions. A database, including toxicological effects caused by short- and long-term exposure to the substance by all routes relevant for man, would be an ideal starting point for deriving an OEL. In practice, such an extensive database is not available for most substances. In such cases, assessment factors are used in the extrapolation of the data to humans, to set OELs that are adapted to the quality and quantity of the available toxicological data.

## *4.1 Setting OELs for Specific Substances*

A number of worldwide organisations have expertise in setting OELs.

In Europe, the regulatory process for developing OELs in the EU is defined in Council Directive 98/24/EC on the protection of the health and safety of workers related to chemical agents at work ('Chemicals Agents Directive'). Under this Directive, the EC can develop OELs to be set at the community level as either indicative occupational exposure limit values (IOELVs) based on a review of the available scientific data or binding occupational exposure limit values (BOELVs) taking the socio-economic and technical feasibility into account (EC, 1998).

The SCOEL is the scientific advisory group responsible for evaluating available scientific information and recommending substance-specific OELs to the EC. The members of SCOEL are scientists from EU Member States appointed by the EC to ensure that the various areas of expertise (chemistry, toxicology, epidemiology, occupational medicine and occupational hygiene) are covered within the Committee (EC, 1995).

SCOEL provides the EC with advice on the setting of OELs based on scientific data and, where appropriate, proposes values that may include an OEL expressed as an 8-hour TWA concentration, a short-term exposure limit (STEL) or a biological limit value (BLV). The OELs may be supplemented, as appropriate by a 'skin notation' if absorption of the substance via the skin and/or mucous membranes can contribute significantly to the overall exposure.

The OELs set by the EC are a reference for the Member States and national limit values may not exceed these. The limit values must be incorporated into national legislation within 3 years.

SCOEL defined its principles and approaches for establishing health-based OELs in its 'Key Documentation' (EC, 1999). In general in establishing OELs, each substance is evaluated

individually. If the critical effect occurs according to a non-threshold mechanism, no health-based OEL can be established.

In general a health-based OEL is derived by means of the following steps:

- Collecting information on all hazards of the substance, i.e. all physical, chemical, toxicological and epidemiological data;
- deciding if data are sufficient to derive a health based OEL;
- evaluating all adverse effects;
- establishing which adverse effect occurs at the lowest exposure. That is the critical effect for setting an OEL;
- selecting relevant human and animal studies of sufficient quality, in which the critical effect has been shown;
- establishing the mode of action and mechanism, threshold or non-threshold;
- evaluating the dose-response relationship for all relevant adverse effects and establishing the NOAEL and the LOAEL;
- recommending a numerical value for an OEL expressed as a TWA of 8 hours for a substance below the NOAEL, while applying appropriate uncertainty factors;
- deciding if a STEL is needed in addition to an OEL expressed as a TWA of 8 hours and recommending a numerical value for a STEL, if necessary;
- documenting the full process of deriving the OEL for the substance;
- determining the appropriate method for air monitoring in human and animal studies.

SCOEL recommends the use of good human data (comprising for example, individual case reports, volunteer studies, cross-sectional studies and cohort and case-control studies) rather than animal data, but recognises that human data are often unavailable or scientifically inadequate. In such cases the OEL is derived from well-conducted animal studies and the use of assessment factors.

In a risk assessment for humans, the NOAEL from an animal study is the typical starting point and assessment factors are then applied to account for both uncertainty and variability in the subsequent extrapolation elements. If an appropriate NOAEL is available, then no extrapolation and hence, no assessment factor is necessary. There are cases where the critical effect NOAEL cannot be determined and also where the LOAEL is considered a more appropriate starting point. Where only the LOAEL is available an additional assessment factor is used typically (Hart *et al*, 1988; Fairhurst, 1995; Naumann and Weideman, 1995).

SCOEL has not developed a standard approach for applying assessment factors in deriving OELs. Substances are evaluated on a case-by-case basis, with higher factors being needed when there is less confidence in the toxicological database. Using a case-by-case approach SCOEL discusses

assessment factors to be applied for extrapolation from animal studies to humans, to derive an OEL in situations where no information on interspecies and intraspecies' differences is available.

The following points are relevant in relation to information on which OELs are set:

- Animal (mostly rodent) experiments provide information on effects by single or repeated exposure and should preferably be conducted via a relevant route. To be relevant for OEL setting, repeated dose studies should have a duration of at least 28 days, to enable the target organs and the types of effects on these target organs to be identified, thus establishing a dose-response relationship.
- Toxicokinetics can provide information on the extent to which the route of exposure, and the distribution, metabolism and excretion of the substance in animals (e.g. rodents) are suitable for setting an OEL in humans. Toxicokinetics can also help in the selection of the most appropriate assessment factors. In addition *in vitro* studies can be used, for instance, to establish the rate of dermal absorption, mechanism of action or the relevant metabolic pathway in man compared to rodents.
- The rate of the onset of effects from exposure in the animal studies should also be considered, to interpret their relevance for setting OELs. Depending on the results, a 15-minute STEL rather than an 8-hour OEL may be appropriate.
- The criteria for selecting a NOAEL as starting point for deriving an OEL includes selecting the most relevant species for man. If several studies are performed with the same most relevant species, the highest NOAEL of these studies should be used, but this highest NOAEL should not exceed the LOAEL in any of the other studies.

The derivation of assessment factors for human health assessment is covered in detail in ECETOC Technical Report No. 86 (ECETOC, 2003a). The report reviews critically publications establishing scientifically-based default assessment factors, using statistical or mechanistic approaches, and derives the most scientifically-supportable values for these factors. Although the recommended assessment factors are similar to those proposed by SCOEL, they are not in full agreement.

In the absence of substance-specific information, the default assessment factors proposed by ECETOC (2003a) include the following salient points:

- LOAEL to NOAEL: A default assessment factor of 3 is proposed. Quantitative analysis of the dose-response is helpful in the extrapolation of a LOAEL to a NOAEL via benchmark dose estimation. The benchmark dose for 5% effect is often considered as a NOAEL (Crump 1984, 1995; Murrell *et al*, 1998).
- Route to route extrapolation is only feasible for substances with a systemic mode of action and should take dose rate and toxicokinetic data into account. If route to route extrapolation

implies a lower rate of dosing this can be considered a built-in safety margin and in such cases no assessment factor is needed, i.e. an assessment factor of 1 is considered appropriate.

- Duration of study: Exposures of workers to levels below the TWA 8-hour OEL should by definition be without adverse health effects, even if these exposures are repeated 5 days a week during a whole working life. This means that the NOAEL from short-term animal studies has to be extrapolated to lifetime exposure. In the extrapolation from animal studies (e.g. rat) to man, the following extrapolation factors can be used to adjust for duration of exposure, unless there is evidence that the NOEL obtained from short-term exposure studies is also appropriate to long-term exposure without the need for an additional assessment factor (Table 1).

***Table 1: Default assessment factors recommended in the absence of substance-specific information*** *(ECETOC, 2003a)*

| Duration of exposure | Default assessment factor |
|---|---|
| Subacute/chronic NOAEL | 6 |
| Subchronic/chronic NOAEL | 2 |
| Local effects by inhalation | 1 |

To take into account the interspecies differences in sensitivity between experimental animals and humans, ECETOC (2003a) concluded:

- In the case of oral exposure to substances with a systemic mode of action, allometric scaling, based on metabolic rate (oxygen consumption per kg body weight) provides a sound default approach for interspecies extrapolation of systemic effects;
- in the case of inhalation exposure to systemically acting substances, the intake is already related to the oxygen consumption and the interspecies assessment factor is equal to 1 for concentrations in the air;
- a default assessment factor of 1 is sufficiently conservative for extrapolation from rodent to humans of local effects of water-soluble gases and vapours;
- a default factor of 1 is considered adequate for extrapolation from rodent to humans for aerosols, since the respiratory rate of rodents leads to a greater respiratory tract burden as compared with humans.

The intraspecies difference in sensitivity is greater in humans than in a homogeneous experimental animal population and greater in the general population than in the more homogeneous worker population. In practice it is not possible to make a clear distinction between interspecies and intraspecies variability and an assessment factor of 5 was considered

sufficient for accounting for (intraspecies) variability within the general population, with a default factor of 3 for the more homogenous worker population (ECETOC, 2003a).

These assessment factors can be adjusted up or down when appropriate substance-specific information is available on the extent of variability between short-term versus long-term effects, between various species and within the human population.

Some of the assessment factors proposed by ECETOC (2003a) are also different from those of the revised EC Technical Guidance Document (TGD) (EC, 2003b). The latter may be used (CEFIC *et al*, 2005a,b) for setting a derived no-effect level (DNEL) which forms part of the output of a chemical safety assessment under the currently proposed REACH regulation (EC, 2003a). According to the TGD the interspecies assessment factor for extrapolation from the species studied to man is the allometric scaling factor multiplied by a factor of 2.5 to account for toxicodynamic variability. The intraspecies factor for workers has been set at 5 (and that for the general population at 10).

In conclusion, the revised EC TGD proposes assessment factors 4.2 times more conservative for workers (and 5 times more conservative for consumers) than those proposed by ECETOC (2003a) due to the use of different inter- and intra-species assessment factors.

### *4.2 Setting OELs for substances occurring as mixtures*

Many commercial chemical substances and products occur as natural or formulated mixtures of chemicals. This means that typical exposure is not to one but to several chemicals simultaneously.

The potential health risk resulting from handling a mixture is defined by a number of factors, such as the toxicity of the individual constituents, their concentration in the mixture, the volatility (or particle size) of the various components and possible interactions between them. The following options for interactions exist:

- Substances with different modes of action and without any mutual interaction;
- substances with the same mode of action where the response is additive;
- substances with the same mode of action where the response is antagonistic;
- substances with synergistic or potentiating interactions.

This section focuses on a methodology for deriving OELs based on a reciprocal calculation procedure (RCP) which takes into account the properties of the individual constituents. The use of the RCP to calculate OELs requires assumptions about similarity in physical/chemical and

toxicological properties and that the individual constituents act in an additive manner. The approach is inappropriate where there is information showing the effects may be synergistic, potentiating or antagonistic.

The RCP methodology is applicable to hydrocarbon solvents. These widely used substances are complex and variable in composition and only a few representative constituents have been studied in details (McKee *et al*, 2005). Some of the components are well characterised and have their own OELs. For these reasons, an approach such as the RCP, which permits the calculation of a unique OEL for each hydrocarbon solvent based on relatively simple compositional information, was proposed by hydrocarbon solvent manufacturers in the USA (Hydrocarbon Solvents Panel) and in Europe (Hydrocarbon Solvent Producers Association). The approach has been the subject of an ECETOC report (ECETOC, 1997). Since then it has been developed further (Appendix C).

# 5. SETTING OCCUPATIONAL EXPOSURE LIMITS FOR DATA-POOR SUBSTANCES

In the context of the management of worker health protection, there is value in setting OELs for data-poor substances. Indirect information on toxicity as a basis for setting an OEL can be derived, for example, from regulatory classification and labelling information, from procedures (in which compounds with similar structures and well known toxicity are compared with the substance for which an OEL needs to be provided), and from structural information related to the TTC. In addition, other relevant information can be used to contribute to a toxicity profile and to making a conservative assessment.

The value of the different procedures is explained below.

## *5.1 Hazard banding based on risk phrases*

A simple scheme has been developed in the UK under the Control of Substances Hazardous to Health (COSHH) regulations, to provide practical control advice to small and medium sized enterprises (HSE, 2004). This scheme, commonly known as 'COSHH Essentials', makes use of the toxicological hazard information indicated by risk phrases used under the EC classification and labelling system to assign substances to hazard (or control) bands. In this scheme, risk phrases are allocated to bands A to E, each of which represents a different target airborne exposure range for dusts and vapours. The target airborne concentration for each hazard band is:

- Band A: > 1 - 10 mg/m3 dust; > 50 - 500 ppm vapour;
- Band B: > 0.1 - 1 mg/m3 dust; > 5 - 50 ppm vapour;
- Band C: > 0.01 - 0.1 mg/m3 dust; > 0.5 - 5 ppm vapour;
- Band D: < 0.01 mg/m3 dust; < 0.5 ppm vapour;
- Band E: No band recommended. Seek specialist advice.

Using risk phrases as indicators of toxicological hazard, many substances can be allocated to a hazard band, which represents an appropriate target airborne exposure concentration range.

Brooke (1998) compared the output of the UK-HSE scheme with established health-based OELs for more than 100 substances. For each substance used in the evaluation, the appropriate classification was identified either from Annex I to the Dangerous Substances Directive 67/548/EEC [as updated by Directive 2004/73/EC, 29th adaptation to technical progress (EC, 2004)] or from the available toxicological data [i.e. self classification according to Directive 93/72/EEC, the 'classification and labelling guide' (EC, 1993)]. Where the substance had more than one risk phrase assigned to it (majority of substances), the risk phrase that led to allocation

to the most stringent hazard band was used. The target airborne exposure concentration range associated with the hazard band identified by the scheme was then compared with the numerical value of the OEL. By this means it could be determined if the use of this scheme to identify a control strategy would lead to an exposure level which was higher, lower or of the same order as the numerical value of the health-based OEL.

For 42% solids and 56% vapours, the use of the scheme recommended a level of control equivalent to that indicated by the health-based OEL; for the remainder, the level of control was more stringent. Thus, for 98% of the substances evaluated, the scheme led to the selection of a control strategy, which provided a level of control equivalent to, or greater, than that required to comply with the health-based OEL.

It was concluded that the results suggested that adherence to the scheme would result in the selection of strategies which would control airborne exposure to levels which should generally be protective of health for substances (solid or vapour) allocated to hazard bands A to D (Brooke, 1998).

Several other organisations, such as the German MAK Commission, have proposed hazard categories (TRGS, 2002) on the basis of risk phrases assigned to substances classified according to EC Directive 67/548/EEC.

ECETOC has derived generic exposure values (comparable to provisional OELs) for use in a targeted risk assessment process, by dividing substances into 4 hazard categories: Low, Medium, High and Very high (ECETOC, 2005). The present Task Force has added a further health hazard category 'Very low' for substances for which sufficient data are available to indicate that they are not hazardous to health according to Directive 67/548/EEC and for which a repeated dose study is available. [This is justified, as it is considered that substances such as isoleucine and sucrose fatty acid esters, which do not possess any significant toxicological properties (Kawabe *et al*, 1996, 2006; Takeda and Flood, 2002) and do not attract a classification according to EC criteria, are less hazardous than, for example, malathion and iodine that are both classified as 'harmful' and assigned to the Low hazard category]. A substance for which no data are available (indicating that it is subject to classification and labelling as a hazardous substance based on Directive 67/548/EEC) and for which no repeated dose study is available, would be assigned to the Medium hazard category (Table 2).

The risk phrases for assignment of substances to a hazard category are presented in Table 2.

***Table 2: Hazard categories*** *(based on ECETOC, 2005)*

| Hazard category/ Risk phrase | Classification | Descriptor |
|---|---|---|
| **Very low** | | |
| None | Not hazardous | Repeated dose study available |
| **Low** | | |
| R20 | Harmful | Acute toxicity inhalation |
| R21 | Harmful | Acute toxicity dermal |
| R22 | Harmful | Acute toxicity oral |
| R65 | Harmful | Aspiration/drowsiness |
| R67 | Harmful | Aspiration/drowsiness |
| R36 | Irritant | Irritation eye |
| R37 | Irritant | Irritation respiratory system |
| R38 | Irritant | Irritation skin |
| R66 | Irritant | Irritation skin (repeated) |
| **Medium** | | |
| Not classified | Not classified due to lack of data | Repeated dose study not available |
| R40 | Harmful | Carcinogen (Category 3) |
| R48/20/21/22 | Harmful | Prolonged exposure |
| R62 | Harmful | Reproductive toxicant (Category 3) |
| R63 | Harmful | Reproductive toxicant (Category 3) |
| R68 | Harmful | Mutagen (Category 3) |
| R41 | Irritant | Severe eye irritation |
| R43 | Irritant | Sensitisation skin |
| R34 | Corrosive | Corrosion |
| R35 | Corrosive | Corrosion |
| R23 | Toxic | Acute toxicity inhalation |
| R24 | Toxic | Acute toxicity dermal |
| R25 | Toxic | Acute toxicity oral |
| R39 | Toxic | Irreversible effects |
| **High** | | |
| R42 | Harmful | Sensitisation inhalation |
| R48/23/24/25 | Toxic | Prolonged exposure |
| R26 | Very toxic | Acute toxicity inhalation |
| R27 | Very toxic | Acute toxicity dermal |
| R28 | Very toxic | Acute toxicity oral |
| **Very high** | | |
| R45 | Toxic | Carcinogen (Category 1, 2) |
| R46 | Toxic | Mutagen (Category 1, 2) |
| R49 | Toxic | Carcinogen (Category 1, 2) |
| R60 [a] | Toxic | Reproductive toxicant (Category 1, 2) |
| R61 [a] | Toxic | Reproductive toxicant (Category 1, 2) |

[a] Hazard category following expert judgment

Substances for which an official UK OEL has been published (UK-HSE, 2005) were assigned to hazard categories Very low, Low, Medium or High on the basis of their most severe risk phrase [allocated according to Annex 1 of the EC Directive 67/548/EC as updated for the 29th time by Directive 2004/73/EC (EC, 2004)]. The OELs in each hazard category formed a log-normal distribution. The geometric mean, the geometric standard deviation and the 10th percentile of the OELs were calculated for gases and/or liquids, and for solids. Outliers at the lower end of the distribution range were attributed in part to inconsistent allocation of risk phrases. Pragmatically, the 10th percentile of the distributions of the OELs in each hazard category was chosen as an estimated OEL for all substances falling into that category (Table 3).

***Table 3: Estimated OELs related to hazard category for gases/liquids and solids***

| Hazard category | Number of substances | OEL UK | | Estimated OEL (10th percentile) |
|---|---|---|---|---|
| | | Geometric mean | Geometric standard deviation | |
| **Gases/liquids** | | **(ppm)** | **(ppm)** | **(ppm)** |
| 0 (Very low) | 24 | 169 | 5.8 | 18 |
| 1 (Low) | 62 | 31.8 | 7.6 | 2.4 |
| 2 (Medium) | 61 | 3.92 | 7.2 | 0.31 |
| 3 (High) | 27 | 0.29 | 8.7 | 0.018 |
| **Solids** | | **($mg/m^3$)** | **($mg/m^3$)** | **($mg/m^3$)** |
| 0 (Very low) | 98 | 5.9 | 1.6 | 3.1 |
| 1 (Low) | 11 | 3.9 | 2.5 | 1.2 |
| 2 (Medium) | 26 | 1.1 | 4.5 | 0.16 |
| 3 (High) | 17 | 0.25 | 7.1 | 0.020 |

Hazard category 4 (Very high) has not been included in Table 3. The assignment of substances to this hazard category is not related to potency, and the fact that a substance has been placed in hazard category 4 is therefore not useful as a criterion for setting an OEL. In addition, substances in this hazard category are likely to have undergone extensive study before being authorised for industrial use and processing under the proposed REACH regulation.

### *5.2 $LD_{50}$, and $LC_{50}$*

It has been suggested that there is a correlation between doses resulting in toxicological effects after short and long-term exposure. Such a relationship might be used to derive an OEL from

acute animal toxicity data, in particular from an oral $LD_{50}$ in the rat (available for many chemicals) or, alternatively, from inhalation $LC_{50}$ values.

### 5.2.1 Use of $LD_{50}$

A possible method for deriving an OEL makes use of the relationship between the oral $LD_{50}$ and the MTD in 2-year rat studies. The oral $LD_{50}$ appears to be predictive of the MTD, as shown by Gombar *et al* (1991) who studied the relationship between the MTD observed in NTP studies and the oral acute $LD_{50}$ in rats; some structural characteristics were also taken into consideration.

The MTD is the highest dose used in chronic toxicity testing that is expected to produce limited toxicity when administered for the duration of the test period. It should not induce:

- Overt toxicity (e.g. appreciable death of cells or organ dysfunction);
- toxic manifestations predicted to reduce the life span of the animals except as the result of neoplastic development;
- 10% or greater retardation of body weight gain compared with control animals. In some studies, toxicity that could interfere with a carcinogenic effect is specifically excluded from consideration.

Gombar *et al* (1991) analysed information on 269 substances for which an NTP 2-year study had been carried out, and concluded that there was a strong correlation between rat oral $LD_{50}$ values and the MTD.

$LD_{50}$ data are available for a large number of substances; however, this value is not always from a rat oral study. Table 4 shows the number of substances for which acute $LD_{50}$ values and $LC_{50}$ values are quoted in the Registry of Toxic Effects of Chemical Substances (RTECS) of the US National Institute for Occupational Safety and Health (NIOSH, 2005).

