WORKING FOR A HEALTHY FUTURE

**IOM Research Project: P937/97**
**July 2010**

# OELs for carcinogens

Alison Searl BSc (Hons), PhD, MEnvS

Len Levy OBE, BSc, MSc, PhD, FFOM, FBTS

WORLD HEALTH ORGANISATION
COLLABORATING CENTRE
FOR OCCUPATIONAL HEALTH

# CONTENTS

SUMMARY ..... 1

1 INTRODUCTION ..... 5

2 REVIEW OF METHODOLOGIES AVAILABLE FOR RISK ASSESSMENT AND MANAGEMENT ..... 6

2.1 Introduction ..... 6
2.2 Sources of uncertainty in risk management common to several or all approaches ..... 6
2.3 Quantitative risk characterisation by linear extrapolation ..... 10
2.4 Quantitative risk assessment based on Toxicodynamic modelling ..... 16
2.5 Quantitative risk assessment based on nonlinear extrapolation ..... 18
2.6 Margin of exposure approach ..... 19
2.7 $T_{25}$ ..... 22
2.8 Derived Minimum Effect Level (DMEL) ..... 24
2.9 Threshold of toxicological concern ..... 26
2.10 Practical threshold ..... 28
2.11 ALARP ..... 30

3 REVIEW RISK CRITERIA USED IN THE MANAGEMENT OF WORKPLACE RISKS ..... 31

3.1 Introduction ..... 31
3.2 Criteria currently applied in consideration of workplace risks within the EU and elsewhere ..... 31
3.3 Risk criteria for environmental, food, drinking water and consumer products ..... 34
3.4 Relationship between methods of risk assessment and risk criteria ..... 36
3.5 Discussion and conclusions ..... 36

4 CASE STUDIES ..... 37

4.1 Introduction ..... 37
4.2 Acrylamide ..... 38
4.3 Benzene ..... 42
4.4 Ethylene oxide ..... 45
4.5 Propylene oxide ..... 50
4.6 Bis(Chloromethyl)ether (BCME) ..... 53
4.7 Trichloroethylene ..... 56

5 ADVANTAGES AND DISADVANTAGES OF USING QUANTITATIVE RISK CRITERIA IN SETTING OEL ..... 60

5.1 Advantages ..... 60
5.2 Disadvantages ..... 60
5.3 Other comments ..... 61

6 RECOMMENDATIONS ..... 61

7 REFERENCES ..... 67

# SUMMARY


## OVERVIEW AND AIMS

This work package reviews the methods currently employed by regulatory and other authorities in the EU and elsewhere for the management of carcinogenic risks in the workplace, wider environment and in relation to food, drinking water and consumer products. The aims were to:

Assess the value of using quantitative risk assessment in setting OELs versus an "ALARP"[1] approach;
Identify the most appropriate methodologies for undertaking quantitative risk assessment; and
Identify appropriate risk criteria for use with the recommended methodologies plus a commentary on what might be appropriate if other methodologies of risk quantification are adopted.

## ADVANTAGES AND DISADVANTAGES OF USING QRA TO INFORM OELS

The major attractions of using QRA are that it would potentially enable consistent regulation of the cancer risks associated with different substances, provide reassurance that risks are controlled to a numerically defined low level and permit the calculation of the benefits associated with the imposition of OELs at different levels. The major problem with the use of QRA is that the uncertainties in the calculated risks may span several orders of magnitude. These uncertainties arise because of the limitations in the data available to inform QRA. There are relatively few substances for which sufficient human data are available to enable an informed risk estimate to be made and differences in the approach taken to risk estimation can give rise to order of magnitude differences in risk estimates even when these are based on relatively good data. There are little or no human data for most carcinogenic substances and the quality of animal data is highly variable.