***Table 4: Number of $LD_{50}$ and $LC_{50}$ data in RTECS***

| Species / Toxic endpoint | Number |
|---|---|
| **Rat** | |
| $LD_{50}$ oral | 15,827 |
| $LC_{50}$ inhalation | 1,466 |
| $LD_{50}$ i.p. | 7,426 |
| **Mouse** | |
| $LD_{50}$ oral | 33,806 |
| $LC_{50}$ inhalation | 870 |
| $LD_{50}$ i.p. | 51,709 |

To assess the value of these data for deriving OELs, the Task Force analysed the ratios between the mouse and rat intraperitoneal (i.p.) $LD_{50}$, the mouse and rat oral $LD_{50}$, and the mouse and rat inhalation $LC_{50}$. The reliability of the rat oral $LD_{50}$ was evaluated by comparing it with other available acute toxicity data. Table 5 shows that there is general consistency between species and exposure route of $LD_{50}$s for the same substance. If the oral $LD_{50}$ rat for a given substance is not consistent with other available $LD_{50}$s (Table 5), this $LD_{50}$ should not be used for MTD estimation.

***Table 5: Statistical findings in RTECS***

| Paramater-ratio | Number of data | Geometric mean | Geometric standard deviation | 90th percentile | 95th percentile |
|---|---|---|---|---|---|
| **$LD_{50}$ (mg/kgbw)** | | | | | |
| Mouse i.p./oral | 5,937 | 0.319 | 2.599 | 1.085 | 1.535 |
| Rat i.p./oral | 2,461 | 0.290 | 3.044 | 1.207 | 1.808 |
| Mouse i.p./rat i.p. | 3,179 | 0.976 | 1.999 | 2.327 | 3.050 |
| Mouse oral/rat oral | 5,027 | 0.845 | 2.087 | 2.170 | 2.834 |
| **$LC_{50}$ ($mg/m^3$)** | | | | | |
| Mouse/rat [a] | 256 | 0.658 | 3.033 | 2.728 | 4.081 |

[a] Normalised to similar exposure duration

The Task Force supplemented the database of Gombar *et al* (1991) with 46 other oral NTP 2-year studies carried out after 1991 (315 studies in total). It was found that the correlation between the

$LD_{50}$ and the MTDs could be improved by introducing log $K_{ow}$ into the equation. For each substance the log $K_{ow}$ was retrieved from the literature, or in a few cases estimated by means of KowWin software (US-EPA, 2000). The log $K_{ow}$ selected was the most reliable value (i.e. that of the free base or acid and not the HCl or NaOH salt.)

The following relationship was established from the data analysis (Appendix D):

$$\log MTD = -0.6727 + 0.9226 \times \log LD_{50} - 0.05383 \times \log K_{ow} \quad \text{..... (Eq. 1)}$$

This equation explained 58.1% of the variance of log MTD and can be used to derive an estimated MTD for NTP 2-year studies in rats, using only an $LD_{50}$ and a log $K_{ow}$ (e.g. by taking the lower 90% confidence limit of the MTD estimate and considering variances and covariances of the regression coefficients). Using the lower 90% confidence limit of the estimated MTD takes into account the statistical uncertainty around the point estimate of the MTD and results in a conservative OEL.

As 68% of the oral $LD_{50}$ rat NTP studies are between 150 and 5,000 mg/kgbw (geometric mean 874 mg/kgbw) and the log $K_{ow}$ between –0.3 and 4.5 (arithmetic mean 2.1), the predicted MTDs are highly accurate for $LD_{50}$s and log $K_{ow}$s in these ranges.

By applying appropriate assessment factors, an OEL can be estimated.

The $LD_{50}$-MTD approach has certain aspects in common with the hazard banding approach, in that certain risk phrases are based on the $LD_{50}$ value of the substance (Section 5.1). However, the estimated MTD from 2-year rat studies and the MTD 5th percentile are related to the $LD_{50}$ in a logarithmic way and on a continuous scale, and not by order of magnitude (hazard bands).

In many studies, so few effects are seen even at the highest dose tested that the highest dose is the MTD as well as the NOAEL. In other studies, the MTD is comparable to the LOAEL. The latter is the case if severe toxicity is observed at the dose above the LOAEL.

The Task Force has proposed a default assessment factor of 10 for the extrapolation from the lower 90% confidence limit of the MTD (LOAEL) to the NOAEL. Finally, to arrive at a provisional OEL, an interspecies factor (rat to man) of 4 and an intraspecies factor of 3 for workers are applied (ECETOC, 2003a).

In conclusion, the oral $LD_{50}$ combined with the log $K_{ow}$ appears to be a reasonable predictor of the MTD. The relationship could be used to obtain some indication of the dose levels at which adverse effects in long-term studies would be expected. It is recommended that the lower 90%

confidence limit of the estimated MTD is used as a starting point for deriving an OEL. This method includes typically the use of appropriate assessment factors.

This method should not be applied to substances suspected of being carcinogenic, mutagenic, or reprotoxic.

#### 5.2.2 Use of $LC_{50}$

The number of reported 4-hour rat $LC_{50}$ studies is much lower than that of reported oral rat $LD_{50}$ studies. In addition, fewer volatile than non-volatile substances are used in industry. However, as the likelihood of relevant exposure to volatile substances is much higher than to non-volatile substances, it was considered worthwhile to explore the relationship between the 4-hour $LC_{50}$ and the OEL.

The 4-hour rat $LC_{50}$ was obtained for 98 substances from RTECS (NIOSH, 2005) and the OELs were derived from Dutch and UK OEL lists. The lower of the two values was selected. For the data set used, the ratio between the $LC_{50}$ and the OEL appeared to be log-normally distributed. The relationship between the OEL and the 4-hour $LC_{50}$ in rat is shown in Appendix E. The results are as follows:

$$\ln OEL = -6.036 + 0.9617 \times \ln LC_{50} \quad \text{(Eq. 2)}$$

where ln is the natural logarithm

The $LC_{50}$ appeared to be a good predictor of the OEL: 68.4% of the variance of the ln OEL was explained by this parameter. The lower 90% confidence limit of the OEL distribution could be used for estimating an OEL.

This method should not be applied to substances suspected of being carcinogenic, mutagenic or reprotoxic.

### *5.3 Substances with similar structures*

#### 5.3.1 Use of (Q)SAR models

(Q)SARs relate features of a molecular structure to a property, effect or biological activity associated with a particular chemical, in order to generalise this knowledge and extrapolate it to

other chemicals for which toxicity data are unavailable. Under the current EC legislation for new and existing chemicals, the regulatory use of (Q)SARs is limited.

In principle, however, (Q)SARs could be used for a number of purposes in the regulatory assessment of chemicals and under the future REACH regulation, it is anticipated that (Q)SARs will be used more extensively than at present, e.g. in priority setting, in assisting in the selection of experimental test methods, in hazard classification and in the provision of dose-response information for use in chemical risk assessment.

The EC chemicals policy calls for (Q)SAR models that are scientifically valid and available to all stakeholders, but does not address concerns about the validity and applicability of currently available (Q)SARs. An EC project has therefore been initiated to develop a framework for the independent development, validation and dissemination of (Q)SARs (IHCP, 2005). It is hoped that the new framework will lead to a more widespread use of (Q)SARs, particularly for regulatory purposes under the proposed REACH regulation. Meanwhile it is considered advisable to await the recommendations of the European framework before formulating general advice on the use of (Q)SARs for classification or dose-response assessments and setting OELs.

ECETOC (2003b) evaluated commercially available (Q)SAR software for human health and environmental endpoints relevant for chemicals management. and concluded that applicability of (Q)SARs was 'limited to good' for *in vitro* mutagenicity, 'limited' for acute oral toxicity, skin irritation, eye irritation and skin sensitisation and 'very limited' for chronic mammalian toxicity, carcinogenicity and teratogenicity. As such, it would appear that (Q)SARs, in the absence of any other information, are of limited value in setting OELs. However, in combination with other information, (Q)SARs may have a useful supportive role.

### 5.3.2 Use of read-across

This approach focuses on groups of substances sharing an active group with similar chemical/toxicological functionality (e.g. isocyanates, nitriles and glycidyl ethers). By comparing the OELs within a particular group of substances, OELs can be proposed for related substances. In the absence of any other relevant information, the lowest OEL from a group of substances with similar toxicologically-active groups could be selected as an OEL. Often the range of OELs of substances with an active sub-structure is smaller than the range of OELs within a risk-phrase based hazard category.

REACH Annex IX would permit toxicological information to be derived using the 'grouping of substances and read-across approach'. The REACH proposal states that "substances whose

physico-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group or 'category' of substances, as they are under the high production volume chemicals initiative (ICCA, 1998). Application of the group concept requires that physico-chemical properties, human health effects and environmental effects or environmental fate may be predicted from data for a reference substance within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint*"* (EC, 2003a).

The identification of substances with similar structure is facilitated by a recently developed internet tool ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus/) (NLM, 2004). The user inputs a drawing of the chemical structure of a substance and in return is provided with CAS numbers of substances with similar structures, listed by decreasing similarity. The CAS numbers have hyperlinks to toxicological databases with information on the toxicity (systemic or local) of these structurally-related substances. This procedure may be a first step towards providing a structure-specific (Q)SAR.

*Examples of structure-related organic compounds (reactivity)*

Principal electrophilic groups in contact allergy are: alkyl halides, aryl halides, aldehydes, esters, amides, epoxides, lactones, lactams, α-β-unsaturated aldehydes and ketones, paraquinone, orthoquinone, and metal salts (Basketter *et al*, 1995). For substances with these structural elements, it is recommended that the skin sensitising potential is studied in the local lymph node assay (ECETOC, 2003c) or alternatively in the guinea pig maximisation test.

There is no established animal test for assessing the respiratory sensitising potential of chemicals and the classification of respiratory allergens is normally based on experience from human exposure. Examples of chemicals known to cause respiratory sensitisation in the workplace are: acid anhydrides of dicarboxylic acids, di-isocyanates, proteins (e.g. enzymes), and β-lactam antibiotics. As a precaution, substances within these groups should generally be considered as respiratory sensitisers if no other data are available to indicate the absence of such effects.

The α-β-unsaturated ketones are highly reactive compounds (by undergoing a Michael addition with nucleophilic moieties) and are therefore (cyto)toxic and sensitising. Unsaturated ketones with a higher spacing than α-β- between the vinyl group and carbonyl function (non-conjugated), however, cannot exert Michael reactions and have much more in common with saturated aliphatic ketones than with α-β-unsaturated ketones.

In contrast, saturated aliphatic ketones are of a relatively low toxicity and usually show no allergenicity and genotoxicity or significant cytotoxicity; they may be treated as a homogeneous

group with only some quantitative differences according to usual physico-chemical descriptors. Toxic effects are limited to irritation of mucous membranes or pre-narcotic effects at relatively high exposure levels.

The γ-diketones are aliphatic ketones with a free $–CH_2–$ grouping-position that may exert neurotoxic properties similar to *n*-hexane. Precursors might be substances with a vinyl group in the γ-position of the keto-group, which may form γ-diketones in the course of metabolic transformation. Chain length and branching type are the main determinants for toxic potency, not physical descriptors.

Vinyl ethers and vinyl esters have quite different toxicological properties. Vinyl ethers show no reactivity with biomacromolecules and not much metabolic transformation, hence no significant (cyto)toxicity. On the contrary, vinyl esters are easily cleaved to vinyl alcohol. The acetaldehyde so formed may cause clastogenic and to some extent carcinogenic effects. Also N-vinyl compounds (e.g. N-vinyl pyrrolidone) are potential precursors of acetaldehyde via hydrolysis or intracellular oxidative pathways. Therefore an evaluation of the potential metabolic and kinetic behaviour of each single compound needs to be included in a (Q)SAR consideration for a toxicity profile. Electronic databases on this matter are becoming increasingly available, but expert judgement is essential.

*Examples of inorganic compounds (similar cations or anions)*

In the absence of data, inorganic materials, may be initially evaluated from a theoretical point of view in a similar way to (Q)SAR assessments in organic chemistry; following categorisation, group approaches may be possible. On the other hand, a great variety of chemical properties may exist within a certain group that determine, for example, solubility, membrane passage, phagocytosis, intercellular bioavailability, and kinetic and toxicological behaviour. This has been well investigated, for example in relation to the various oxides and sulphides of nickel (ECETOC, 1989).

Similarities in chemical behaviour may exist among metals within a certain group of elements, and behaviour is quite often independent of the corresponding anion. On the other hand, certain anions are known to have a high systemic toxicity that may overwhelm the activity of the metal cation. It should be established initially whether a metal (anion or oxide) exerts systemic toxicity or whether local toxicity is predominant. Even if local toxicity appears to be predominant, the potential for systemic effects (e.g. oncogenicity) must not be disregarded, particularly if the compound (or ion) is bioaccumulative or has genotoxic properties.

Cations with suspected systemic toxicity (distant from the entrance site) on inhalation include certain heavy metals such as mercury, arsenic, lead and silver. Others such as cadmium, chromium, and nickel compounds are mainly carcinogens at the respiratory site, but may also exert other effects (e.g. allergy, kidney toxicity). The oxidation state (e.g. $Cr^{III/VI}$) may be important for membrane passage and intracellular bioavailability.

Anions with potential systemic toxicity include cyanide, azide, bromides and soluble sulphides. Cations may modify the toxicity of these anions to some extent but in general the overall toxicity profile of these toxic salts is characterised by the systemic toxicity of the anions.

Metallo-organic compounds (including carbonyls) have to be evaluated as a separate group. They are often much more toxic than would be expected from the organic or metallic moiety alone. The organic moiety facilitates membrane passage of the metal and thus increases the bioavailability at the intracellular level. Examples are, nickel carbonyl [$Ni(CO)_4$], iron pentacarbonyl, [$Fe(CO)_5$] and iron nitrilotriacetate (FeNTA).

### 5.3.3 Sensory irritation related to physico-chemical properties

The extent of mucous membranes irritation (local effect) can often be directly related to simple physico-chemical properties. Alarie *et al* (1995) showed that an increased vapour pressure of substances from a homologous series correlated with an increased $RD_{50}$ (the concentration in air which decreases the breathing rate of mice by 50%). Furthermore, an increase of the log (octanol-air partition coefficient) was related to a decrease in the $RD_{50}$. Thus, an increase in vapour pressure lowered sensory irritation and an increase in octanol-air partition ($K_{oa}$) increased irritation. This finding is not only related to the $RD_{50}$. Hau *et al* (2000) showed a correlation between the $K_{oa}$ and odour thresholds, nasal pungency thresholds and median lethal concentrations for alkanes, alcohols, ketones and acetates. The findings of Hau *et al* (2000) on the relationship between the nasal pungency threshold (as dependent variable) and the air-water coefficient (or dimensionless Henry's Law constant) ($K_{aw}$) and the octanol-water coefficient ($K_{ow}$) (as independent variables) support the earlier observations of Alarie *et al* (1995).

The present Task Force studied the relationship between the logarithm of $K_{aw}$ and $K_{ow}$ and the logarithm of the $RD_{50}$, using the $RD_{50}$ of all 75 substances in Table 1 of Alarie *et al* (1995). The log $K_{aw}$ and the log $K_{ow}$ were derived from EpiSuite (US-EPA, 2000). The following relationship was obtained (Appendix F):

$$\log RD_{50} = 6.346 - 0.8333 \times \log K_{ow} + 0.7139 \times \log K_{aw} \quad \text{..... (Eq. 3)}$$

This equation explains 74.9% of the variance of the log $RD_{50}$ with the log $K_{aw}$ and the log $K_{ow}$ as independent variables. Thus, an increase of the log $K_{ow}$ is related to an increase of the irritation. If it is to be based only on sensory irritation, an OEL can be derived by means of the equation above, using the lower 90% confidence limit of the $RD_{50}$ as a starting point, divided by an arbitrary assessment factor of 10 (calculated examples are given in Chapter 6 and Appendix G). This relationship might also be useful for estimating the $RD_{50}$ of a substance that is a member of a series of homologous substances, for some of which the $RD_{50}$ has been experimentally measured. The ratio between the OELs is assumed to be identical to the ratio between the $RD_{50}$s, if the OELs are based only on sensory irritation.

### *5.4 Threshold of toxicological concern*

The threshold of toxicological concern (TTC) is a concept developed for pragmatic risk assessment of food contaminants. It is based on the principle of establishing a human exposure threshold value for chemicals, below which there is a very low probability of an appreciable risk to human health. The derivation of a TTC has been developed for substances with a systemic mode of action and with exposure via ingestion. The TTC principle proposes that a *de minimis* value can be identified for many chemicals, in the absence of a full toxicity database, based on their chemical structures and the known toxicity of chemicals that share similar structural characteristics. The TTC approach includes elements of structure-activity relationship (SAR) considerations to exclude substances of concern.

The TTC concept has been developed and examined for various endpoints (Munro, 1990; Munro *et al,* 1996). In a first step, the concept was evaluated for general toxicity, carcinogenicity, neurotoxicity, developmental neurotoxicity, developmental toxicity and immunotoxicity. An expert group of the European branch of the International Life Sciences Institute (ILSI Europe) has recently examined the application of the TTC principle for metabolism and accumulation, structural alerts, endocrine disrupting effects and further explored specific endpoints, such as neurotoxicity, teratogenicity, developmental toxicity, allergenicity and immunotoxicity. Proteins, heavy metals, polyhalogenated dibenzodioxins and related compounds were excluded from this approach (Kroes *et al*, 2000, 2004).

The initial step in the application of the TTC concept for a particular substance is the identification of possible genotoxic and/or high potency carcinogens. For high potency carcinogens, compound-specific toxicity data are required and for genotoxins, a default TTC of 0.15 µg/person/d is applied. Following this step, non-genotoxic substances are evaluated in a sequence of steps related to the concerns for health. If the estimated intake does not exceed 1.5 µg/person/d, the substance would not be expected to be a safety concern and no further evaluation is necessary. For organophosphates, a TTC of 18 µg/person/d is proposed.

Substances that are not organophosphates are grouped according to their structure in one of 3 'Cramer classes' (Cramer *et al*, 1978) with TTCs of 1,800, 540 and 90 µg/person/day (30, 9 and 1.5 µg/kgbw/d based on 60 kgbw) for Cramer Classes I, II and III, respectively.

The TTC concept formed the scientific basis of the US Food and Drug Administration threshold of regulation for indirect food additives (US-FDA, 1993). The TTC principle has also been adopted by the Joint FAO/WHO Expert Committee on Food Additives in its evaluation of flavouring substances (JECFA, 1993, 1995, 1999). Since 1996 a decision tree incorporating different TTCs related to structural class has been used for the safety evaluation of over 1,200 flavouring substances.

TTC may also be considered for deriving OELs. The classification into Cramer classes is, however, a relatively complex exercise, requiring detailed knowledge about structural chemical classes, and this expertise might not be available in small and medium chemical enterprises. The OELs generated by this method are conservative estimates intended to protect the general public, which is assumed to have a wide inter-individual variability. This assumption is likely to be overly protective for a worker population, which consists typically of people who are healthy and within certain age limits. The worker population is exposed for 40 years (8 h/d, 5 d/wk) and, on average, includes fewer potentially sensitive individuals (very young, very old, severely ill people) than the general population.

The conservatism of the TTC approach is illustrated for some substances of Cramer class I in Table 6.

***Table 6: Some official OELs and OELs generated by the TTC method***

| Substance name | CAS number | Official OEL [a] ($mg/m^3$) | TTC-OEL ($mg/m^3$) |
|---|---|---|---|
| Acetone | 67-64-1 | 1,210 | 0.18 |
| *sec*-Butanol | 78-92-2 | 308 | 0.18 |
| Butyl acetate | 123-86-4 | 724 | 0.18 |
| Cyclohexanol | 108-93-0 | 208 | 0.18 |
| Toluene | 108-88-3 | 191 | 0.18 |

[a] UK values

The TTC for Cramer class I compounds is only 30 µg/kgbw/d, which would correspond to an OEL of 0.18 $mg/m^3$ (assuming 10 $m^3$ of air inhaled during an 8-hour work shift and a body weight of 60 kg). As can be seen in Table 6, all the selected official UK OELs are more than 1,000 times higher than the OELs calculated from the TTCs. Using the TTC concept for deriving

OELs for compounds with systemic toxicity appears to result in overly conservative values and an adjustment to the different circumstances for the workers population is required.