One source of uncertainty is the difficulty in reliably detecting the presence or absence of an excess risk of cancer in workers or in an animal experiment where the expected incidence rate is low. Animal experiments normally employ high doses to increase the likelihood of detecting a cancer excess. There are a range of uncertainties associated with extrapolating from the findings of high dose animal experiments to human risk assessment at very much lower levels of exposure. The data from animal experiments may involve tumours at a variety of sites with different apparent exposure-response relationships for each site, both in terms of dose and in terms of the type of function that gives the best fit curve. In addition, the tumour response may be very different in different species or even different strains of the same species and the relative susceptibility of humans is highly uncertain. Many cancers appear to be species specific or even strain specific and unless mechanistic data are available, the relevance to humans is uncertain. Most animal experiments employ very few dose levels and there are usually insufficient data points to characterise the shape of the exposure-response function. It may be possible to fit a variety of different shaped curves to the available data, giving rise to very different estimated levels of risk at doses outside of the observed data range. There is no certainty that the curve giving the best statistical fit within the observed data range is the most appropriate for risk


[1] Reducing exposure to levels that are "as low as reasonably practicable"

estimation at much lower dose levels which may be associated with very different disease or cellular defence mechanisms. There are also often considerable uncertainties in the dose information available to QRA. Traditionally, epidemiological studies in humans focussed on establishing whether or not an excess of cancer was associated with a particular agent or industry and the information underlying exposure estimates in epidemiological studies is often fairly sparse and there are considerable uncertainties in the exposure estimates used to inform QRA. There are also uncertainties in scaling from animal dose data to equivalent human doses. Different authorities take different approaches resulting in order of magnitude differences between risk estimates based on a common data set.

## APPROPRIATE METHODOLOGIES

A range of approaches to QRA are available together with alternative approaches to risk management. The different mechanisms by which different substances may cause cancer and very different data availability for different substances mean that different approaches to QRA may be appropriate under different circumstances. There are also circumstances where QRA is unlikely to be appropriate. In order develop authoritative guidance on when to use which approach, it is necessary to gain a consensus view among relevant experts and we recommend that is achieved through a workshop hosted by SCOEL. A provisional framework is outlined in the Table overleaf. In terms of risk communication, it might be preferable to express risks in terms of a margin of exposure relative to the estimated dose associated with a 10% cancer response ($BMDL_{10}$). In terms of lifetime cancer risks of $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$, this would equate to margins of exposure of 100, 10000, 100000 and 1000000.

| Data availability | Steps towards determining an OEL |
|---|---|
| Good human epidemiological data; good understanding of mechanisms underlying carcinogenesis | Review mechanistic information to establish whether threshold is likely to exist; use mechanistic information to establish threshold level of exposure in humans if possible or to inform QRA based on human epidemiological data. If no threshold apparent, use QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, establish health benefits in terms of cancers avoided across EU at each exposure level. If threshold identified, use as basis of OEL taking account of uncertainty in data. |
| Good human epidemiological data; poor understanding of mechanisms underlying carcinogenesis | Use epidemiological data to establish exposure response relationships, examine evidence for a threshold, undertake QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, establish health benefits in terms of cancers avoided across EU at each level. If threshold identified, use as basis of OEL taking account of data uncertainties. If no threshold, review QRA taking account of uncertainties. If data inadequate to reliably establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, use comparison of cancer incidence under different exposure regimes (eg low to high exposure groups) to estimate number of cancers avoided by imposing different OELs. |
| Limited human data, good quality animal data, good understanding of mechanisms | Examine mechanistic data to confirm carcinogenic process relevant to humans and determine whether there is a threshold for effect. If threshold exists, establish equivalent human exposure level and use as basis of OEL. In no threshold, undertake QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, establish health benefits in terms of cancers avoided across EU at each exposure level. Review results of QRA taking account of uncertainties and assess plausibility against findings of workplace studies. |
| Very limited or no human data, good quality animal data | Consider potential mechanisms underlying carcinogenic process and likely relevance to humans and whether a threshold is likely. In absence of a threshold, undertake QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risk, establish health benefits in terms of cancers avoided across EU at each level. Review QRA results taking account of uncertainties and assess plausibility against findings of workplace studies. If no and/or lowest effects levels identified and a threshold seems likely, use as basis for OEL with appropriate scaling factors to account for uncertainties. |
| Very limited or no human data, poor quality animal data | QRA will give rise to highly uncertain results and should not be used as main rationale underlying an OEL. Given that it is desirable to set an OEL avoid excessive exposures, it may be appropriate to determine a generic low level of exposure that is applied as an OEL for suspected carcinogens where the data are inadequate to assess relative potency compared with other carcinogens. If there are data that allow estimation of potency relative to other carcinogens, OEL could be derived by comparison with OELs for other similar substances. If work-related cancers, OELs should be set that will reduce exposure levels. |