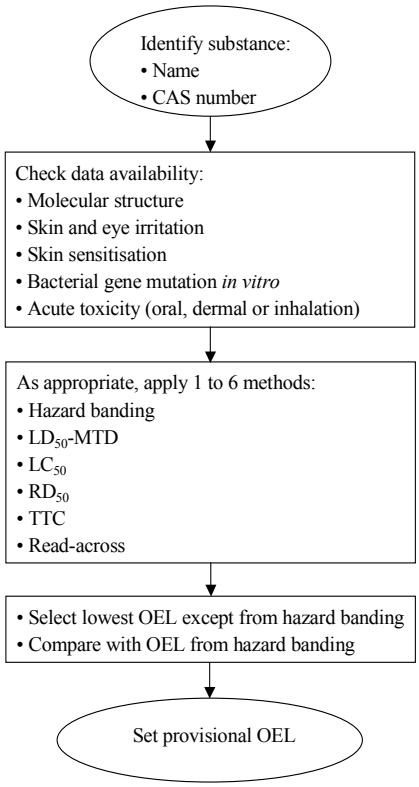
In deriving OELs with this methodology, the definition of an OEL (8-h/d, 5 d/wk) and the target population (healthy workers) must be taken into consideration. The Task Force recommends that the TTC multiplied by a factor of 100 is used. Thus, OEL = TTC x 100/10 mg/m$^3$, where 10 m$^3$ is the volume of air inhaled by a worker during an 8-hour work shift. A factor of 100 was chosen because, typically, exposures considered permissible for the general population are 100 to 1,000 times lower than those for a healthy working population (UK-EA, 2003).

Assigning chemicals to Cramer classes I, II and III has been facilitated by a software application of Cramer's decision tree (Cramer *et al*, 1978) commissioned by the European Chemicals Bureau (ECB, 2006). The Task Force has used this tool in the worked examples discussed in Chapter 6.

# 6. APPLICATION OF PROPOSED APPROACH

The Task Force proposes an approach (Figure 1) for deriving OELs for data-poor substances based on the individual methods outlined in Chapter 5.

***Figure 1: Proposed approach for setting an OEL for a data-poor substance***




To judge the quality of the OELs estimated following the approach proposed in Figure 1, a limited data set was selected for 10 substances for which official OELs exist currently. This consisted of:

- Risk phrases,
- $LD_{50}$ (mg/kgbw),
- log $K_{ow}$ (dimensionless),
- log $K_{aw}$,
- 4-hour $LC_{50}$ rat (mg/$m^3$),
- TTC (mg/kgbw/d), corresponding to a specific Cramer class (human body weight 60 kg).

Read-across was not applied because data were available for each of the specific substances selected. OELs were estimated for each of the 10 substances by means of the other five proposed methods as follows:

- Hazard banding: the 10th percentile of the OELs corresponding to the pertinent hazard category (Table 3) (Section 5.1) was selected;
- The MTD in mg/kgbw/d was calculated from the $LD_{50}$ and log $K_{ow}$. To arrive at an estimated OEL, the lower 90% confidence limit of the MTD was divided by the appropriate assessment factors (10 x 3 x 4 = 120), multiplied by a body weight of 60 kg and divided by 10 $m^3$/d (standard volume of air inhaled during an 8-hour work shift) (Section 5.2.1);
- The lower 90% confidence limit of the estimated OEL from the 4-hour rat $LC_{50}$ (Section 5.2.2) was selected;
- The $RD_{50}$ in ppm was calculated from log $K_{ow}$ and log $K_{aw}$. One tenth of the lower 90% confidence limit of the $RD_{50}$ was estimated as the OEL; this was converted to mg/$m^3$ by means of the molecular weight and molar vapour volume (Section 5.3.2);
- The OEL was calculated from the TTC (mg/kgbw/d) multiplied by a factor of 100 to account for worker population, multiplied by a body weight of 60 kg and divided by 10 $m^3$/d (standard volume of air inhaled during an 8-hour work shift) (Section 5.4).

The OELs estimated by the methods outlined were compared with the official OELs for the 10 substances. The results are presented in Table 7. Details of the specific calculations and considerations are given in Appendix G.

***Table 7: Comparison of OELs for 10 substances***

| Substance | OEL (mg/m$^3$) | | | | | |
|---|---|---|---|---|---|---|
| | Existing [a] | Hazard banding | MTD ($LD_{50}$) | $LC_{50}$ | $RD_{50}$ | TTC |
| Acrylic acid | 5.9 | 0.9 | 6.7 | 4.7 | 80 | 5.4 |
| Aniline | 1 | 0.07 | 3.2 | 5.2 | 100 | 0.9 |
| *sec*-Butanol | 450 | 7.3 | 16 | 52 | 860 | 18 |
| *p-tert*-Butylphenol | 0.5 | 0.16 | 11 | 7.1 | 6.1 | 18 |
| Caprolactam | 10 [b] | 1.2 | 7.8 | 10 | 5.9 | 0.9/18 [c] |
| Cyclohexanone | 25 | 9.6 | 8.3 | 13 | 1,005 | 5.4 |
| Ethylenediamine | 18 | 0.04 | 6.5 | 5.2 | 70 | 0.9/18 [c] |
| Glutaraldehyde | 0.25 | 0.07 | 1.7 | 0.12 | 87 | 18 |
| Isoprene | 5.7 [d] | Carcinogen | 7.9 | 162 | 7,475 | 18 |
| Melamine | 10 [d] | 3.1 | 17 | 4.2 | 0.038 | 0.9/18 [c] |

[a] The Netherlands, unless indicated otherwise
[b] IOELV (EC)
[c] See last paragraph of this chapter
[d] Workplace environmental exposure level (WEEL)

The following comments are relevant with regard to the values obtained:

- The use of the 10th percentile of OELs of substances within a specific hazard category consistently resulted in OELs that were lower than official OEL values. These values appeared to be unnecessarily conservative in some cases.
- Using the estimated MTD (calculated from $LD_{50}$ and log $K_{ow}$) for deriving an OEL, provided reasonable estimated OELs for substances with a systemic mode of action. All were within a factor of 10 of the official OEL except for those of *sec*-butanol and *p-tert*-butylphenol. Even though the OEL for *sec*-butanol was among the highest calculated with this method, it was still significantly lower than the official OEL, which is based on both irritation and systemic effect (narcosis). The official OEL for *p-tert*-butylphenol is based on skin effects (allergy and vitiligo). These effects are not expected to be captured by the MTD ($LD_{50}$) method.
- A somewhat surprising result was the reasonable prediction of the OEL on the basis of the 4-hour $LC_{50}$. Outliers were isoprene, which is considered to be weakly carcinogenic, and *p-tert*-butylphenol, which is a skin sensitiser and causes vitiligo in animals and humans at low exposure levels. The $LC_{50}$ as starting point has the advantage that it can be applied to substances with potentially both systemic and local modes of action.

- The OELs derived from the $RD_{50}$ are generally higher (up to 10 times) than the official OELs. This is not surprising, as the substances selected do not belong to the chemical domain for which the regression equation was established.
- Using the TTC concept, the estimated OELs were reasonably close to the official OELs for all substances, except *p-tert*-butylphenol and glutaraldehyde. The official OEL for glutaraldehyde is based on local effects and for *p-tert*-butylphenol on skin allergy and vitiligo in animals and humans. The TTC concept is intended to cover only ingested substances with a systemic mode of action; substances with a local mode of action and those inducing effects by skin contact only do not fit into the TTC concept. Furthermore, following strictly the ECB (2006) tool, classification of caprolactam, ethylene diamine and melamine into Cramer class III (high toxic hazard) would lead to overly conservative OELs. It is suggested that these substances are classified as Class I (low hazard) on the basis of the NOAELs referred to in Cramer *et al* (1978), particularly as the metabolites of caprolactam and ethylene diamine are normal constituents of the body. The revised TTC-OELs are 18 $mg/m^3$.

# 7. DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

Established mechanisms exist for setting OELs for data-rich substances. Generally, the NOAEL for a critical effect is known from a repeated dose toxicity study in an appropriate animal species. Suitable assessment factors can then be applied to extrapolate the NOAEL in animals to humans and arrive at an OEL. The magnitude of those assessment factors, however, remains a point of debate. This method applies to single substances. In the case of substances, such as the hydrocarbon solvents that are mixtures, a meaningful OEL can be calculated from the reciprocal OELs of the individual constituents.

The companies represented in the Task Force possess in-house procedures for setting OELs, but those are mainly focused on data-rich substances. In general, companies do not establish OELs for data-poor substances; generally a banding approach is applied in providing advice on controlling exposure to such substances. This results in the substances being handled according to standard or default 'good hygiene practices', defined for each band and exposure scenario (HSE, 2004).

The purpose of this report was to explore ways of deriving OELs for data-poor substances. This is particularly relevant towards providing reliable risk management advice on the handling of such substances, and in the context of hazard information required by the REACH proposal (EC, 2003a). There is substantially more inherent uncertainty when setting OELs for such substances, as information on the key NOAEL from a repeat dose study is generally lacking.

The Task Force has explored several methods that might be useful in generating a provisional OEL.

- The control (hazard) banding concept uses risk phrases as defined in Directive 67/548/EEC to assign substances to hazard categories for human health. Established OELs and EC risk phrases for substances in every hazard category were gathered; the distribution of the OELs in each category was analysed and found to be log-normal. The geometric standard deviation appeared to be wide, and in relation to a single risk phrase (e.g. R20 or R37 being the most severe) OELs were found to differ by 3 orders of magnitude. In the light of this wide spread of values, the 10th percentile of OELs of substances, assigned to a specific hazard category is estimated as an OEL for all substances in any given category, including those with a limited set of data.
- To validate the hypothesis that the $LD_{50}$ could be used potentially as a predictor of chronic toxicity, the rat oral $LD_{50}$s were compared with the MTDs observed in 2-year studies carried out under the US-NTP. The rat oral $LD_{50}$ (as modified by the $K_{ow}$) appeared to be highly predictive of the MTD. It is suggested that the 5th percentile of the distribution of the estimated MTD could be used as critical effect level for deriving an estimated OEL. This

method should not be applied to substances suspected of being carcinogenic, mutagenic or reprotoxic.

- Since inhalation is the most relevant route of workplace exposure, the relationship between the official OEL and the 4-hour rat $LC_{50}$ was evaluated. For the data set used, the ratio between the $LC_{50}$ and the OEL was log-normally distributed and the $LC_{50}$ appeared to be a direct predictor of the OEL. It is suggested that the lower 90% confidence limit of the estimated OEL distribution is appropriate as an (estimated) OEL. This method should not be applied to substances suspected of being carcinogenic, mutagenic or reprotoxic.
- Comparing the chemical structure of a substance without toxicological data with substances of similar structure but with known toxicity, is potentially a useful way to get an understanding of the type and severity of the effects of the substance. This read-across approach can be used in combination with the hazard banding method or the relationship of $LD_{50}$ and MTD. The approach seems promising considering the increasing availability of internet-based tools that from a molecular structure can generate a list of similar molecules of structural similarity, with links to their toxicological profiles. Experiences with these new internet sources have not yet been published.
- Using data on the $RD_{50}$ (airborne concentration in ppm, which decreases the breathing frequency of mice by 50%), an OEL can be estimated for those substances expected to exhibit sensory irritation. A few authors have shown that the $K_{oa}$ is closely related to the $RD_{50}$, and as such this can be used to predict the severity of the sensory irritation for substances from a homologous series with the same mode of action, for which no $RD_{50}$ has been established. The $K_{oa}$ can be estimated from the $K_{aw}$ and $K_{ow}$.
- The TTC concept, widely applied in the risk assessment of the general population for protection from food and feed contaminants, might also be used to set OELs for substances with a systemic mode of action. The tolerable dose level for (healthy) workers is assumed to be 100 to 1,000 times higher than for the general population, (as shown in this report for some substances belonging to Cramer class I). This means that an OEL could be based on a value of about 100 times any TTC established for the general population. The TTC concept has been based on the Cramer scheme, designed to prevent underestimation of toxicity; overestimation has not received much attention. This may result in certain OELs being overly conservative, as observed for some substances assigned to Cramer class III.

The use of (Q)SARs is considered to be of limited value for setting OELs, because of the inadequate prediction of qualitative and in particular quantitative toxicological endpoints (ECETOC, 2003b).

To demonstrate the validity of the above methods, OELs were estimated with the approaches described above for 10 substances that already possess an established OEL. When deriving such estimated OELs, only the EC risk phrases and a limited data set were used [acute oral and

inhalation rat data ($LD_{50}$, $LC_{50}$), log $K_{ow}$, log $K_{aw}$, and the Cramer class derived from the chemical structure]. Any additional experimental data available on the substances were ignored.

- The OELs predicted from the most stringent risk phrases (hazard banding procedure) appeared to be more conservative than the existing OELs.
- Using the estimated MTD (calculated from $LD_{50}$ and the log $K_{ow}$) for deriving an OEL provided reasonable estimated OELs for substances with a systemic mode of action. Seven out of the ten OELs were within a factor of 10 of the official OEL.
- The prediction of the OEL from the $LC_{50}$ was mostly within one order of magnitude of the existing OEL. Outliers are isoprene, which is considered to be weakly carcinogenic, and *p-tert*-butylphenol, which is a skin sensitiser and causes vitiligo in animals and humans at low exposure levels. The $LC_{50}$ as starting point has the potential advantage that it can be applied to substances with both systemic and local modes of action.
- The OELs derived from the $RD_{50}$ were generally higher than the official OELs; a majority of the OELs differed from the official OELs by more than a factor of 10. This is not surprising as several of the substances did not belong to the domain of substances for which the regression equation was established.
- The performance of the TTC concept for OEL setting is ambiguous. The estimated OELs were reasonably close to the established OELs for all substances except two. Substances with a local mode of action and those inducing effects by skin contact only do not fit into the TTC concept. The assignment of a substance to one of the Cramer classes might overestimate toxicity for some substances (lactams, secondary amines, aliphatic diamines).

These findings appear to suggest the following:

- The method based on risk phrases results in an over-conservative OEL in many cases.
- The lowest result of the remaining approaches provides an estimated OEL in line with official OELs.

The following steps (Figure 1) are recommended to establish an OEL for a data-poor substance:

1. Determine whether the substance is expected (e.g. based on structure) to exhibit local and/or systemic effects or sensory irritation, and apply the OEL methods considered appropriate for these different modes of action;
2. select the lowest estimated OEL, excluding the OEL derived from hazard banding (most stringent risk phrase);
3. using expert judgment, compare this lowest OEL with the OEL derived from hazard banding;
4. set a provisional OEL.

Completing the programme of testing and evaluation of substances, according to current protocols and as required by the EC existing chemicals programme and the proposed REACH regulation, will inevitably be a lengthy process. Furthermore, it is apparent that only provisional OELs can be established for substances to which Annex V of the REACH proposal applies. The Task Force has concluded that the approach outlined in Figure 1 will prove to be a valuable pragmatic tool for providing provisional OELs as an interim measure to protect the workforce.

## LIST OF SPECIAL ABBREVIATIONS

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| BEI | Biological exposure index |
| DNEL | Derived no-effect level |
| EC | European Commission |
| EEC | European Economic Community |
| HSE | Health and Safety Executive |
| $K_{aw}$ | Air-water partition coefficient |
| $K_{oa}$ | Octanol-air partition coefficient |
| $K_{ow}$ | Octanol-water partition coefficient |
| $LC_{50}$ | Median lethal concentration |
| $LD_{50}$ | Median lethal dose |
| log | Logarithm |
| ln | Natural logarithm |
| LOAEL | Lowest observed adverse effect level |
| MAK | Maximale Arbeitsplatzkonzentration |
| MTD | Maximum tolerated dose |
| NOAEL | No observed adverse effect level |
| NOEL | No observed effect level |
| NTP | National Toxicology Program |
| OEL | Occupational exposure limit |
| QSAR | Quantitative structure-activity relationship |
| RCP | Reciprocal calculation procedure |
| $RD_{50}$ | Median respiratory dose |
| REACH | Registration, evaluation and authorisation of chemicals |
| RTECS | Registry of toxic effects of chemical substances |
| SAR | Structure-activity relationship |
| SCOEL | Scientific Committee for Occupational Exposure Limits |
| STEL | Short-term exposure limit |
| TGD | Technical guidance document |
| TLV | Threshold limit value |
| TTC | Threshold of toxicological concern |
| TWA | Time-weighted average |
| WEEL | Workplace environmental exposure level |

## BIBLIOGRAPHY

ACGIH. 2006. TLVs and BEIs. Threshold limit values for chemical substances and physical agents. American Conference of Governmental and Industrial Hygienists, Cincinnati, OH, USA [www.acgih.org/Products/tlvintro.htm].

Alarie Y. 1973. Sensory irritation by airborne chemicals. *CRC Crit Rev Toxicol* 2:299-366.

Alarie Y, Nielsen GD, Andonian-Haftvan J, Abraham MH. 1995. Physicochemical properties on nonreactive volatile organic chemicals to estimate $RD_{50}$: alternatives to animal studies. *Toxicol Appl Pharmacol* 134:92-99.

Bartsch R, Forderkunz S, Reuter U, Sterzl-Eckert H, Greim H. 1998. Maximum workplace concentration values and carcinogenicity classification for mixtures. *Environ Health Perspect* 106:1291-1293.

Basketter D, Dooms-Goossens A, Karlberg AT, Lepoittevin JP. 1995. The chemistry of contact allergy: why is a molecule allergenic? *Contact Dermatitis* 32:65-73.

Brooke IM. 1998. A UK scheme to help small firms control health risks from chemicals: Toxicological considerations. *Ann Occup Hyg* 42:377-390.

Caldwell D, Armstrong T, Barone N, Suder J, Evans M. 2000. Hydrocarbon solvent exposure data: Compilation and analysis of the literature. *Am Ind Hyg Ass J* 61:881-894.

Carpenter C, Kinkead E, Geary D, Sullivan L, King J. 1975. Petroleum hydrocarbon toxicity studies. III. Animal and human response to vapors of Stoddard solvent. *Toxicol Appl Pharmacol* 32:282-297.

CEFIC, DHI, BfR, Ökopol, TNO, ECETOC, RIVM, BAUA. 2005a. Derivation of the DNEL. In WP3-1b: Preliminary technical guidance document, part C: Reference preliminary technical guidance document (reference p-TGD). European Chemical Industry Council, Brussels, Belgium, pp 102-119.

CEFIC, DHI, BfR, Ökopol, TNO, ECETOC, RIVM, BAUA. 2005b. Derivation of DNELs. In CSA scoping studies WP2-1a: Development of the concept of chemical safety assessment, WP1-1b: Development of a flexible CSA structure, WP2-1b: Development of new risk assessment elements, final report. European Chemical Industry Council, Brussels, Belgium, pp 50-64.

CIIT. 1999. MPPDep v1.1, developed by CIIT in collaboration with the Netherlands Institute for Public Health and the Environment (RIVM) and Ministry of Spatial Planning, Housing and the Environment (VROM), the Netherlands. Chemical Institute of Toxicology, Research Triangle Park, North Carolina, USA.

Cramer GM, Ford RA, Hall RL. 1978. Estimation of toxic hazard, a decision tree approach. *Food Cosmet Toxicol* 16:255-276.

Crump KS. 1984. A new method for determining allowable daily intakes. *Fund Appl Toxicol* 4: 854-871.

Crump KS. 1995. Calculation of benchmark dose from continuous data. *Risk Anal* 15: 79-89.

DFG. 2005. MAK- und BAT-Werte-Liste 2005. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Mitteilung 41. Deutsche Forschungsgemeinschaft, Wiley-VCH, Weinheim, Germany.

EC. 1993. (European) Commission Directive 93/72/EEC of 1 September 1993 adapting to technical progress for the 19th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Off J Eur Comm* L258, L258A.

EC. 1995. 95/320/EC: Commission Decision of 12 July 1995 setting up a Scientific Committee for Occupational Exposure Limits to Chemical Agents. *Off J Eur Comm* L188:14-15.

EC. 1998. Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC. *Off J Eur Comm* L131:11-23.

EC. 1999. Report EU 19253 EN. Methodology for the derivation of occupational exposure limits: Key documentation. Scientific Committee on Occupational Exposure Limits (SCOEL). European Commission, Luxembourg [ISBN 92-828-8106-7].

EC. 2003a. Proposal for a regulation of the European Parliament and of the Council concerning the registration, evaluation, authorisation and restrictions of chemicals (REACH), establishing a European Chemicals Agency and amending Directive 1999/45/EC and Regulation (EC) [on persistent organic pollutants]. 29 October 2003. European Commission, Brussels, Belgium.

EC. 2003b. Second edition of Technical guidance document in support of commission directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) no. 1488/94 on risk assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Office for official Publications of the European Communities, Luxembourg, Luxembourg.