## RISK TOLERABILITY

There is no societal agreement on the level of calculated cancer risk that is considered acceptable or as to whether or how judgement of risk acceptability might take account of uncertainties in the database. Risk tolerability varies widely in different situations. Higher levels of risk are likely to be tolerated in the workplace than for wider population exposure.
OELs have generally been set at levels that are believed to be achievable and there are substantial variations in the effectiveness of exposure control and levels of exposure to carcinogens in different industry sectors.

Guidance produced by ECHA for the derivation of DMELs suggests that a lifetime cancer risk of $10^{-5}$ should be regarded as tolerable for workplace exposure to chemicals and we have asked by the Commission to consider $10^{-5}$, $10^{-6}$ and $10^{-7}$ as the potential criteria for acceptable risk. These are considerably lower levels of risk than currently regarded as tolerable for workplace exposures in some member states ($10^{-3}$ to $10^{-4}$). The benefits of setting OELs that based on $10^{-6}$ or $10^{-7}$ cancer risks over an OEL based on a $10^{-5}$ cancer risk are dubious. It is unlikely that sufficient workers would be exposed to a substance across Europe for this reduction in risk to lead to any avoided cases. Socio-economic considerations may play a role in the determination of risk tolerability for individual carcinogens.

## RECOMMENDATIONS

We recommend that a flexible approach to setting OELs for carcinogens within the EU is retained, but that is approach is underpinned by suitable guidance developed as a consensus view of experts at a SCOEL-hosted workshop. We also recommend that the following issues are taken into account in the proposed guidance:

1. The extent to which the results of QRA are taken into account in setting OELs should reflect the certainty of the data.

2. The extent to which animal data are taken into account should reflect study quality and the whether it is likely that the toxicological mechanisms leading to cancer and reported tumours could reasonably be expected to be relevant to humans.

3. Health impact assessment should be used as a tool to inform the setting of OELs. Where possible the number of cases avoided within the EU as a result of imposing OELs at different levels should be estimated together with an indication of the timescale over which these benefits would accrue, taking account of foreseeable changes in patterns of use.

4. There is a need to determine a minimum dataset that satisfies a number of criteria including relevance to human exposure, data quality, dosing regime and cancer response for QRA to be used for genotoxic carcinogens.

5. There is also a need develop a clear set of options that can be employed where it is not appropriate to use QRA. To a great extent, some of these possible approaches are addressed in current SCOEL procedures (Bolt and Huici-Montagud, 2007). Other options might include consideration of analogous substances, for example, for RCF a worst case cancer risk estimate could be based on risk estimates for chrysotile.

# 1 INTRODUCTION

This work package reviews the methods currently employed by regulatory and other authorities in the EU and elsewhere for the management of carcinogenic risks in the workplace, wider environment and in relation to food, drinking water and consumer products.

The aims of this work package were to:

- Assess the value of using quantitative risk assessment in setting OELs versus an “ALARP” approach;
- Identify the most appropriate methodologies for undertaking quantitative risk assessment; and
- Identify appropriate risk criteria for use with the recommended methodologies plus a commentary on what might be appropriate if other methodologies of risk quantification are adopted.