EC. 2004. Commission Directive 2004/73/EC of 29 April 2004 adapting to technical progress for the 29th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Off J Eur Comm* L152.

ECB. 2006. ToxTree Version 1.00. N Jeliazkova, Ideaconsult Sofia, Bulgaria. European Chemicals Bureau, Ispra, Italy [downloadable from http://ecb.jrc.it/QSAR/].

ECETOC. 1989. Nickel and nickel compounds: Review of toxicology and epidemiology with special reference to carcinogenesis. Technical Report No. 33. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 1994. Testing for worker protection. Technical Report No. 59. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 1996. Chronic neurotoxicity of solvents. Technical Report No. 70. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 1997. Occupational exposure limits for hydrocarbon solvents. Special Report No. 13. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 2003a. Derivation of assessment factors for human health risk assessment. Technical Report No. 86. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 2003b. (Q)SARs: Evaluation of the commercially available software for human health and environmental endpoints with respect to chemical management applications. Technical Report No. 89. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 2003c. Contact sensitisation: classification according to potency. Technical Report No. 87. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

ECETOC. 2005. Targeted risk assessment. Technical Report No. 93. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

Fairhurst S. 1995. The uncertainty factor in the setting of occupational exposure standards. *Ann Occup Hyg* 39:375-385.

Gombar VK, Enslein K, Hart JB, Blake BW, Borgstedt HH. 1991. Estimation of maximum tolerated dose for long-term bioassay from acute lethal dose and structure by QSAR. *Risk Analysis* 11:509-517.

Hart WL, Reynolds RC, Krassavage WJ, Ely TS, Bell RH, Raleigh RS. 1988. Evaluation of developmental toxicity data: a discussion of some pertinent factors and a proposal. *Risk Anal* 8:59-69.

Hau KM, Connell DW, Richardson BJ. 2000. Use of partition models in setting health guidelines for volatile organic compounds. *Reg Toxicol Pharmacol* 31:22-29.

HSE. 2004. A step by step guide to COSHH assessment, 2nd ed. Report HSG 97. Health and Safety Executive. HSE books, Sudbury, Suffolk, UK.

HSE. 2005. Workplace exposure limits: Containing the list of workplace exposure limits for use with the Control of Substances Hazardous to Health Regulations 2002 (as amended). Report EH40/2005. HSE books, Sudbury, Suffolk, UK.

ICCA. 1998. High production volume (HPV) chemicals initiative. OECD and International Council of Chemical Associations. European Chemical Industry Council (CEFIC), Brussels, Belgium [www.icca-chem.org/section02b.html].

IHCP. 2005. Action No 1321, computational toxicology (incl QSARs). Worth A, European Centre for the Validation of Alternative Methods. In Institute for Health and Consumer Protection, Joint Research Centre Work Programme 2005. JRC, Ispra, Italy [http://projects-2005.jrc.cec.eu.int], pp 69-70.

JECFA. 1993. Evaluation of certain food additives and contaminants. Safety evaluation of flavouring agents. Forty-first report of the joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 837. World Health Organization, Geneva, Switzerland.

JECFA. 1995. Evaluation of certain food additives and contaminants. Safety evaluation of flavouring agents. Forty-fourth report of the joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 859. World Health Organization, Geneva, Switzerland.

JECFA. 1999. Evaluation of certain food additives and contaminants. Procedure for the safety evaluation of flavouring agents. Forty-ninth report of the joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 884. World Health Organization, Geneva, Switzerland.

Kawabe M, Takesada Y, Tamano S, Hagiwara A, Ito N, Shirai T. 1996. Subchronic toxicity study of L-isoleucine in F344 rats. *J Toxicol Environ Health* 47:499-508.

Kawabe M, Sano M, Hagiwara A, Tamano S, Suzuki S, Shirai T. 2006. Lack of carcinogenicity of L-isoleucine in F344/DuCrj rats. *Food Chem Toxicol* 44:278-285.

Kroes R, Galli C, Munro I, Schilter B, Tran LA, Walker A, Würtzen G. 2000. Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. *Food Chem Toxicol* 38:255-312.

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Würtzen G. 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem Toxicol* 42:65-83.

McKee R, Medeiros A, Daughtrey W. 2005. A proposed methodology for setting occupational exposure limits for hydrocarbon solvents. *J Occup Environ Hyg* 2:524-542.

Munro IC. 1990. Safety assessment procedures for indirect food additives: an overview. Report of a workshop. *Reg Toxicol Pharmacol* 12:2-12.

Munro IC, Ford RA, Kennepohl E, Sprenger JG. 1996. Correlation of structural classwith no-observed effect levels: a proposal for establishing a threshold of concern. *Food Chem Toxicol* 37:207-232.

Murrell JA, Portier CJ, Morris RW. 1998. Characterizing dose-response 1: Critical assessment of the benchmark dose concept. *Risk Anal* 18:13-26.

Naumann BD, Sargent EV, Starkman BS, Fraser WJ, Becker GT, Kirk GD. 1996. Performance based exposure control limits for pharmaceutical active ingredients. *Am Ind Hyg Ass J* 57:33-42.

Naumann BD, Weideman PA. 1995. Scientific basis for uncertainty factors used to establish occupational exposure limits for pharmaceutical active ingredients. *Hum Ecol Risk Assess* 1:590-613.

Nessel C, Owen D, Lammers J, Muijser H, Kulig B. 2000. Neurobehavioral assessment of hydrocarbons and its application to the development of occupational exposure limits for hydrocarbon solvents. *Toxicologist* 54:360.

NIOSH. 2005. Registry of toxic effects of chemical substances (RTECS). National Institute for Occupational Safety and Health, Washington DC, USA [www.cdc.gov/niosh/rtecs/default.html].

NLM. 2004. ChemIDplus advanced. Specialized Information Services Division, National Library of Medicine. Rockville Pike, Bethesda, Maryland, USA [http://chem.sis.nlm.nih.gov/chemidplus/].

OECD. 2002. SIDS initial assessment report for 10th SIAM (Japan, March 15-17, 2000), chemical name: *p-tert*-butylphenol, CAS No. 98-54-4, sponsor country: Japan. Organisation for Economic Co-operation and Development, Paris, France. UNEP, Geneva, Switzerland [http://cs3-hq.oecd.org/scripts/hpv/].

Ogata M, Fiserova-Bergerova V, Droz P. 1993. Biological Monitoring VIII: Occupational Exposures to Mixtures of Industrial Chemicals. *Appl Occup Environ Hyg* 8:609-617.

Ridgway P, Nixon T, Leach J-P. 2003. Occupational exposure to organic solvents and long-term nervous system damage detectable by brain imaging, neurophysiology or histopathology. *Food Chem Toxicol* 41:153-187.

Takeda K, Flood M. 2002. Chronic toxicity and carcinogenicity of sucrose fatty acid esters in Fischer 344/DuCrj rats. *Regul Toxicol Pharmacol* 35:157-164.

Ten Berge W. 2005. Software tool for estimation of OELs from simple data (Excel spreadsheet). Personal communication. *European Centre for Ecotoxicology and Toxicology of Chemicals*, Brussels, Belgium.

TRGS (Technische Regeln für Gefahrstoffe). 2002. TRGS 440. Ermitteln und Beurteilen der Gefährdungen durch Gefahren am Arbeitzplatz: Ermittlen von Gefahrstoffen und Methoden zur Ersatzstoffprüfung. *BArbBl* 3:19.

UK-EA. 2003. Integrated Pollution Prevention and Control (IPPC), Environmetal assessment and appraisal of BAT, appendix D: Environmental benchmarks. Horizontal guidance note IPPC H1, version 6 July 20003 [ISBN 011 3101082]. Environment Agency, Almondsbury, Bristol, UK, pp 92-93.

US-EPA. 2000. KowWin program v1.67. Estimation program interface (EPI) suite v3.11. US Environmental Protection Agency, Washington, DC, USA [www.epa.gov/ opptintr/exposure/docs/episuite.htm].

US-FDA. 1993. Food and Drug Administration. Food additives; threshold of regulation for substances used in food contact articles. *Fed Reg* 58:52719-52727.

US-NTP. 1999. NTP technical report on the toxicology and carcinogenesis studies of isoprene (CAS No. 78-79-5) in F344/N rats (inhalation studies). National Toxicology Program, technical report 486. National Institutes of Health, publication 99-3976. US Department of Health and Human Services, Public Health Service, Research Triangle Park, North Carolina, USA.

# APPENDIX A: INFORMATION REQUIREMENTS PROPOSED UNDER REACH

***Information Requirements - e.g. Toxicology***

| **e.g. Toxicological Information** | **V** | **VI** | **VII** | **VIII** |
|---|---|---|---|---|
| 6.1 skin irritation/corrosion – *in vitro* | X | | | |
| 6.11 skin irritation – *in vivo* | | X | | |
| 6.2 eye irritation – *in vitro* | X | | | |
| 6.2.1 eye irritation – *in vivo* | | X | | |
| 6.3 skin sensitisation | X | | | |
| 6.4.1 *in vitro* gene mutation study in bacteria | X | | | |
| 6.4.2 *in vitro* cytogenicity study in mammalian cells | (X) | X | | |
| 6.4.3 *in vitro* gene mutation study in mammalian cells | (X) | X | | |
| 6.4 *in vivo* mutagenicity studies | (X) | (X) | (XX) | (XX) |
| 6.5.1 acute oral toxicity | | X | | |
| 6.5.2 acute inhalation toxicity | | Or X | | |
| 6.5.3 acute dermal toxicity | | Or X | | |
| 6.6.1 short-term repeated dose toxicity study (28 days) | | X | XX | |
| 6.6.2 sub-chronic toxicity study (90 days) | | (XX) | XX | |
| 6.6.3 long-term toxicity (=12 months) | | | | [XX] |
| Further studies | | (XX) | (XX) | (XX) |
| 6.7.1 screening for reproductive/developmental toxicity study | | X | | |
| 6.7.2 developmental toxicity study | | X, if possible in 6.7.1 | XX | |
| 6.7.3/4 two-generation reproduction toxicity study | | (XX) | (XX) | XX |
| 6.8.1 assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information | | X | | |
| 6.9 carcinogenicity | | | | [XX] |

X study shall be conducted unless …
(X) study shall be considered unless, if …
XX study shall be proposed, unless
(XX) study shall be proposed, if …/in case of …
[XX] study may be proposed, if …

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Annexes V, VI, VII and VIII of the REACH proposal refer to manufactured or imported quantities of 1 - 10, 10 - 100, 100 - 1,000 and > 1,000 t/y, respectively.

## APPENDIX B: TERMS OF REFERENCE

1. Review the available guidance (regulatory, company and other sources) on the derivation of OELs from available effects data with the aim of developing a science based approach that will enable health-protective workplace exposure limits to be consistently developed by chemical suppliers.

2. Clearly specify the uncertainty factors that should be considered in the development of OELs, accounting for the availability and quality of available data.

3. Identify the boundary conditions within which the guidance is applicable.

4. Apply and validate the approach using representative case studies for a range of typical industrial chemicals.

These terms of reference were proposed by the Scientific Committee and adopted on 19 September 2003.

# APPENDIX C: SETTING AN OEL FOR HYDROCARBON SOLVENTS

Hydrocarbon solvents that are derived from petroleum contain predominantly individual hydrocarbons of between 5 and 15 carbon atoms (although individual hydrocarbon solvents seldom span a range of more than 5 carbons) and boil in the range of 35 to 320°C. They are generally described as aliphatic (*n*- or *iso*-paraffins), alicyclic or 'naphthenic' (cycloalkanes), or aromatic (1- and/or 2-ring aromatic molecules), but in practice generally contain mixtures of these three types of molecules. Olefins (alkenes) and alkynes are not normally present and were not considered in the development of the guidance values described below.

Hydrocarbon solvents can be composed of a unique constituent (e.g. *n*-heptane), a group of constituents of one specific type (e.g. *n*-paraffins), a molecular weight range (e.g. C9 aromatics), or may contain molecules of more than one type encompassing a range of carbon numbers (e.g. Stoddard Solvent). There are other types of complex hydrocarbon substances (e.g. fuels, lubricating oils), which are not intended for solvent use. These are generally not as highly refined as the hydrocarbon solvents, and, in some cases, may contain significant quantities of more toxic constituents (e.g. benzene, polycyclic aromatic hydrocarbons). Generally, fuels and other petroleum products have wider boiling ranges and/or constituents that do not satisfy the criteria that must be met before the reciprocal calculation procedure (RCP) method can be applied (e.g. additivity). Thus, the RCP is not recommended as a means of calculating OELs for substances other than aliphatic, alicyclic and aromatic hydrocarbon solvent. The German MAK Commission has similarly advised against the use of the RCP for petroleum-derived fuels and similar materials (Bartsch *et al*, 1998).

## *C.1 Use of the reciprocal calculation procedure (RCP) to calculate OELs for hydrocarbon solvents*

The most generic advice for calculating OELs for complex substances and mixtures is the method recommended by the ACGIH (2006) with further elaboration by Ogata *et al* (1993). For this method to be applicable, the effects of the different substances must be additive, and the individual constituents must not differ greatly in their degree of toxicity.

Mathematically this is expressed as:

$$Fr_a/OEL_a + Fr_b/OEL_b + \ldots. = 1/OEL_s \quad \text{(Eq. C)}$$

in which $Fr_a$, $Fr_b$ are the fractions of the components a and b

$OEL_a$ and $OEL_b$ are the exposure limits for the constituents a and b

$OEL_s$ is the overall exposure limit for the complex substance.

The ACGIH considers this method to be applicable to mixtures if the toxic effects of individual constituents are additive. The principal toxicological effect of constituents of hydrocarbon solvents is acute central nervous system (CNS) depression, characterised by effects ranging from dizziness and drowsiness to anaesthesia (Ridgway *et al*, 2003; ECETOC, 1996). As this is a common property of volatile hydrocarbons, it satisfies the requirement for additivity, i.e. that constituents produce the same effect on the same organ system by a common process (Ogata *et al*, 1993).

A sample calculation using the above formula for determining an OEL for Stoddard Solvent is shown at the end of this appendix.

## *C.2 Development of guidance values*

For calculations using the above formula, each constituent must have its own OEL (in $mg/m^3$). However, it is not always possible to identify all of the constituents of complex hydrocarbon solvents, and most of the toxicology data available is on representative hydrocarbon solvents rather than on their constituents. Thus constituents of similar physical, chemical and toxicological properties were grouped and assigned guidance values (Table C.1).

***Table C.1: Proposed substance grouping and guidance values for use in RCP Calculations of OELs*** (adapted from Nessel *et al*, 2000 and McKee *et al*, 2005)

| Hydrocarbon group | Guidance value ($mg/m^3$) | Basis for guidance value |
|---|---|---|
| C5 - C8 aliphatics/cycloaliphatics | 1,500 | Eye and respiratory tract irritation, CNS effects (human) |
| C9 - C15 aliphatics/cycloaliphatics | 1,200 | CNS effects (rat) |
| C7 - C8 aromatics | 200 | Eye and respiratory tract irritation, CNS effects (human) |
| C9 - C15 aromatics | 100 | Eye and respiratory tract irritation (human), CNS effects (rat) |
| *n*-Hexane (ACGIH TLV) | 175 [a] | Peripheral neuropathy |
| Naphthalene (ACGIH TLV) | 50 [a] | Eye and respiratory tract irritation |

a TLV (ACGIH, 2006)

The specific guidance values were developed from published data on representative substances, although regulatory recommendations, where available, were also taken into account. The basis for the grouping and documentation for each of these recommendations can be found in and Nessel *et al* (2000) and McKee *et al* (2005).

### *C.3 High molecular weights hydrocarbon constituents*

In some cases high boiling, low volatility hydrocarbon solvents may contain molecules greater than C15. Guidance values for these molecules have not been assigned, in part because they have such low volatility that they are unlikely to make a significant contribution to overall exposure. It is unlikely that these constituents would volatilise to any great extent, but they could form stable aerosols if fugitive emissions were created. To carry out the RCP calculation a numerical value is assigned to each constituent. For the purpose of calculating the OEL the liquid composition is 'normalised' to the volatile fraction i.e. to the fraction of the liquid comprising constituents that contain no more than 15 carbons.

### *C.4 Rounding rules*

To avoid greater than warranted precision, it is recommended that the calculated OELs are rounded (up or down) to conform to a series of preferred values. For calculated values < 100 mg/m$^3$, round to the nearest 25. For calculated values between 100 and 600 mg/m$^3$, round to the nearest 50, and for calculated values > 600 mg/m$^3$, round to the nearest 200 mg/m$^3$.

### *C.5 Sample calculation*

Based on the compositional data on Stoddard Solvent (Table C.2) and the guidance values listed in Table C.1, the calculated OEL is 500 mg/m$^3$ (or 85 ppm).

***Table C.2: Example of an RCP-derived OEL for Stoddard Solvent***

| Hydrocarbon group | Guidance value [a] (mg/m$^3$) | Fraction [b] (%) |
|---|---|---|
| C5 - C8 aliphatics/cycloaliphatics | 1,500 | 7.6 |
| C9 - C15 aliphatics/cycloaliphatics | 1,200 | 78.3 |
| C7 - C8 aromatics | 200 | 1.8 |
| C9 - C15 aromatics | 100 | 12.3 |

a Table C.1

b Adapted from Carpenter *et al*, 1975

The calculation follows Equation C:

$$1/OEL = 0.076/1{,}500 + 0.783/1{,}200 + 0.018/200 + 0.123/100 = 0.0020$$

$$OEL = 500 \text{ mg/m}^3$$

$$OEL \text{ (ppm)} = [OEL \text{ (mg/m}^3\text{)} \times 24.45]/\text{Mean MW} = [500 \times 24.45]/144 = 85 \text{ ppm}$$

where MW is the average molecular weight of 144 provided by Carpenter *et al*, 1975.

By comparison, the current ACGIH recommendation is 525 mg/m$^3$ (100 ppm). The RCP thus resulted in a recommended OEL that is similar to, but somewhat lower than, the current advice from the ACGIH (2006).

The sample analysed by Carpenter *et al* (1975) was a commercial product representative of that time. The product was analysed about 30 years ago, and current products may be different in composition. There have also been changes in the occupational environment including lowered OELs and generally reduced exposures (Caldwell *et al,* 2000).

## APPENDIX D: PREDICTION OF AN ORAL MTD FROM AN $LD_{50}$ AND A LOG $K_{ow}$

The Task Force explored whether the acute oral $LD_{50}$ was relevant for the risk assessment of long-term exposure to substances with a systemic mode of action.

Gombar *et al* (1991) studied the relationship between the MTD and the $LD_{50}$ of rats, as observed in NTP studies of 269 substances. The Task Force supplemented the Gombar database with an additional 46 NTP oral toxicity studies carried out after 1991. The log $K_{ow}$ was retrieved from the literature and in a few cases estimated by means of KowWin v1.67 (USA-EPA, 2000). [In all cases the log $K_{ow}$ selected was that of the free base or free acid (assuming the value is more reliable than that of the HCl or NaOH salt)]. Some structural characteristics were also taken into consideration.

The following linear relationship was studied:

$$\log MTD = b_0 + b_1 \times \log LD_{50} + b_2 \times \log K_{ow} \quad \text{.....(Eq. D)}$$

Multiple regression according to the relationship above provided the estimates for $b_0$, $b_1$ and $b_2$:

Residual variance = 0.3626
Degrees of freedom = 312
Variance explained = 0.581 (58.1%)

$b_0$ = –0.6727 Student t for $b_0$ = –4.748
$b_1$ = 0.9226 Student t for $b_1$ = 20.32
$b_2$ = –0.05383 Student t for $b_2$ = –3.798

Variance $b_0\, b_0$ = 0.02007
Covariance $b_0\, b_1$ = –0.006103
Covariance $b_0\, b_2$ = –0.0004674
Variance $b_1\, b_1$ = 0.002062
Covariance $b_1\, b_2$ = 0.00001803
Variance $b_2\, b_2$ = 0.0002010

In Table D the MTD, $LD_{50}$ and log $K_{ow}$ for the 315 substances is presented, together with the 5th percentile of the distribution of the MTD-estimates and log (MTD observed/predicted 5th percentile). The MTD 5th percentile is a conservative estimate of the MTD that might be used as a surrogate for the NOAEL in rats exposed for 2 years via diet, drinking water or by gavage.

Conclusion: From the data presented, the oral $LD_{50}$ appeared to be highly predictive of the MTD.