The first section of this chapter reviews the various approaches taken to risk quantification and other approaches used in risk management. This includes different approaches to risk estimation, the development of benchmark doses, the concept of Margin of Exposure (MOE), practical thresholds, “thresholds of toxicological concern (TTC)”, Derived Minimum Effect Levels (DMELs – as proposed within REACH) and approaches based on risk minimisation: “as low as reasonably practicable” (ALARP). Issues considered include data requirements, calculation methods and sources and scale of uncertainties. The main advantages and disadvantages of each approach are outlined.

The second section of this chapter reviews “risk acceptability” including the criteria currently employed by regulatory and other authorities in the EU and elsewhere in relation to workplace risks. It also examines risk criteria employed for environmental, food, drinking water and consumer products to establish the extent of international consistency in managing these types of risk in relation to workplace risks. The relationship between methods of risk assessment and risk criteria is also explored in order to assess whether the use of different approaches to risk assessment has a practical implication in terms of OEL determination.

The third section of the chapter outlines some case studies for some representative carcinogens for which OELs have been set in EU member states and/or SCOEL and examines how an OEL developed using quantitative risk assessment compares with existing OELs based on other criteria.

The final sections of this chapter assess the advantages and disadvantages in employing quantitative risk assessment in setting OELs and make some recommendations on the use of quantitative risk assessment for the purposes of informing the setting of OELs within the EU.

# 2 REVIEW OF METHODOLOGIES AVAILABLE FOR RISK ASSESSMENT AND MANAGEMENT

## 2.1 INTRODUCTION

This section reviews the various methods that have been employed to support risk assessment and management for carcinogens. The quantitative approaches considered include linear and nonlinear extrapolation, benchmark dose/margin of exposure approaches, the derivation of Toxicological Thresholds of Concern, Practical Thresholds and the derivation of Derived Minimum Effect Levels (DMELs) as outlined in the guidance to support REACH. Although the main focus of this section is on quantitative approaches to risk management, brief consideration is also give to the alternative approach currently employed in some EU member states where risk management is based on exposure minimisation without explicit quantification of risk.

The first part of this section considers some uncertainties that are common to most or all of the approaches to risk assessment considered. This includes differences in the approach taken to interspecies differences and dose quantification. The main part of this section reviews the individual approaches to risk management including data requirements, calculation methods, the sources and scale of uncertainties specific to individual methods and the main advantages and disadvantages of the available methodologies. The evaluation of the outcomes of the different approaches is addressed in a separate section on risk acceptance criteria.

## 2.2 SOURCES OF UNCERTAINTY IN RISK MANAGEMENT COMMON TO SEVERAL OR ALL APPROACHES

### 2.2.1 Limitations in exposure-response information

It is difficult to reliably detect the presence or absence of an excess risk of cancer in workers or in an animal experiment where the expected incidence rate is low. The sensitivity of a study to detect excess risks at low levels of exposure will depend on the study size with larger studies having greater power to detect small risks.

Most animal experiments have employed only a very few dose levels and there are usually insufficient data points to characterise the shape of the exposure-response function. It may be possible through using a number of mathematical assumptions to fit a variety of different shaped curves to the available data, giving rise to very different estimated levels of risk at doses outside of the observed data range. Although curves may vary in their statistical goodness of fit to the data, there is no certainty that the curve giving the best statistical fit within the observed data range is the most appropriate for risk estimation at much lower dose levels which may be associated with very different disease or cellular defence mechanisms.