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number[a]***

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 50-29-3 | Clofenotane | 113 | 6.91 | 28.89 | 5.111 | 0.752 |
| 50-33-9 | Phenylbutazone | 245 | 3.16 | 100 | 19.4 | 0.712 |
| 50-55-5 | Reserpine | 420 | 3.32 | 3 | 31.75 | –1.025 |
| 50-81-7 | Ascorbic acid | 11,900 | –1.85 | 2,250 | 1,128 | 0.3 |
| 51-03-6 | 2-(2-Butoxyethoxy)-ethylpropylpiperonyl ether | 7,500 | 4.75 | 450 | 344 | 0.117 |
| 52-68-6 | Trichlorfon | 150 | 0.51 | 50 | 16.56 | 0.48 |
| 54-31-9 | Furosemide | 2,600 | 2.03 | 31.5 | 200.7 | –0.804 |
| 55-38-9 | Fenthion | 215 | 4.09 | 0.9 | 14.91 | –1.219 |
| 56-23-5 | Carbontetrachloride | 2,920 | 2.83 | 50 | 200.2 | –0.602 |
| 56-38-2 | Parathion | 13 | 3.83 | 2.83 | 0.9926 | 0.455 |
| 56-72-4 | Coumaphos | 41 | 4.13 | 0.9 | 2.954 | –0.516 |
| 57-06-7 | Allyl-isothiocyanate | 148 | 2.15 | 25 | 13.6 | 0.264 |
| 57-41-0 | 5,5-Diphenylhydantoin | 1,635 | 2.47 | 40 | 125.6 | –0.497 |
| 57-41-0 | Phenytoin | 2,195 | 2.47 | 108 | 163.3 | –0.18 |
| 57-66-9 | Probenecid | 1,600 | 3.21 | 400 | 111 | 0.557 |
| 58-55-9 | Theophylline | 225 | –0.02 | 7.5 | 25.81 | –0.537 |
| 58-89-9 | γ-HCH or γ-BHC | 88 | 3.72 | 21.24 | 6.623 | 0.506 |
| 59-87-0 | Nitrofural | 590 | 0.23 | 27.9 | 63.05 | –0.354 |
| 60-51-5 | Dimethoate | 152 | 0.78 | 13.95 | 16.32 | –0.068 |
| 60-57-1 | Dieldrin | 69 | 5.4 | 2.25 | 4.057 | –0.256 |
| 61-76-7 | Phenylephrine-hydrochloride | 350 | –0.31 | 56.25 | 40.42 | 0.143 |
| 62-23-7 | *p*-Nitrobenzoic acid | 1,960 | 1.89 | 100 | 159 | –0.201 |
| 62-73-7 | Dichlorvos | 80 | 1.47 | 8 | 8.075 | –0.004 |
| 64-75-5 | Tetracycline-hydrochloride | 6,443 | –2.18 | 1,125 | 675.4 | 0.222 |
| 64-77-7 | Tolbutamide | 2,490 | 2.34 | 1,080 | 185.8 | 0.764 |
| 67-20-9 | Nitrofurantoin | 604 | –0.47 | 112.5 | 68.56 | 0.215 |
| 67-66-3 | Chloroform | 1,186 | 1.97 | 80 | 100.2 | –0.098 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical Name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 67-72-1 | Hexachloroethane | 6,000 | 4.14 | 20 | 310.8 | –1.191 |
| 69-65-8 | D-Mannitol | 13,500 | –3.1 | 2,250 | 1,403 | 0.205 |
| 70-30-4 | Hexachlorophene | 66 | 7.54 | 6.75 | 2.75 | 0.39 |
| 71-43-2 | Benzene | 4,894 | 2.13 | 200 | 344.9 | –0.237 |
| 71-55-6 | 1,1,1-Trichloroethane | 12,300 | 2.49 | 750 | 730.4 | 0.012 |
| 72-20-8 | Endrin | 17 | 5.2 | 0.22 | 1.064 | –0.684 |
| 72-43-5 | Methoxychlor | 5,000 | 5.08 | 38.03 | 228.7 | –0.779 |
| 72-54-8 | TDE | 880 | 6.02 | 148.23 | 40.92 | 0.559 |
| 72-55-9 | 2,2-Bis(*p*-chlorophenyl)-1,1-dichloroethylene | 880 | 6.51 | 37.75 | 37.64 | 0.001 |
| 72-56-0 | 1,1-Dichloro-2,2-bis(4-ethyl-phenyl)ethane | 8,170 | 6.66 | 315 | 272.7 | 0.063 |
| 73-22-3 | L-Tryptophan | 2,250 | –1.06 | 1,634 | 240.5 | 0.832 |
| 75-09-2 | Dichloromethane | 2,136 | 1.25 | 1,000 | 184.7 | 0.734 |
| 75-25-2 | Bromoform | 1,147 | 2.4 | 200 | 92 | 0.337 |
| 75-27-4 | Bromodichloromethane | 430 | 2 | 25 | 38.81 | –0.191 |
| 75-27-4 | Bromodichloromethane | 916 | 2 | 100 | 78.79 | 0.104 |
| 75-34-3 | 1,1-Dichloroethane | 1,308 | 1.79 | 764 | 111.9 | 0.834 |
| 75-35-4 | 1,1-Dichloroethylene | 200 | 2.13 | 5 | 18.28 | –0.563 |
| 75-47-8 | Iodoform | 355 | 3.03 | 141 | 28.21 | 0.699 |
| 75-65-0 | *tert*-Butylalcohol | 2,743 | 0.35 | 90 | 253 | –0.449 |
| 75-65-0 | 2-Methylpropan-2-ol | 3,500 | 0.35 | 900 | 313.9 | 0.457 |
| 75-69-4 | Trichlorofluoromethane | 993 | 2.53 | 977 | 79.26 | 1.091 |
| 76-01-7 | Pentachloroethane | 4,000 | 3.22 | 150 | 249.8 | –0.221 |
| 76-06-2 | Trichloronitromethane | 250 | 2.09 | 26 | 22.81 | 0.057 |
| 76-44-8 | Heptachlor | 100 | 6.1 | 3.51 | 5.194 | –0.17 |
| 76-57-3 | Codeine | 427 | 1.19 | 30 | 42.28 | –0.149 |
| 77-65-6 | Carbromal | 316 | 1.54 | 112.5 | 30.51 | 0.567 |
| 77-79-2 | 2,5-Dihydrothiophene-1,1-dioxide | 2,830 | –0.45 | 372 | 280.2 | 0.123 |
| 78-34-2 | Dioxathion | 118 | 3.45 | 8.1 | 9.167 | –0.054 |
| 78-42-2 | Tris(2-ethylhexyl)-phosphate | 37,000 | 9.49 | 4,000 | 645 | 0.792 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 78-59-1 | 3,5,5-Trimethylcyclohex-2-enone | 2,330 | 1.7 | 500 | 189.6 | 0.421 |
| 78-87-5 | 1,2-Dichloropropane | 2,196 | 1.98 | 125 | 173.9 | –0.143 |
| 79-00-5 | 1,1,2-Trichloroethane | 835 | 1.89 | 92 | 73.31 | 0.099 |
| 79-01-6 | Trichloroethylene | 7,159 | 2.42 | 1,000 | 462.2 | 0.335 |
| 79-11-8 | Chloroacetic acid | 580 | 0.22 | 30 | 62.1 | –0.316 |
| 79-34-5 | 1,1,2,2-Tetrachloroethane | 250 | 2.39 | 108 | 21.96 | 0.692 |
| 80-05-7 | 4,4'-Isopropylidenediphenol | 4,040 | 3.32 | 90 | 248.4 | –0.441 |
| 80-08-0 | Dapsone | 630 | 0.97 | 54 | 62.43 | –0.063 |
| 81-11-8 | 4,4'-Diaminostilbene-2,2'-disulphonic acid | 5,200 | –1.42 | 1,125 | 523.7 | 0.332 |
| 82-28-0 | 1-Amino-2-methylanthraquinone | 7,700 | 4.07 | 90 | 390.4 | –0.637 |
| 82-68-8 | Quintozene | 1,650 | 4.64 | 393.75 | 91.41 | 0.634 |
| 83-79-4 | (2*r*,6*as*,12*as*)-1,2,6,6*a*,12,12*a*-Hexa-hydro-2-isopropenyl-8,9-dimethoxychromeno [3,4-*b*]furo[2,3-*h*]chromen-6-one | 60 | 4.1 | 3.37 | 4.31 | –0.107 |
| 85-44-9 | Phthalic anhydride | 4,020 | 1.6 | 675 | 309.9 | 0.338 |
| 85-68-7 | Butylbenzylphtalate | 2,330 | 4.73 | 240 | 122.8 | 0.291 |
| 85-68-7 | Benzylbutylphthalate | 2,330 | 4.73 | 540 | 122.8 | 0.643 |
| 86-30-6 | Nitrosodiphenylamine | 1,650 | 3.13 | 180 | 115.5 | 0.193 |
| 86-50-0 | Azinphos-methyl | 26 | 2.75 | 7.02 | 2.276 | 0.489 |
| 86-57-7 | 1-Nitronaphthalene | 120 | 3.19 | 81 | 9.665 | 0.923 |
| 87-29-6 | Cinnamyl-anthranilate | 5,000 | 4.74 | 1,350 | 241.4 | 0.748 |
| 87-62-7 | 2,6-Xylidine | 840 | 1.84 | 135 | 74.15 | 0.26 |
| 87-86-5 | Pentachlorophenol | 27 | 5.12 | 10 | 1.695 | 0.771 |
| 88-06-2 | 2,4,6-Trichlorophenol | 820 | 3.69 | 450 | 56.16 | 0.904 |
| 88-72-2 | *o*-Nitrotoluene | 891 | 2.3 | 12 | 73.96 | –0.79 |
| 88-96-0 | Phthalamide | 1,800 | –1.73 | 1,350 | 207.6 | 0.813 |
| 89-25-8 | 3-Methyl-1-phenyl-5-pyrazolone | 3,500 | 2.56 | 225 | 243.5 | –0.034 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 90-94-8 | 4,4'-Bis(dimethylamino)-benzophenone | 1,600 | 3.87 | 22.5 | 100.5 | –0.65 |
| 91-23-6 | *o*-Nitroanisole | 740 | 1.73 | 30 | 66.79 | –0.348 |
| 91-23-6 | 2-Nitroanisole | 740 | 1.73 | 90 | 66.79 | 0.13 |
| 91-64-5 | Coumarin | 293 | 1.39 | 25 | 28.86 | –0.062 |
| 91-64-5 | Coumarin | 293 | 1.39 | 100 | 28.86 | 0.54 |
| 91-84-9 | Mepyramine | 318 | 3.27 | 135 | 24.54 | 0.741 |
| 91-93-0 | 4,4'-Diisocyanato-3,3'-dimethoxy-biphenyl | 2,000 | 5.12 | 1,980 | 100.5 | 1.294 |
| 93-15-2 | Methyleugenol | 810 | 3.03 | 18 | 61.28 | –0.532 |
| 94-20-2 | Chlorpropamide | 2,390 | 2.27 | 270 | 180.8 | 0.174 |
| 94-52-0 | 5-Nitrobenzimidazole | 500 | 1.5 | 225 | 47.47 | 0.676 |
| 95-06-7 | Sulphallate | 850 | 3.15 | 18.45 | 62.97 | –0.533 |
| 95-14-7 | Benzotriazole | 1,000 | 1.44 | 618.75 | 91.16 | 0.832 |
| 95-50-1 | 1,2-Dichlorobenzene | 500 | 3.43 | 120 | 36.83 | 0.513 |
| 95-74-9 | 3-Chloro-*p*-toluidine | 1,500 | 2.27 | 147.1 | 119.3 | 0.091 |
| 95-79-4 | 5-Chloro-*o*-toluidine | 464 | 2.27 | 225 | 40.33 | 0.747 |
| 95-80-7 | 4-Methyl-*m*-phenylenediamine | 260 | 0.14 | 7.92 | 29.21 | –0.567 |
| 95-83-0 | 4-Chloro-*o*-phenylene-diamine | 916 | 1.28 | 450 | 85.57 | 0.721 |
| 96-09-3 | (Epoxyethyl)benzene | 2,000 | 1.61 | 550 | 167.3 | 0.517 |
| 96-12-8 | 1,2-Dibromo-3-chloro-propane | 300 | 2.96 | 219 | 24.25 | 0.956 |
| 96-18-4 | 1,2,3-Trichloropropane | 320 | 2.27 | 30 | 28.29 | 0.025 |
| 96-45-7 | Imidazolidine-2-thione | 265 | –0.66 | 11.25 | 31.98 | –0.454 |
| 96-48-0 | γ-Butyrolactone | 1,800 | –0.64 | 225 | 189.8 | 0.074 |
| 96-48-0 | γ-Butyrolactone | 1,540 | –0.64 | 225 | 164.7 | 0.135 |
| 96-69-5 | 4,4'-Thiobis(6-*t*-butyl-*m*-cresol) | 2,345 | 8.24 | 100 | 68.3 | 0.166 |
| 96-69-5 | 6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol | 752 | 8.24 | 112.5 | 24.15 | 0.668 |
| 97-53-0 | Eugenol | 2,680 | 2.27 | 270 | 200 | 0.13 |
| 97-77-8 | Disulfiram | 4,950 | 3.88 | 27 | 273.2 | –1.005 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical Name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 98-01-1 | 2-Furaldehyde | 65 | 0.41 | 60 | 7.393 | 0.909 |
| 98-85-1 | 1-Phenylethylalcohol | 750 | 1.42 | 400 | 70.05 | 0.757 |
| 99-55-8 | 5-Nitro-*o*-toluidine | 574 | 1.87 | 4.5 | 51.8 | –1.061 |
| 99-56-9 | 4-Nitro-*o*-phenylenediamine | 681 | 0.88 | 33.75 | 67.76 | –0.303 |
| 99-59-2 | 5-Nitro-*o*-anisidine | 704 | 1.47 | 360 | 65.67 | 0.739 |
| 99-99-0 | *p*-Nitrotoluene | 1,960 | 2.37 | 60 | 149.6 | –0.397 |
| 100-40-3 | 4-Vinylcyclohexene | 2,563 | 3.93 | 400 | 151.8 | 0.421 |
| 100-42-5 | Styrene | 5,000 | 2.95 | 2,000 | 315.2 | 0.802 |
| 100-44-7 | α-Chlorotoluene | 1,231 | 2.3 | 30 | 99.4 | –0.52 |
| 100-51-6 | Benzyl alcohol | 1,230 | 1.1 | 400 | 114.2 | 0.544 |
| 100-52-7 | Benzaldehyde | 1,300 | 1.48 | 400 | 115.3 | 0.54 |
| 101-05-3 | Anilazine | 2,700 | 3.88 | 45 | 160.2 | –0.551 |
| 101-54-2 | N-(4-Aminophenyl)aniline | 464 | 1.82 | 54 | 42.63 | 0.103 |
| 101-61-1 | N,N,N',N'-Tetramethyl-4,4'-methylenedianiline | 500 | 4.37 | 33.75 | 31.83 | 0.025 |
| 101-80-4 | 4,4'-Oxydianiline | 725 | 1.36 | 22.5 | 68.32 | –0.482 |
| 101-90-6 | *m*-Bis(2,3-epoxypropoxy)-benzene | 2,570 | 1.23 | 25 | 218.1 | –0.941 |
| 102-50-1 | 4-Methoxy-*o*-toluidine | 1,100 | 1.23 | 80 | 101.8 | –0.105 |
| 102-96-5 | β-Nitrostyrene | 1,400 | 2.11 | 300 | 114.4 | 0.419 |
| 103-23-1 | Bis(2-ethylhexyl) adipate | 33,290 | 8.12 | 1,125 | 737.3 | 0.183 |
| 103-33-3 | Azobenzene | 1,000 | 3.82 | 18 | 66.07 | –0.565 |
| 103-85-5 | Phenyl-2-thiourea | 8 | 0.71 | 5.4 | 0.9042 | 0.776 |
| 103-90-2 | Paracetamol | 2,400 | 0.46 | 270 | 222.3 | 0.084 |
| 105-11-3 | *p*-Benzoquinone dioxime | 464 | 1.49 | 33.75 | 44.28 | –0.118 |
| 105-55-5 | 1,3-Diethyl-2-thiourea | 316 | 0.57 | 11.25 | 33.79 | –0.478 |
| 105-60-2 | ε-Caprolactam | 1,650 | 0.66 | 337.5 | 155.8 | 0.336 |
| 105-87-3 | Geranyl-acetate | 6,330 | 4.04 | 2,000 | 330.6 | 0.782 |
| 106-46-7 | 1,4-Dichlorobenzene | 500 | 3.44 | 300 | 36.77 | 0.912 |
| 106-47-8 | 4-Chloroaniline | 310 | 1.83 | 22.5 | 28.97 | –0.11 |
| 106-93-4 | 1,2-Dibromoethane | 125 | 1.96 | 4 | 11.81 | –0.47 |
| 107-05-1 | 3-Chloropropene | 700 | 1.93 | 77 | 61.94 | 0.095 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 107-06-2 | 1,2-Dichloroethane | 770 | 1.48 | 95 | 71.3 | 0.125 |
| 108-30-5 | Succinic-anhydride | 1,510 | 0.81 | 100 | 141.7 | –0.151 |
| 108-46-3 | Resorcinol | 301 | 0.8 | 112 | 31.52 | 0.551 |
| 108-46-3 | Resorcinol | 301 | 0.8 | 225 | 31.52 | 0.854 |
| 108-60-1 | Bis(2-chloro-1-methylethyl) ether | 240 | 2.48 | 200 | 20.87 | 0.982 |
| 108-78-1 | Melamine | 3,200 | –1.37 | 202.5 | 338.5 | –0.223 |
| 108-90-7 | Chlorobenzene | 2,910 | 2.84 | 120 | 199.3 | –0.22 |
| 108-94-1 | Cyclohexanone | 1,535 | 0.81 | 315 | 143.8 | 0.34 |
| 108-95-2 | Phenol | 480 | 1.46 | 225 | 45.87 | 0.691 |
| 109-69-3 | 1-Chlorobutane | 2,670 | 2.64 | 120 | 189.8 | –0.199 |
| 110-80-5 | 2-Ethoxyethanol | 3,000 | –0.32 | 2,000 | 291.7 | 0.836 |
| 110-86-1 | Pyridine | 891 | 0.65 | 7 | 88.94 | –1.104 |
| 110-86-1 | Pyridine | 891 | 0.65 | 40 | 88.94 | –0.347 |
| 111-42-2 | 2,2'-Iminodiethanol | 710 | –1.43 | 50 | 86.25 | –0.237 |
| 115-28-6 | 1,4,5,6,7,7-Hexachloro-8,9,10-trinorborn-5-ene-2,3-dicarboxylic acid | 1,770 | 3.14 | 56.25 | 122.8 | –0.339 |
| 115-29-7 | Endosulfan | 43 | 3.83 | 42.84 | 3.231 | 1.123 |
| 115-32-2 | Dicofol | 1,100 | 5.02 | 42.39 | 59.41 | –0.147 |
| 115-96-8 | Tris(2-chloroethyl)-phosphate | 1,230 | 1.44 | 88 | 110.1 | –0.097 |
| 116-06-3 | Aldicarb | 1 | 1.13 | 0.27 | 0.1092 | 0.393 |
| 117-39-5 | 3,3',4',5,7-Pentahydroxy-flavone | 1,800 | 1.48 | 161 | 154.5 | 0.018 |
| 117-39-5 | Quercetine | 161 | 1.48 | 500 | 15.99 | 1.495 |
| 117-79-3 | 2-Aminoanthraquinone | 7,800 | 2.43 | 310.5 | 497.1 | –0.204 |
| 117-81-7 | Bis(2-ethylhexyl)phthalate | 30,600 | 7.6 | 540 | 745.6 | –0.14 |
| 118-92-3 | Anthranilic acid | 4,600 | 1.21 | 1350 | 364.5 | 0.569 |
| 119-34-6 | 4-Amino-2-nitrophenol | 1,470 | 0.96 | 112.5 | 136.2 | –0.083 |
| 119-53-9 | Benzoin | 1,600 | 2.13 | 11.25 | 128.7 | –1.058 |
| 119-84-6 | 3,4-Dihydrocoumarin | 1,460 | 0.97 | 100 | 135.3 | –0.131 |
| 119-84-6 | 3,4-Dihydrocoumarin | 1,460 | 0.97 | 600 | 135.3 | 0.647 |
| 119-90-4 | 3,3'-Dimethoxybenzidine | 1,920 | 1.81 | 14.85 | 157.6 | –1.026 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical Name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 119-93-7 | 4,4'-Bi-*o*-toluidine | 404 | 2.34 | 6.75 | 35.04 | –0.715 |
| 120-32-1 | *o*-Benzyl-*p*-chlorophenol | 1,700 | 4.18 | 120 | 101.1 | 0.074 |
| 120-32-1 | Clorofene | 1,700 | 4.18 | 120 | 101.1 | 0.074 |
| 120-61-6 | Dimethylterephthalate | 4,390 | 2.25 | 225 | 309 | –0.138 |
| 120-62-7 | 1-(3,4-Methylenedioxyphenyl)-isopropyl-octylsulphoxide | 2,000 | 4.89 | 135 | 104.4 | 0.112 |
| 120-71-8 | 6-Methoxy-*m*-toluidine | 1,450 | 1.74 | 450 | 123.5 | 0.561 |
| 120-83-2 | 2,4-Dichlorophenol | 580 | 3.06 | 225 | 44.71 | 0.702 |
| 121-14-2 | 2,4-Dinitrotoluene | 270 | 1.98 | 9 | 24.9 | –0.442 |
| 121-66-4 | 5-Nitrothiazol-2-ylamine | 1,100 | 0.83 | 27 | 106 | –0.594 |
| 121-69-7 | N,N'-Dimethylaniline | 1,410 | 2.31 | 30 | 112.2 | –0.573 |
| 121-75-5 | Malathion | 1,375 | 2.36 | 180 | 109 | 0.218 |
| 121-79-9 | Propyl-3,4,5-trihydroxy-benzoate | 2,600 | 1.8 | 540 | 206.4 | 0.418 |
| 121-88-0 | 2-Amino-5-nitrophenol | 1,100 | 0.99 | 200 | 104.4 | 0.283 |
| 122-66-7 | Hydrazobenzene | 301 | 2.94 | 13.5 | 24.39 | –0.257 |
| 123-31-9 | Hydroquinone | 320 | 0.59 | 50 | 34.14 | 0.166 |
| 123-91-1 | 1,4-Dioxane | 4,200 | –0.27 | 450 | 391.2 | 0.061 |
| 124-48-1 | Dibromochloromethane | 848 | 2.16 | 80 | 71.93 | 0.046 |
| 125-33-7 | Primidone | 1,500 | 0.91 | 25 | 139.5 | –0.746 |
| 126-72-7 | Tris(2,3-dibromopropyl)-phosphate | 810 | 4.29 | 4.5 | 50.52 | –1.05 |
| 126-92-1 | Sodium-η-sulphate | 4,000 | –0.35 | 900 | 377.5 | 0.377 |
| 126-98-7 | Methacrylonitrile | 120 | 0.68 | 10 | 13.1 | –0.117 |
| 127-00-4 | 1-Chloro-2-propanol | 220 | 0.53 | 65 | 23.95 | 0.434 |
| 127-18-4 | Tetrachloroethylene | 12,982 | 3.4 | 750 | 676.3 | 0.045 |
| 127-69-5 | Sulfafurazole | 10,000 | 1.01 | 400 | 731.2 | –0.262 |
| 128-37-0 | 2,6-Di-*tert*-butyl-*p*-cresol | 1,670 | 5.1 | 270 | 85.7 | 0.498 |
| 129-15-7 | 2-Methyl-1-nitroanthra-quinone | 7,400 | 3.71 | 54 | 397.8 | –0.867 |
| 131-17-9 | Diallylphthalate | 770 | 3.23 | 100 | 56.8 | 0.246 |
| 132-98-9 | Phenoxymethylpenicillin-potassium | 1,040 | –2.99 | 1000 | 138.5 | 0.859 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical Name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 133-06-2 | Captan | 1,200 | 2.8 | 272.25 | 90.79 | 0.477 |
| 133-90-4 | Chloramben | 5,620 | 1.9 | 900 | 400.2 | 0.352 |
| 134-72-5 | Bis([R-(R*,S*)]-β-hydroxy-α-methyl-phenethyl]methyl-ammonium) sulphate | 404 | 1.13 | 11.25 | 40.36 | –0.555 |
| 135-20-6 | N-Nitroso-N-phenylhydroxyl-amine, ammonium salt | 250 | –3.16 | 180 | 37.05 | 0.686 |
| 135-88-6 | N-2-Naphthylaniline | 8,730 | 4.38 | 225 | 415.6 | –0.267 |
| 136-40-3 | Phenazopyridine-hydrochloride | 403 | 2.77 | 337.5 | 33.01 | 1.01 |
| 136-77-6 | 4-Hexylresorcinol | 550 | 3.45 | 125 | 40.16 | 0.493 |
| 137-09-7 | 2,4-Diaminophenol dihydrochloride | 240 | –0.87 | 25 | 29.62 | –0.074 |
| 137-17-7 | 2,4,5-Trimethylaniline | 1,250 | 2.27 | 36 | 101.2 | –0.449 |
| 139-13-9 | Nitrilotriacetic acid | 1,470 | –3.81 | 675 | 202.4 | 0.523 |
| 139-65-1 | 4,4'-Thiodianiline | 1,100 | 2.18 | 135 | 91.11 | 0.171 |
| 139-94-6 | 1-Ethyl-3-(5-nitrothiazol-2-yl)-urea | 2,150 | 1.23 | 56.25 | 186.2 | –0.52 |
| 140-11-4 | Benzylacetate | 2,490 | 1.96 | 500 | 194.9 | 0.409 |
| 140-11-4 | Benzylacetate | 2,490 | 1.96 | 500 | 194.9 | 0.409 |
| 140-49-8 | N-[4-(Chloroacetyl)-phenyl]-acetamide | 2,150 | 1.03 | 90 | 190.2 | –0.325 |
| 140-56-7 | Fenaminosulf | 60 | –1.66 | 45 | 8.332 | 0.732 |
| 140-88-5 | Ethylacrylate | 1,020 | 1.32 | 200 | 94.06 | 0.328 |
| 142-04-1 | Aniliniumchloride | 1,070 | –2.61 | 270 | 138.1 | 0.291 |
| 142-83-6 | 2,4-Hexadienal | 300 | 1.37 | 45 | 29.58 | 0.182 |
| 147-24-0 | Diphenhydramine hydrochloride | 500 | 3.11 | 28.17 | 38.6 | –0.137 |
| 148-24-3 | Quinolin-8-ol | 1,200 | 2.02 | 135 | 100.6 | 0.128 |
| 149-30-4 | Benzothiazole-2-thiol | 1,680 | 2.42 | 750 | 129.5 | 0.763 |
| 150-38-9 | Trisodium-hydrogen-ethylene-diaminetetra-acetate | 2,150 | –13.15 | 350 | 562.7 | –0.206 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 150-68-5 | Monuron | 1,480 | 1.94 | 67.5 | 122.8 | –0.26 |
| 151-21-3 | Sodium-dodecyl-sulphate | 1,288 | 1.6 | 54 | 112.8 | –0.32 |
| 156-10-5 | 4-Nitroso-N-phenylaniline | 2,140 | 3.16 | 225 | 145.1 | 0.191 |
| 298-00-0 | Parathion-methyl | 14 | 2.86 | 1.8 | 1.216 | 0.17 |
| 298-59-9 | Methylphenidate hydrochloride | 350 | 2.78 | 5 | 28.82 | –0.761 |
| 298-81-7 | 9-Methoxyfuro[3,2-*g*]-chromen-7-one | 791 | 2 | 75 | 68.8 | 0.037 |
| 303-34-4 | (-)-Lasiocarpine | 110 | 1.28 | 1.35 | 11.28 | –0.922 |
| 303-47-9 | (R)-N-((5-Chloro-3,4-dihydro-8-hydroxy-3-methyl-1-oxo-1*h*-benzo-[*c*]pyran-7-yl)carbonyl)-3-phenylalanine | 210 | 4.74 | 20 | 13.18 | 0.181 |
| 309-00-2 | Aldrin | 39 | 6.5 | 5.4 | 1.96 | 0.44 |
| 315-18-4 | Mexacarbate | 37 | 2.56 | 18.81 | 3.306 | 0.755 |
| 333-41-5 | Diazinon | 250 | 3.81 | 36 | 17.99 | 0.301 |
| 389-08-2 | Nalidixic acid | 1,160 | 1.59 | 180 | 102.7 | 0.244 |
| 396-01-0 | Triamterene | 400 | 0.98 | 27 | 40.61 | –0.177 |
| 396-01-0 | Triamterene | 400 | 0.98 | 30 | 40.61 | –0.132 |
| 434-13-9 | Lithocholic acid | 3,900 | 6.19 | 500 | 153 | 0.514 |
| 469-21-6 | Doxylamine | 357 | 2.37 | 90 | 31.02 | 0.463 |
| 486-12-4 | Triprolidine | 153 | 3.92 | 90 | 11.02 | 0.912 |
| 504-88-1 | 3-Nitropropionic acid | 68 | –0.29 | 3.4 | 8.29 | –0.387 |
| 510-15-6 | Chlorobenzilate | 1,130 | 4.74 | 134.78 | 63.77 | 0.325 |
| 512-56-1 | Trimethylphosphate | 3,437 | –0.65 | 100 | 339.1 | –0.53 |
| 513-37-1 | 1-chloro-2-methylpropene | 200 | 2.58 | 150 | 17.26 | 0.939 |
| 518-47-8 | Disodium 2-(3-oxo-6-oxidoxanthen-9-yl)-benzoate | 6,721 | –0.67 | 225 | 614 | –0.436 |
| 536-33-4 | Ethionamide | 1,320 | 1.52 | 135 | 116.4 | 0.064 |
| 538-23-8 | Tricaprylin | 33,300 | 9.2 | 5,000 | 617 | 0.909 |
| 542-75-6 | 1,3-Dichloropropene | 250 | 2.03 | 50 | 22.98 | 0.338 |
| 556-52-5 | 2,3-Epoxypropan-1-ol | 420 | –0.95 | 75 | 50.74 | 0.17 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 563-47-3 | 3-Chloro-2-methylpropene | 580 | 2.48 | 150 | 48.44 | 0.491 |
| 597-25-1 | Dimethylmorpholino-phosphora-midate | 5,910 | –0.86 | 600 | 558.1 | 0.031 |
| 599-79-1 | Salicylazosulphapyridine | 15,600 | 3.81 | 168 | 747.5 | –0.648 |
| 609-20-1 | 2,6-Dichlorobenzene-1,4-diamine | 700 | 0.9 | 90 | 69.38 | 0.113 |
| 619-17-0 | 4-Nitroanthranilic acid | 675 | 1.91 | 640 | 60.01 | 1.028 |
| 624-18-0 | Benzene-1,4-diamine dihydrochloride | 80 | –0.3 | 56.25 | 9.725 | 0.762 |
| 630-20-6 | 1,1,1,2-Tetrachloroethane | 670 | 2.93 | 250 | 52.12 | 0.681 |
| 636-21-5 | *o*-Toluidinium chloride | 900 | 1.32 | 270 | 83.83 | 0.508 |
| 828-00-2 | 2,6-Dimethyl-1,3-dioxan-4-yl acetate | 1,930 | 0.49 | 125 | 182.4 | –0.164 |
| 834-28-6 | Phenformin hydrochloride | 938 | –0.34 | 36 | 102 | –0.452 |
| 842-07-9 | 1-Phenylazo-2-naphthol | 1,100 | 5.51 | 22.5 | 54.75 | –0.386 |
| 924-42-5 | N-(Hydroxymethyl)-acrylamide | 474 | –1.81 | 12 | 60.95 | –0.706 |
| 961-11-5 | 2-Chloro-1-(2,4,5-tri-chlorophenyl)-vinyl-dimethylphosphate | 4,000 | 3.53 | 382.5 | 238.8 | 0.205 |
| 968-81-0 | Acetohexamide | 5,000 | 2.44 | 900 | 337.7 | 0.426 |
| 1116-54-7 | 2,2'-(Nitrosoimino)-bisethanol | 7,500 | –1.28 | 1,125 | 714.7 | 0.197 |
| 1156-19-0 | Tolazamide | 1,600 | 2.69 | 450 | 119.6 | 0.576 |
| 1212-29-9 | 1,3-(Dicyclohexyl)thiourea | 2,250 | 3.69 | 500 | 140.2 | 0.552 |
| 1330-78-5 | Tricresylphosphate | 3,000 | 6.34 | 13 | 118 | –0.958 |
| 1582-09-8 | Trifluralin | 1,400 | 5.34 | 360 | 70.19 | 0.71 |
| 1596-84-5 | Daminozide | 8,230 | –1.5 | 450 | 790.8 | –0.245 |
| 1634-78-2 | Malaoxon | 158 | 0.52 | 45 | 17.4 | 0.413 |
| 1746-01-6 | 2,3,7,8-Tetrachlorodi-benzo-*p*-dioxin | 0.02 | 6.8 | 0.00001 | 0.001068 | –2.029 |
| 1777-84-0 | N-(4-Ethoxy-3-nitro-phenyl)acetamide | 664 | 2.21 | 171 | 56.95 | 0.478 |
| 1825-21-4 | Pentachloroanisole | 437 | 5.45 | 40 | 23.51 | 0.231 |
| 1836-75-5 | Nitrofen | 640 | 4.64 | 270 | 38.38 | 0.847 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 1897-45-6 | Chlorothalonil | 10,000 | 3.05 | 455.67 | 566.9 | –0.095 |
| 1918-02-1 | 4-Amino-3,5,6-trichloro-pyridine-2-carboxylic acid | 6,000 | 1.36 | 669.37 | 451.6 | 0.171 |
| 1948-33-0 | *tert*-Butylhydroquinone | 700 | 2.94 | 100 | 54.22 | 0.266 |
| 1955-45-9 | Pivalolactone | 1,470 | 0.07 | 300 | 148.4 | 0.306 |
| 1972-08-3 | 1-*trans*-δ9-Tetrahydrocannabinol | 666 | 6.79 | 50 | 27.74 | 0.256 |
| 2164-17-2 | Fluometuron | 8,910 | 2.42 | 11.25 | 558.3 | –1.696 |
| 2243-62-1 | 1,5-Naphthylenediamine | 921 | 0.89 | 450 | 89.56 | 0.701 |
| 2244-16-8 | (S)-2-Methyl-5-(1-methyl-vinyl)-cyclohex-2-en-1-one | 375 | 2.71 | 4 | 31.08 | –0.89 |
| 2425-85-6 | 1-(4-Methyl-2-nitro-phenyl-azo)-2-naphthol | 1,125 | 6.45 | 1,000 | 47.65 | 1.322 |
| 2432-99-7 | 11-Amino-undecanoic acid | 4,200 | –0.16 | 675 | 387.2 | 0.241 |
| 2438-88-2 | 2,3,5,6-Tetrachloro-4-nitroanisole | 260 | 4.47 | 5.4 | 16.87 | –0.495 |
| 2475-45-8 | 1,4,5,8-Tetraamino-anthraquinone | 6,000 | 2.98 | 225 | 367.9 | –0.214 |
| 2489-77-2 | Trimethyl-2-thiourea | 316 | 0.1 | 22.5 | 35.34 | –0.196 |
| 2784-94-3 | 2,2'-([4-(Methylamino)-3-nitrophenyl]imino)-bisethanol | 4,000 | 0.66 | 135 | 342.2 | –0.404 |
| 2832-40-8 | N-(4-[(2-Hydroxy-5-methylphenyl)azo]phenyl)-acetamide | 1,700 | 3.98 | 450 | 104.3 | 0.635 |
| 2835-39-4 | Allylisovalerate | 230 | 2.62 | 62 | 19.66 | 0.499 |
| 2871-01-4 | 2-(4-Amino-2-nitro-anilino)ethanol | 2,300 | –0.42 | 500 | 232.1 | 0.333 |
| 3296-90-0 | 2,2-Bis(bromomethyl)-1,3-propanediol | 1,880 | 1.06 | 70 | 168.2 | –0.381 |
| 3567-69-9 | Disodium 4-hydroxy-3-[(4-sulphonatonaphthyl)-azo]naphthalenesulphonate | 10,000 | 0 | 562.2 | 814 | –0.161 |
| 5131-60-2 | 4-Chlorobenzene-1,3-diamine | 915 | 0.85 | 180 | 89.37 | 0.304 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 5307-14-2 | 2-Nitro-*p*-phenylene-diamine | 3,080 | 0.53 | 49.5 | 275.4 | –0.745 |
| 5392-40-5 | Citral | 4,960 | 3.45 | 100 | 291.6 | –0.465 |
| 5989-27-5 | (R)-*p*-Mentha-1,8-diene | 4,400 | 4.38 | 150 | 228.2 | –0.182 |
| 6109-97-3 | (9-Ethyl-9h-carbazol-3-yl)ammonium chloride | 234 | 3.41 | 80 | 17.91 | 0.65 |
| 6369-59-1 | 2-Methyl-*p*-phenylene-diamine sulphate | 98 | –3.73 | 90 | 15.89 | 0.753 |
| 6471-49-4 | 3-Hydroxy-4-[(2-methoxy-5-nitrophenyl)azo]-N-(3-nitrophenyl) naphthalene-2-carboxamide | 2,250 | 8.3 | 1,300 | 65.11 | 1.3 |
| 6533-68-2 | Scopolamine hydro-bromide trihydrate | 3,800 | 0.98 | 5 | 316.3 | –1.801 |
| 6959-47-3 | 2-(Chloromethyl)-pyridinium chloride | 316 | 1.61 | 150 | 30.27 | 0.695 |
| 6959-48-4 | 3-(Chloromethyl)-pyridinium chloride | 316 | 1.61 | 150 | 30.27 | 0.695 |
| 7487-94-7 | Mercuric chloride | 1 | –0.22 | 1 | 0.1273 | 0.895 |
| 7632-00-0 | Sodium nitrite | 180 | –2.37 | 70 | 25.49 | 0.439 |
| 7775-09-9 | Sodium clorate | 1,200 | –3 | 75 | 158.1 | –0.324 |
| 9005-65-6 | Polysorbate 80 | 34,500 | –0.67 | 2500 | 2542 | –0.007 |
| 10034-96-5 | Manganese(II) sulphate monohydrate | 2,200 | –3 | 250 | 275 | –0.041 |
| 10326-27-9 | Barium chloride dihydrate | 140 | –3 | 50 | 21.09 | 0.375 |
| 13171-21-6 | Phosphamidon | 24 | 0.79 | 7.2 | 2.66 | 0.433 |
| 13552-44-8 | 4,4'-Methylenedianilinium dichloride | 830 | 1.59 | 13.5 | 75.5 | –0.748 |
| 14371-10-9 | *trans*-Cinnamaldehyde | 3,350 | 1.9 | 100 | 254.9 | –0.406 |
| 15356-70-4 | D-Menthol | 3,180 | 3.19 | 337.5 | 205.1 | 0.216 |
| 17026-81-2 | N-(3-Amino-4-ethoxyphenyl)-acetamide | 675 | 0.75 | 631 | 68.07 | 0.967 |
| 20265-97-8 | *p*-Methoxyaniline hydrochloride | 1,400 | 1.59 | 270 | 121.8 | 0.346 |
| 25265-71-8 | Dipropylene glycol | 14,850 | –0.64 | 500 | 1,223 | –0.388 |

***Table D: MTD (observed and predicted), $LD_{50}$ and log $K_{ow}$ for substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LD_{50}$ (mg/kgbw) | log $K_{ow}$ | Observed MTD (mg/kgbw/d) | Predicted MTD 5th percentile | log (MTD observed/ predicted 5%) |
|---|---|---|---|---|---|---|
| 26628-22-8 | Sodium azide | 27 | 0.16 | 5 | 3.197 | 0.194 |
| 28407-37-6 | C.I. Direct blue 218 | 3,290 | –0.77 | 120 | 329.6 | –0.439 |
| 33229-34-4 | 2,2'-[[4-[(2-Hydroxyethyl)-amino]-3-nitrophenyl]imino]-bisethanol | 7,300 | –0.32 | 450 | 638.7 | –0.152 |
| 57117-31-4 | 2,3,4,7,8-Pentachlorodi-benzo-furan | 0.92 | 6.92 | 0.00002 | 0.0466 | –3.367 |

[a] CAS numbers appearing twice refer to two data sets for the same compound

## APPENDIX E: RELATIONSHIP BETWEEN A 4-HOUR $LC_{50}$ AND AN OEL

Although the number of volatile substances used by industry is much lower than that of non-volatile substances, the probability of significant exposure to volatile substances is much higher than to non-volatile substances. As many volatile substances are irritant to the respiratory tract or cause systemic effects by inhalation, it is not appropriate to study them by the oral route. For this reason, the relationship between the 4-hour $LC_{50}$ and the OEL was explored. The 4-hour $LC_{50}$ values were obtained from RTECS and the OELs from the Dutch and UK lists; if divergent, the lower value was taken.

The Task Force studied the relationship between the 4-hour rat $LC_{50}$ as an independent variable and the OEL. The ratio between the $LC_{50}$ and the OEL appeared to be log-normally distributed for the data set chosen:

$$\ln OEL = b_0 + b_1 \times \ln LC_{50} \quad \text{(Eq. E)}$$

Where ln is the natural logarithm

Residual variance = 3.173

Degrees of freedom = 96

Variance explained = 0.6844 (68.44%)

$b_0 = -6.036$ Student t for $b_0 = -10.42$

$b_1 = 0.9617$ Student t for $b_1 = 14.43$

Variance $b_0\, b_0 = 0.3354$

Covariance $b_0\, b_1 = -0.03670$

Variance $b_1\, b_1 = 0.004443$

The data are presented in Table E, together with the 5th percentile of the OEL estimate and the ratio between the estimated 5th percentile and an official OEL.

Conclusion: The LC50 appears to be a strong predictor of the OEL: 68.4% of the variance of the ln OEL was explained by this variable. Most of the substances, for which the 5th percentile estimates result in too high an OEL, are substances that are classified as carcinogenic, mutagenic or reprotoxic according to the Dangerous Substance Directive 67/548/EEC. The method should not be applied to such substances.

***Table E: $LC_{50}$s and official and estimated OELs for selected substances by CAS number***

| CAS number | Chemical name | $LC_{50}$ ($mg/m^3$) | OEL ($mg/m^3$) | Estimated OEL (5th percentile) | Estimated 5th percentile/OEL |
|---|---|---|---|---|---|
| 56-23-5 | Carbontetrachloride | 5,1270 | 6.41 | 53.7 | 8.38 |
| 56-38-2 | Parathion | 84 | 0.1 | 0.101 | 1.01 |
| 60-57-1 | Dieldrin | 13 | 0.25 | 0.01411 | 0.0565 |
| 62-73-7 | Dichlorvos | 15 | 0.92 | 0.0164 | 0.0179 |
| 67-56-1 | Methanol | 85,467 | 267 | 84.3 | 0.315 |
| 67-66-3 | Chloroform | 47,702 | 9.9 | 50.4 | 5.09 |
| 68-11-1 | Mercaptoacetic acid | 210 | 3.8 | 0.265 | 0.0696 |
| 68-12-2 | N,N-Dimethyl-formamide | 5,934 | 15.2 | 7.53 | 0.495 |
| 71-55-6 | 1,1,1-Trichloroethane | 94,492 | 556 | 92 | 0.166 |
| 74-87-3 | Chloromethane | 5,300 | 52 | 6.77 | 0.13 |
| 74-88-4 | Methyl iodide | 1,300 | 10 | 1.72 | 0.172 |
| 74-96-4 | Bromoethane | 5,340 | 22 | 6.82 | 0.310 |
| 75-07-0 | Acetaldehyde | 24,417 | 22 | 2.77 | 1.26 |
| 75-08-1 | Ethanethiol | 11,444 | 1.29 | 13.9 | 10.7 |
| 75-21-8 | Ethylene oxide | 1,469 | 0.918 | 1.94 | 2.11 |
| 75-34-3 | 1,1-Dichloroethane | 53,603 | 412 | 55.8 | 0.135 |
| 75-35-4 | 1,1-Dichloroethylene | 25,649 | 20.2 | 28.9 | 1.43 |
| 75-43-4 | Dichlorofluoromethane | 213,988 | 42.9 | 188 | 4.38 |
| 75-56-9 | Propylene oxide | 9,682 | 9.68 | 11.9 | 1.23 |
| 75-61-6 | Dibromodifluoromethane | 210,600 | 872 | 185 | 0.213 |
| 75-63-8 | Bromotrifluoromethane | 430,000 | 6,190 | 345 | 0.0557 |
| 76-06-2 | Trichloronitromethane | 99 | 0.685 | 0.12 | 0.175 |
| 76-11-9 | 1,2,2,2-Tetrachloro-1,1-difluoroethane | 125,000 | 847 | 118 | 0.139 |
| 76-12-0 | 1,1,2,2-Tetrachloro-1,2-difluoroethane | 125,000 | 847 | 118 | 0.139 |
| 76-13-1 | 1,1,2-Trichloro-1,2,2-trifluoroethane | 300,573 | 1,170 | 253 | 0.216 |
| 76-15-3 | Chloropentafluoroethane | 488,000 | 6,420 | 385 | 0.0599 |
| 77-73-6 | Dicyclopentadiene | 3,636 | 2.75 | 4.72 | 1.71 |
| 77-78-1 | Dimethylsulphate | 45 | 0.26 | 0.0525 | 0.202 |
| 78-83-1 | 2-Methyl-1-propanol | 19,200 | 154 | 22.3 | 0.145 |

***Table E: $LC_{50}$s and official and estimated OELs for selected substances by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LC_{50}$ ($mg/m^3$) | OEL ($mg/m^3$) | Estimated OEL (5th percentile) | Estimated 5th percentile/OEL |
|---|---|---|---|---|---|
| 78-92-2 | *sec*-Butanol | 48,500 | 308 | 51.1 | 0.166 |
| 79-27-6 | 1,1,2,2-Tetrabromoethane | 549 | 7.2 | 0.715 | 0.0993 |
| 80-62-6 | Methyl methacrylate | 78,000 | 40 | 77.7 | 1.94 |
| 95-13-6 | Indene | 14,000 | 48 | 16.7 | 0.348 |
| 95-63-6 | 1,2,4-Trimethylbenzene | 18,000 | 100 | 210 | 0.210 |
| 96-33-3 | Methyl acrylate | 4,843 | 17.9 | 6.21 | 0.346 |
| 98-00-0 | Furfuryl alcohol | 952 | 20.4 | 1.25 | 0.0614 |
| 98-82-8 | Cumene | 39,000 | 100 | 42.1 | 0.421 |
| 98-95-3 | Nitrobenzene | 2,852 | 1.03 | 3.73 | 3.64 |
| 100-42-5 | Styrene | 11,800 | 107 | 14.3 | 0.134 |
| 102-36-3 | 3,4-Dichlorophenyl isocyanate | 2,700 | 0.08 | 3.54 | 44.2 |
| 104-12-1 | Isocyanic acid, *p*-chlorophenyl ester | 113 | 0.08 | 0.138 | 1.73 |
| 106-42-3 | 1,4-Xylene | 20,130 | 221 | 23.3 | 0.105 |
| 106-46-7 | 1,4-Dichlorobenzene | 5,000 | 122 | 6.4 | 0.0525 |
| 106-50-3 | *p*-Phenylenediamine | 920 | 0.1 | 1.21 | 12.1 |
| 106-97-8 | Butane | 658,000 | 1,450 | 498 | 0.344 |
| 106-99-0 | 1,3-Butadiene | 285,000 | 22 | 241 | 11 |
| 107-02-8 | Acrolein | 19 | 0.234 | 0.0207 | 0.0888 |
| 107-13-1 | Acrylonitrile | 736 | 4.42 | 0.966 | 0.218 |
| 107-31-3 | Methyl formate | 5,200 | 120 | 6.65 | 0.0554 |
| 108-01-0 | Dimethylaminoethanol | 6,096 | 7.43 | 7.73 | 1.04 |
| 108-05-4 | Vinyl acetate | 11,400 | 18 | 13.9 | 0.769 |
| 108-24-7 | Acetic anhydride | 4,254 | 2.13 | 5.49 | 2.58 |
| 108-88-3 | Toluene | 49,000 | 150 | 51.6 | 0.344 |
| 108-94-1 | Cyclohexanone | 32,720 | 40.9 | 36.0 | 0.88 |
| 108-95-2 | Phenol | 316 | 8 | 0.405 | 0.0506 |
| 108-98-5 | Benzenethiol | 151 | 0.459 | 0.188 | 0.41 |
| 109-89-7 | Diethylamine | 12,193 | 15.2 | 14.7 | 0.967 |
| 110-54-3 | Hexane | 172,400 | 71.8 | 156 | 2.17 |
| 111-30-8 | Glutaraldehyde | 480 | 0.08 | 0.623 | 7.79 |
| 111-76-2 | 2-Butoxyethanol | 2,216 | 98.5 | 0.292 | 0.0296 |
| 111-84-2 | Nonane | 17,105 | 53.5 | 20.1 | 0.375 |

***Table E: $LC_{50}$s and official and estimated OELs for selected substances by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LC_{50}$ ($mg/m^3$) | OEL ($mg/m^3$) | Estimated OEL (5th percentile) | Estimated 5th percentile/OEL |
|---|---|---|---|---|---|
| 115-29-7 | Endosulfan | 80 | 0.1 | 0.0963 | 0.963 |
| 121-75-5 | Malathion | 4,3790 | 10 | 46.7 | 4.67 |
| 123-86-4 | Butyl acetate | 188,793 | 484 | 169 | 0.348 |
| 126-99-8 | Chloroprene | 11,800 | 18 | 14.3 | 0.794 |
| 137-26-8 | Thiram | 500 | 0.2 | 0.65 | 3.25 |
| 140-88-5 | Ethyl acrylate | 5,899 | 20.9 | 7.49 | 0.359 |
| 141-32-2 | Butyl acrylate | 14,582 | 10.7 | 17.4 | 1.62 |
| 141-79-7 | Ethyl acetoacetate | 9,000 | 61 | 11.1 | 0.182 |
| 151-67-7 | Halothane | 120,000 | 41 | 114 | 2.77 |
| 302-01-2 | Hydrazine | 761 | 0.0134 | 0.99 | 74.8 |
| 333-41-5 | Diazinon | 3,500 | 0.1 | 4.55 | 45.5 |
| 584-84-9 | 4-Methyl-*m*-phenylene isocyanate | 102 | 0.04 | 0.142 | 3.1 |
| 591-78-6 | Methyl *n*-butyl ketone | 33,393 | 20.9 | 36.7 | 17.6 |
| 822-06-0 | Hexamethylene diisocyanate | 124 | 0.04 | 0.0153 | 3.81 |
| 1310-65-2 | Lithium hydroxide, anhydrous | 960 | 0.2 | 1.26 | 6.32 |
| 1330-20-7 | Xylene(s) | 22,121 | 221 | 25.3 | 0.115 |
| 1634-04-4 | Methyl-*t*-butyl ether | 86,612 | 91.8 | 85.2 | 0.928 |
| 2238-07-5 | Diglycidyl ether | 1,085 | 0.542 | 1.43 | 2.64 |
| 2699-79-8 | Sulphuryl fluoride | 4,214 | 10.2 | 5.44 | 0.533 |
| 2909-38-8 | 1-Chloro-3-isocyanato-benzene | 42 | 0.08 | 0.0488 | 0.61 |
| 3173-72-6 | 1,5-Naphthylene di-isocyanate | 270 | 0.08 | 0.344 | 4.3 |
| 3689-24-5 | Sulfotep | 38 | 0.1 | 0.0439 | 0.439 |
| 4098-71-9 | 5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-cyclohexane | 123 | 0.04 | 0.151 | 3.78 |
| 7616-94-6 | Trioxychlorofluoride | 1,643 | 12.8 | 2.17 | 0.169 |
| 7664-41-7 | Ammonia | 1,420 | 14.2 | 1.87 | 0.132 |
| 7697-37-2 | Nitric acid | 176 | 0.525 | 0.22 | 0.419 |
| 7719-12-2 | Phosphorous trichloride | 595 | 1.14 | 0.777 | 0.679 |
| 7722-84-1 | Hydrogen peroxide | 2,000 | 1.4 | 2.63 | 1.88 |
| 7803-62-5 | Monosilane | 12,852 | 0.669 | 15.5 | 23.1 |
| 8006-64-2 | Turpentine | 13,700 | 566 | 16.4 | 0.029 |
| 10025-67-9 | Sulphur monochloride | 2,500 | 1 | 3.28 | 3.28 |

***Table E: $LC_{50}$s and official and estimated OELs for selected substances by CAS number*** *(cont'd)*

| CAS number | Chemical name | $LC_{50}$ ($mg/m^3$) | OEL ($mg/m^3$) | Estimated OEL (5th percentile) | Estimated 5th percentile/OEL |
|---|---|---|---|---|---|
| 10025-87-3 | Phosphoryl trichloride | 204 | 0.639 | 0.257 | 0.403 |
| 10102-43-9 | Nitric oxide | 1,068 | 3 | 1.41 | 0.469 |
| 10102-44-0 | Nitrogen dioxide | 169 | 0.767 | 0.211 | 0.275 |
| 13463-40-6 | Iron carbonyl compounds | 82 | 0.0816 | 0.0984 | 1.21 |
| 16752-77-5 | Methomyl | 520 | 0.676 | 0.677 | 1 |
| 19287-45-7 | Diborane | 46 | 0.015 | 0.0539 | 4.68 |

## APPENDIX F: $RD_{50}$, AS A MEASURE OF SENSORY IRRITATION, CALCULATED FROM LOG $K_{aw}$ AND LOG $K_{ow}$

The Task Force studied the relationship between log $K_{aw}$ and log $K_{ow}$, and log $RD_{50}$, using 75 observed $RD_{50}$ values for 58 volatile organic substances (Alarie *et al*, 1995) and log $K_{aw}$ and log $K_{ow}$ values derived from the EpiSuite program (US-EPA, 2000) (Table F).

The following linear relationship was used, in which the regression coefficients $b_0$, $b_1$ and $b_2$ were estimated by multiple regression:

$$\log RD_{50} = b_0 + b_1 \times \log K_{ow} + b_2 \times \log K_{aw} \quad \text{(Eq. F)}$$

Residual variance = 0.1559
Degrees of freedom = 72
Variance explained = 0.749 (74.9%)

$b_0 = 6.346$ Student t for $b_0 = 25.89$
$b_1 = -0.8333$ Student t for $b_1 = -14.47$
$b_2 = 0.7139$ Student t for $b_2 = 11.22$

Variance $b_0$ $b_0$ = 0.06010
Covariance $b_0$ $b_1$ = –0.01330
Covariance $b_0$ $b_2$ = 0.01486
Variance $b_1$ $b_1$ = 0.003315
Covariance $b_1$ $b_2$ = –0.003147
Variance $b_2$ $b_2$ = 0.004052

Conclusion: The regression equation shows that 74.9% of the variance of the log $RD_{50}$ is explained by $K_{aw}$ and $K_{ow}$. The remaining 25% results from other types of variability in the database, such as particular properties related to substance classes. If the relationship was determined for alcohols, ketones and hydrocarbons separately, the regression might be improved. However, this equation clearly shows that $K_{aw}$ and $K_{ow}$ are largely controlling the sensory irritation in this set of substances (Alarie *et al*, 1995).

***Table F: Observed and predicted $RD_{50}$s for volatile organic substances listed by CAS number***

| CAS number | Chemical name | log $K_{ow}$ | log $K_{aw}$ | log $RD_{50}$ observed (ppm) | log $RD_{50}$ predicted (ppm) | log $RD_{50}$ predicted/observed |
|---|---|---|---|---|---|---|
| 64-17-5 | Ethanol | –0.31 | –3.68934 | 4.13 | 3.971 | –0.159 |
| 64-17-5 | Ethanol | –0.31 | –3.68934 | 4.44 | 3.971 | –0.469 |
| 67-56-1 | Methanol | –0.77 | –3.730298 | 4.62 | 4.325 | –0.295 |
| 67-56-1 | Methanol | –0.77 | –3.730298 | 4.4 | 4.325 | –0.075 |
| 67-63-0 | Propanol-2 | 0.05 | –3.479825 | 3.7 | 3.82 | 0.12 |
| 67-63-0 | Propanol-2 | 0.05 | –3.479825 | 4.25 | 3.82 | –0.43 |
| 67-64-1 | Propanone | –0.24 | –2.789519 | 4.89 | 4.555 | –0.335 |
| 67-64-1 | Propanone | –0.24 | –2.789519 | 4.37 | 4.555 | 0.185 |
| 71-23-8 | Propanol-1 | 0.25 | –3.518492 | 3.68 | 3.626 | –0.054 |
| 71-23-8 | Propanol-1 | 0.25 | –3.518492 | 4.1 | 3.626 | –0.474 |
| 71-23-8 | Propanol-1 | 0.25 | –3.518492 | 4.14 | 3.626 | –0.514 |
| 71-36-3 | Butanol-1 | 0.88 | –3.443334 | 3.1 | 3.155 | 0.055 |
| 71-36-3 | Butanol-1 | 0.88 | –3.443334 | 3.77 | 3.155 | –0.615 |
| 71-41-0 | Pentanol-1 | 1.51 | –3.274366 | 3.61 | 2.75 | –0.86 |
| 71-41-0 | Pentanol-1 | 1.51 | –3.274366 | 2.78 | 2.75 | –0.03 |
| 75-89-8 | 2,2,2-Trifluoroethanol | 0.41 | –3.150264 | 4.32 | 3.756 | –0.564 |
| 75-97-8 | 3,3-Dimethylbutanone-2 | 1.2 | –2.049853 | 3.75 | 3.883 | 0.133 |
| 78-83-1 | 2-Methylpropanol-1 | 0.76 | –3.397971 | 3.26 | 3.287 | 0.027 |
| 78-93-3 | Butanone-2 | 0.29 | –2.633197 | 4.03 | 4.225 | 0.195 |
| 78-93-3 | Butanone-2 | 0.29 | –2.633197 | 3.95 | 4.225 | 0.275 |
| 78-93-3 | Butanone-2 | 0.29 | –2.633197 | 4.5 | 4.225 | –0.275 |
| 95-47-6 | *o*-Xylene | 3.12 | –0.6739799 | 3.17 | 3.265 | 0.095 |
| 95-49-8 | 2-Chlorotoluene | 3.42 | –0.8356414 | 2.76 | 2.9 | 0.14 |
| 95-50-1 | 1,2-Dichlorobenzene | 3.43 | –1.105008 | 2.26 | 2.699 | 0.439 |
| 98-01-1 | Furfural | 0.41 | –3.86068 | 2.46 | 3.248 | 0.788 |
| 98-06-6 | *tert*-Butylbenzene | 4.11 | –0.2677357 | 2.88 | 2.73 | –0.15 |
| 98-51-1 | 4-*tert*-Butyltoluene | 5.17 | –0.2007889 | 2.56 | 1.895 | –0.665 |
| 98-82-8 | Isopropylbenzene | 3.66 | –0.3276118 | 3.29 | 3.062 | –0.228 |
| 98-82-8 | Isopropylbenzene | 3.66 | –0.3276118 | 3.4 | 3.062 | –0.338 |
| 98-83-9 | α-Methylstyrene | 3.48 | –0.9817695 | 2.44 | 2.745 | 0.305 |

***Table F: Observed and predicted $RD_{50}$s for volatile organic substances listed by CAS number*** *(cont'd)*

| CAS number | Chemical name | log $K_{ow}$ | log $K_{aw}$ | log $RD_{50}$ observed (ppm) | log $RD_{50}$ predicted (ppm) | log $RD_{50}$ predicted/observed |
|---|---|---|---|---|---|---|
| 98-86-2 | Acetophenone | 1.58 | –3.371276 | 2.01 | 2.623 | 0.613 |
| 100-41-4 | Ethylbenzene | 3.15 | –0.4917834 | 3.16 | 3.37 | 0.21 |
| 100-41-4 | Ethylbenzene | 3.15 | –0.4917834 | 3.61 | 3.37 | –0.24 |
| 100-42-5 | Styrene | 2.95 | –0.948977 | 2.77 | 3.21 | 0.44 |
| 100-42-5 | Styrene | 2.95 | –0.948977 | 2.75 | 3.21 | 0.46 |
| 100-52-7 | Benzaldehyde | 1.48 | –2.961798 | 2.52 | 2.998 | 0.478 |
| 103-65-1 | *n*-Propylbenzene | 3.69 | –0.3671204 | 3.18 | 3.009 | –0.171 |
| 104-51-8 | *n*-Butylbenzene | 4.38 | –0.1869126 | 2.85 | 2.563 | –0.287 |
| 104-76-7 | 2-Ethylhexanol-1 | 2.73 | –2.965064 | 1.64 | 1.955 | 0.315 |
| 106-42-3 | *p*-Xylene | 3.15 | –0.5494606 | 3.12 | 3.329 | 0.209 |
| 107-87-9 | Pentanone-2 | 0.91 | –2.466103 | 3.77 | 3.827 | 0.057 |
| 108-11-2 | 4-Methylpentanol-2 | 1.68 | –2.73995 | 2.63 | 2.99 | 0.36 |
| 108-11-2 | 4-Methylpentanone-2 | 1.68 | –2.73995 | 3.5 | 2.99 | –0.51 |
| 108-83-8 | 2,6-Dimethyl-heptanone-4 | 2.56 | –2.320124 | 2.51 | 2.557 | 0.047 |
| 108-86-1 | Bromobenzene | 2.99 | –0.9956127 | 2.61 | 3.144 | 0.534 |
| 108-88-3 | Toluene | 2.73 | –0.5661416 | 3.53 | 3.667 | 0.137 |
| 108-88-3 | Toluene | 2.73 | –0.5661416 | 3.71 | 3.667 | –0.043 |
| 108-90-7 | Chlorobenzene | 2.84 | –0.8955493 | 3.02 | 3.34 | 0.32 |
| 108-94-1 | Cyclohexanone | 0.81 | –3.434067 | 2.88 | 3.22 | 0.34 |
| 110-12-3 | 5-Methylhexanone-2 | 1.88 | –2.226942 | 3.09 | 3.19 | 0.1 |
| 110-43-0 | Heptanone-2 | 1.98 | –2.160423 | 2.95 | 3.154 | 0.204 |
| 110-49-6 | 2-Methoxyethylacetate | 0.1 | –3.953741 | 2.76 | 3.44 | 0.68 |
| 111-13-7 | Octanone-2 | 2.37 | –2.114152 | 2.68 | 2.862 | 0.182 |
| 111-15-9 | 2-Ethoxyethylacetate | 0.59 | –3.88316 | 2.86 | 3.082 | 0.222 |
| 111-27-3 | Hexanol-1 | 2.03 | –3.155313 | 2.38 | 2.402 | 0.022 |
| 111-65-9 | n-Octane | 5.18 | 2.118195 | 4.26 | 3.542 | –0.718 |
| 111-70-6 | Heptanol-1 | 2.62 | –3.114152 | 1.99 | 1.94 | –0.05 |
| 111-76-2 | 2-Butoxyethanol | 0.83 | –4.18419 | 3.45 | 2.667 | –0.783 |
| 111-87-5 | Octanol-1 | 3 | –2.999144 | 1.67 | 1.705 | 0.035 |
| 112-12-9 | Undecanone-2 | 4.09 | –2.584852 | 1.56 | 1.093 | –0.467 |

***Table F: Observed and predicted $RD_{50}$s for volatile organic substances listed by CAS number*** [a] *(cont'd)*

| CAS number | Chemical name | log $K_{ow}$ | log $K_{aw}$ | log $RD_{50}$ observed (ppm) | log $RD_{50}$ predicted (ppm) | log $RD_{50}$ predicted/ observed |
|---|---|---|---|---|---|---|
| 123-19-3 | Heptanone-4 | 1.73 | –2.648737 | 3.04 | 3.014 | –0.026 |
| 123-51-3 | 3-Methylbutanol-1 | 1.16 | –3.23909 | 3.65 | 3.067 | –0.583 |
| 123-51-3 | 3-Methylbutanol-1 | 1.16 | –3.23909 | 2.86 | 3.067 | 0.207 |
| 123-92-2 | Isoamyl acetate | 2.26 | –1.619672 | 3.02 | 3.307 | 0.287 |
| 142-82-5 | *n*-Heptane | 4.66 | 1.91272 | 4.19 | 3.828 | –0.362 |
| 142-92-7 | *n*-Hexyl acetate | 2.83 | –1.664034 | 2.87 | 2.8 | –0.07 |
| 502-56-7 | Nonanone-5 | 2.88 | –1.924417 | 2.44 | 2.572 | 0.132 |
| 538-68-1 | *n*-Pentylbenzene | 4.9 | 0.01652404 | 2.36 | 2.275 | –0.085 |
| 541-85-5 | 5-Methylheptanone-3 | 2.15 | –2.07868 | 2.88 | 3.071 | 0.191 |
| 591-78-6 | Hexanone-2 | 1.38 | –2.418894 | 3.41 | 3.469 | 0.059 |
| 622-24-2 | 2-Chloroethylbenzene | 2.95 | –0.9442649 | 1.92 | 3.214 | 1.294 |
| 628-63-7 | *n*-Pentylacetate | 2.3 | –1.799478 | 3.17 | 3.145 | –0.025 |
| 628-63-7 | *n*-Pentylacetate | 2.3 | –1.799478 | 3.19 | 3.145 | –0.045 |
| 1077-16-3 | *n*-Hexylbenzene | 5.52 | 0.06.805636 | 2.1 | 1.795 | –0.305 |
| 1321-74-0 | 1,4-Divinylbenzene | 3.8 | –1.236021 | 1.89 | 2.297 | 0.407 |

[a] CAS numbers appearing more than once refer to multiple data sets for the same compound

# APPENDIX G: ESTIMATED OELS FOR SELECTED CHEMICALS USING PROPOSED METHODS

OELs were derived for selected substances using acute toxicity data and applying five of the methods indicated in Figure 1 (Chapter 6), i.e. risk phrases (for hazard banding), $LD_{50}$ and $K_{ow}$ (to derive an MTD), $LC_{50}$, $K_{ow}$ and $K_{aw}$ (to derive an $RD_{50}$), and Cramer class based on the structure of the molecule (for TTC). Read-across was not applied, as the substances selected were data-rich. The estimates obtained were compared with official OELs. If Dutch OELs were not available, IOELVs and WEELs were used for comparison (Table G.1 to G.10) [a].

***Table G.1: Acrylic acid***

| | | Criterion | OEL (NL) |
|---|---|---|---|
| CAS | 79-10-7 | | 5.9 mg/m$^3$ |
| Molecular weight | 72.06 | | |
| Appearance | Liquid | | **Estimated OEL** |
| Risk phrases | 10-20/21/22-35-50 | Medium hazard (0.31 ppm) | 0.91 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 1,350 | MTD = 134 mg/kgbw/d | 6.7 mg/m$^3$ |
| log $K_{ow}$ | 0.35 | | |
| log $K_{aw}$ | –4.81 | $RD_{50}$ = 273 ppm | 80 mg/m$^3$ |
| 4-h $LC_{50}$ rat mg/m$^3$ | 3,600 | | 4.7 mg/m$^3$ |
| Cramer class II | TTC = 9 µg/kgbw/d | | 5.4 mg/m$^3$ |

Deriving a provisional OEL on the basis of systemic effects via the oral route (MTD and TTC methods) is not meaningful as acrylic acid has a local mode of action. Moreover, an OEL cannot be derived on the basis of the $RD_{50}$, as organic acids are not included in the chemical domain of the linear regression relationship for the $RD_{50}$. The most appropriate OELs are those based on the 4-hour rat $LC_{50}$ or on risk phrases as local effects are considered. These values are 4.7 mg/m$^3$ and 0.9 mg/m$^3$, respectively.

The estimate derived from the 4-hour $LC_{50}$ is in line with the official Dutch OEL. The estimate derived from the risk phrase appears to be conservative.

[a] The estimates (tables) were generated by means of a simple software tool (spreadsheet) (Ten Berge, 2005).

***Table G.2: Aniline***

| | | Criterion | OEL (NL) |
|---|---|---|---|
| CAS | 62-53-3 | | 1 mg/m$^3$ |
| Molecular weight | 93.13 | | |
| Appearance | Liquid | | **Estimated OEL** |
| Risk phrases | 23/24/25-40-41-43-48/23/24/25-68-50 | High hazard (0.018 ppm) | 0.069 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 640 | MTD = 63.8 mg/kgbw/d | 3.2 mg/m$^3$ |
| log $K_{ow}$ | 0.9 | | |
| log $K_{aw}$ | –4.22 | $RD_{50}$ = 265 ppm | 101 mg/m$^3$ |
| 4-h $LC_{50}$ rat mg/m$^3$ | 4,000 (estimated) | | 5.2 mg/m$^3$ |
| Cramer class III | TTC = 1.5 µg/kgbw/d | | 0.9 mg/m$^3$ |

Aniline causes systemic effects at the level of sensory irritation. Therefore, the $RD_{50}$ method is not appropriate for deriving an OEL. Three of the remaining procedures (MTD, $LC_{50}$ and TTC) provide OEL estimates close to the Dutch OEL. The OEL on the basis of risk phrases appears to be over-conservative.

The OEL nearest to the Dutch OEL was derived from the TTC.

***Table G.3: sec-Butanol***

| | | Criterion | OEL (NL) |
|---|---|---|---|
| CAS | 78-79-2 | | 450 mg/m$^3$ |
| Molecular weight | 74.12 | | |
| Appearance | Liquid | | **Estimated OEL** |
| Risk phrases | 36/37-67 | Low hazard (2.4 ppm) | 7.3 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 3,800 | MTD = 329 mg/kgbw/d | 16 mg/m$^3$ |
| log $K_{ow}$ | 0.61 | | |
| log $K_{aw}$ | –3.2 | $RD_{50}$ = 2,831 ppm | 858 mg/m$^3$ |
| 4-h $LC_{50}$ rat mg/m$^3$ | 49,000 | | 52 mg/m$^3$ |
| Cramer class I | TTC = 30 µg/kgbw/d | | 18 mg/m$^3$ |

All five methods can be used for developing an OEL for *sec*-butanol. Compared to the Dutch OEL, the estimate on the basis of the $RD_{50}$ had the highest value (twice the Dutch OEL), and that

based on risk phrases the lowest value (over-conservative). The OELs derived on the basis of the MTD, the $LC_{50}$ and the TTC provide reasonable estimates.

The estimated OEL from the $LC_{50}$ method is nearest to, and does not exceed, the Dutch OEL.

***Table G.4: p-tert-Butylphenol***

| | | **Criterion** | **OEL (NL)** |
|---|---|---|---|
| CAS | 98-54-4 | | 0.5 mg/m$^3$ |
| Molecular weight | 150.22 | | |
| Appearance | Solid | | **Estimated OEL** |
| Risk phrases | 36/37/38-43 | Medium (0.16 mg/m$^3$) | 0.16 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 3,500 | MTD = 219 mg/kgbw/d | 11 mg/m$^3$ |
| log $K_{ow}$ | 3.31 | | |
| log $K_{aw}$ | –3.28 | $RD_{50}$ = 9.95 ppm | 6.1 mg/m$^3$ |
| 4-h $LC_{50}$ rat, mg/m$^3$ | 5,600 | | 7.1 mg/m$^3$ |
| Cramer class I | TTC=30 µg/kgbw/d | | 18 mg/m$^3$ |

Note: Vitiligo in animals and humans

*p-tert*-Butylphenol causes local and systemic effects. The $RD_{50}$ method is not appropriate, because phenols do not fit in the domain of substances covered by the $RD_{50}$ method. The estimates derived from the MTD, $LC_{50}$ and TTC methods are of the same order but one order of magnitude higher than the Dutch OEL. The OEL estimated from risk phrases is one order of magnitude lower than the other estimates. The risk phrase R43 has been based on human workplace experience. *p-tert-B*utylphenol was not a sensitiser in the guinea pig maximisation test (OECD, 2002). The compound causes vitiligo in humans and animals via direct contact and via systemic absorption and the current OEL aims to protect workers from skin sensitisation and vitiligo.

The OEL estimate based on risk phrases is nearest to the Dutch OEL.

***Table G.5: Caprolactam***

| | | Criterion | IOELV |
|---|---|---|---|
| CAS | 105-60-2 | | 10 mg/m$^3$ |
| Molecular weight | 113.16 | | |
| Appearance | Solid | | **Estimated OEL** |
| Risk phrases | 20/22-36-37-38 | Low hazard (1.2 mg/m$^3$) | 1.2 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 1,660 | MTD = 157 mg/kgbw/d | 7.8 mg/m$^3$ |
| log $K_{ow}$ | 0.66 | | |
| log $K_{aw}$ | –6.11 | $RD_{50}$ = 12.9 ppm | 5.9 mg/m$^3$ |
| 4-h $LC_{50}$ rat mg/m$^3$ | 8,160 | | 10 mg/m$^3$ |
| Cramer class III | TTC = 1.5 µg/kgbw/d | | 0.9 mg/m$^3$ |

Irritation of the respiratory tract is the main effect of caprolactam. In addition, caprolactam is classified as harmful for systemic toxicity. Caprolactam does not fit in the domain of substances covered by the $RD_{50}$ method. The estimated OELs on the basis of MTD and $LC_{50}$ were of the same order of magnitude and close to the IOELV. The estimated OELs using risk phrases and the TTC were both a factor of 10 lower than the IOELV. The lowest estimated OEL on the basis of the TTC was attributed to the assignment of caprolactam to Cramer class 3 (most toxic group of substances) using the ECB (2006) software tool. This assignment is considered questionable.

The OEL estimated with the $LC_{50}$ method is nearest to the IOELV.

***Table G.6: Cyclohexanone***

| | | Criterion | OEL (NL) |
|---|---|---|---|
| CAS | 108-94-1 | | 25 mg/m$^3$ |
| Molecular weight | 98.15 | | |
| Appearance | Liquid | | **Estimated OEL** |
| Risk phrases | 20 | Low hazard (2.4 ppm) | 9.6 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 1,800 | MTD = 166 mg/kgbw/d | 8.3 mg/m$^3$ |
| log $K_{ow}$ | 0.81 | | |
| log $K_{aw}$ | –3.05 | $RD_{50}$ = 2,500 ppm | 1,005 mg/m$^3$ |
| 4-h $LC_{50}$ rat mg/m$^3$ | 10,700 | | 13 mg/m$^3$ |
| Cramer class II | TTC = 9 µg/kgbw/d | | 5.4 mg/m$^3$ |

An OEL for cyclohexanone may be estimated from a consideration of both systemic and local (sensory irritation) effects, i.e. by all five methods. Four of the estimated OELs are of the same order of magnitude as the Dutch OEL. The exception is the estimate based on the $RD_{50}$. It is likely that systemic effects occur at lower levels than sensory irritation. This is reflected in the allocation of risk phrase R20 only (harmful by inhalation), with no risk phrase for irritation. The TTC method provided the lowest value.

The OEL estimated with the $LC_{50}$ method is nearest to the Dutch OEL.

***Table G.7: Ethylenediamine***

| | | Criterion | OEL (NL) |
|---|---|---|---|
| CAS | 107-15-3 | | 18 mg/m$^3$ |
| Molecular weight | 60.1 | | |
| Appearance | Liquid | | **Estimated OEL** |
| Risk phrases | 21/22-34-42/43 | High hazard (0.016 ppm) | 0.044 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 1,050 | MTD = 130 mg/kgbw/d | 6.5 mg/m$^3$ |
| log $K_{ow}$ | –2.04 | | |
| log $K_{aw}$ | –7.4 | $RD_{50}$ = 285 ppm | 70 mg/m$^3$ |
| 4-h $LC_{50}$ rat, mg/m$^3$ | 4,000 | | 5.2 mg/m$^3$ |
| Cramer class III | TTC = 1.5 µg/kgbw/d | | 0.9 mg/m$^3$ |

As ethylenediamine is a strongly basic compound with local effect on the respiratory tract, the use of the MTD and the TTC methods is not appropriate. The $RD_{50}$ procedure is not appropriate either as ethylenediamine does not fall into the chemical domain on which the linear regression relationship for the $RD_{50}$ was based. The risk phrases and the $LC_{50}$ are thus the only relevant methods for estimating the OEL for ethylenediamine.

Using the $LC_{50}$ resulted in an OEL estimate nearest to the Dutch OEL. The estimate based on the risk phrase was over-conservative.

***Table G.8: Glutaraldehyde***

| | | Criterion | OEL (NL) |
|---|---|---|---|
| CAS | 111-30-8 | | 0.25 mg/m$^3$ |
| Molecular weight | 100.12 | | |
| Appearance | Liquid | | **Estimated OEL** |
| Risk phrases | 23/25-34-42/43-50 | High hazard (0.018 ppm) | 0.074 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 300 | MTD = 34 mg/kgbw/d | 1.7 mg/m$^3$ |
| log $K_{ow}$ | –0.01 | | |
| log $K_{aw}$ | –5.34 | $RD_{50}$ = 213 ppm | 87 mg/m$^3$ |
| 4-h $LC_{50}$ rat, mg/m$^3$ | 100 | | 0.12 mg/m$^3$ |
| Cramer class I | TTC = 30 µg/kgbw/d | | 18 mg/m$^3$ |

As glutaraldehyde has a severe irritant effect on the respiratory tract, methods based on systemic effects (MTD and TTC) are not appropriate. The chemical domain of the linear regression equation for the $RD_{50}$ does not include highly irritant substances such as glutaraldehyde. Only the methods based on the $LC_{50}$ and risk phrases are appropriate for estimating an OEL.

The estimated OEL from the $LC_{50}$ was nearer to the Dutch OEL than that based on risk phrases.

***Table G.9: Isoprene***

| | | Criterion | WEEL |
|---|---|---|---|
| CAS | 78-79-5 | | 5.7 mg/m$^3$ |
| Molecular weight | 68.12 | | |
| Appearance | liquid | | **Estimated OEL** |
| Risk phrases | 45-68-52-53 | Very high | Carcinogen |
| $LD_{50}$ mg/kgbw | 2,100 | MTD = 158 mg/kgbw/d | 7.9 mg/m$^3$ |
| log $K_{ow}$ | 2.42 | | |
| log $K_{aw}$ | 0.49 | $RD_{50}$ = 26,850 ppm | 7,475 mg/m$^3$ |
| 4-h $LC_{50}$ rat, mg/m$^3$ | 180,000 | | 162 mg/m$^3$ |
| Cramer class I | TTC = 30 µg/kgbw/d | | 18 mg/m$^3$ |

On the basis of studies in rats, isoprene has been officially classified as a carcinogen. Therefore it is not possible to estimate an OEL on the basis of risk phrases. The $RD_{50}$ method cannot be used

either, because the mode of action of isoprene is systemic, while the $RD_{50}$ is based on local sensory irritation. The remaining 3 methods (MTD, $LC_{50}$ and TTC) may be used for estimating an OEL. It is assumed that the mechanism for the carcinogenicity of isoprene involves a threshold because the substance is not mutagenic in most test systems. The OELs estimated on the basis of the MTD and the TTC were nearest to the WEEL. The $LC_{50}$ method produced an OEL that appeared to be around 30 times too high.

The OEL for isoprene estimated with the MTD-method (7.9 mg/m$^3$) is nearest to the WEEL of 2 ppm (5.7 mg/m$^3$). In an NTP 2-year study on isoprene an MTD of 220 ppm was observed (US-NTP, 1999). Using this experimental MTD would have been resulted in an OEL of 20 mg/m$^3$ (7 ppm).

***Table G.10: Melamine***

| | | **Criterion** | **WEEL** |
|---|---|---|---|
| CAS | 108-78-1 | | 10 mg/m$^3$ |
| Molecular weight | 126.12 | | |
| Appearance | Solid | | **Estimated OEL** |
| Risk phrases | None based on testing | Very low (3.1 mg/m$^3$) | 3.1 mg/m$^3$ |
| $LD_{50}$ mg/kgbw | 3,160 | MTD = 335 mg/kgbw/d | 16.7 mg/m$^3$ |
| log $K_{ow}$ | –1.37 | | |
| log $K_{aw}$ | –11.1 | $RD_{50}$ = 0.0745 ppm | 0.038 mg/m$^3$ |
| 4-h $LC_{50}$ rat, mg/m$^3$ | 3,248 | | 4.2 mg/m$^3$ |
| Cramer class III | TTC = 1.5 µg/kgbw/d | | 0.9 mg/m$^3$ |

As melamine is a solid, the $RD_{50}$ approach cannot be used (solids are excluded from the chemical domain for which the linear regression equation was derived). Melamine has been extensively investigated in short- or long-term repeated dose studies and it is not considered a dangerous substance according to Directive 67/548/EEC (risk phrase not required). The absence of risk phrases, together with the MTD and $LC_{50}$ values, indicate low toxicity. An OEL may be estimated from all methods except the $RD_{50}$ methods.

The MTD, $LC_{50}$, and risk phrase methods resulted in OEL-estimates within one order of magnitude; the risk phrases produced the lowest estimate. The TTC method resulted in an OEL of 0.9 mg/m$^3$, based on the assignment of melamine to Cramer class 3 substance (the most toxic group of substances). This assignment is considered questionable.

The OEL estimate based on the $LC_{50}$ is nearest to the WEEL of 10 mg/m$^3$.

### *Conclusions*

From the 10 worked examples, it was concluded that:

- The method based on risk phrases resulted in the lowest OEL in 9 out of 10 cases (provided questionable TTC-OELs were excluded). In addition, the OEL estimated from risk phrases was found to be 2.6 to 400 times lower than the official OEL.
- The lowest result of the remaining appropriate methods provided an estimated OEL in line with official OELs.

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