### 2.2.2 Reliability of exposure estimation in human studies

Whereas exposures are generally well characterised in animal experiments, there are often considerable uncertainties in the exposure characterisation in human epidemiological studies. Traditionally, epidemiological studies focussed on establishing whether or not an excess of cancer was associated with a particular agent or industry and the information underlying exposure estimates in epidemiological studies is often fairly sparse. Uncertainties arise because of the long time period over which exposures

may occur, the potential delay between exposure and the development of cancer and also the changing nature of tasks and exposure through time which introduces uncertainty into the reconstruction of historical exposures. There are likely to be uncertainties in the exposure data that are available for the cohort as a whole in relation to sampling and analytical methods, the purpose for which measurements were made and how representative any measurement data are of exposures associated with specific tasks or job titles. The reconstruction of an individual's exposure history may be uncertain because of poor job history information, uncertainty in the exposures associated with a given job title and the difference in exposures experienced by individuals who are nominally employed in the same task. Often the investigation of exposure-response relationships is limited to considering fairly broad bands of exposure with arbitrarily defined boundaries. If the data analysis indicates an excess cancer risk in particular groups, it is uncertain whether a given risk level should be attributed to the midpoint (median, mode or mean?) or at the top of the range. Similarly if no excess risk is apparent for a given exposure group, it is uncertain whether an excess risk might exist for exposures at the upper end of the range. These uncertainties in workplace exposure data exist even for carcinogens that have been extensively studied.

### 2.2.3 Relevance of animal data to human risk assessment

Animal cancer bioassays are usually undertaken at doses that are most likely to evoke a carcinogenic response (in the medium and highest dose groups) and often the "maximum tolerated dose" used is a toxic dose. Exposure levels are usually orders of magnitude above potential human exposure scenarios. This is because the numbers in animal groups are relatively small (≤100) compared to the large human population that might be exposed to that substance. Toxicologists have greater confidence in a positive result if a dose response relationship can be demonstrated. Normally, if the substance is shown to be a carcinogen, we are left with the problem of extrapolating the response in high-dosed animals to humans experiencing very much lower levels of exposure.

There are a range of uncertainties associated with extrapolating from the findings of animal experiments to human risk assessment. Many cancers appear to be species specific but in the absence of data to demonstrate a species specific mechanism (eg the involvement of a hormonal or specific critical enzyme pathway not believed important in humans), tumours observed in animal experiments would normally be considered relevant to human risk assessment. Ideally, however, data are required to demonstrate the relevance of the results of animal experiments to humans. This might include data demonstrating a similar metabolic fate for the substance of interest in humans and the selected animal species and also data that demonstrate that the mechanisms underlying the development of cancer in animals are also relevant to humans. The data from animal experiments may involve tumours at a variety of sites with very different apparent exposure-response relationships for each site, both in terms of dose and in terms of the type of function that gives the best fit curve. In the absence of good human data, it may be difficult to determine which tumours are of greatest relevance to human risk assessment and whether to base any risk assessment on the most sensitive tumour site or some combination of tumour sites. In addition, the tumour response may be very different in different species or even different strains of the same species. Although there is a tendency to base risk assessments on the most sensitive strain or species, there is considerable uncertainty as to the relative sensitivity of humans versus that of the test animals and it is likely that human susceptibility relative to that of other species would vary by substance.

### 2.2.4 Extrapolation between species

Where cancer risks are estimated on the basis of animal data, it may be appropriate to scale the dose to take account of interspecies differences in size and metabolic rate. Different agencies have used different scaling factors to extrapolate from animal data to human exposure and individual agencies have changed practice over time. Differences in the approach to scaling between species account for some of the differences in OELs adopted by different regulatory regimes for carcinogens (Seeley et al, 2001).

Where animal inhalation data are available, some agencies have used experimental concentrations as a direct input into risk assessment without scaling for any interspecies differences (for example, the IPCS assessment of ethylene oxide). It is argued that the tissue dose for a given concentration is similar in humans and rodents. Other agencies have scaled in terms of estimated internal dose. The received dose is calculated from the respiratory volume of the experimental species. The REACH guidance (ECHA, 2008) indicates that no scaling of inhalation concentrations is required to take account of species differences in metabolism as metabolic rates would be anticipated to scale with oxygen utilisation. The guidance provides the following formula to take account of differences in absorption (ABS) in rats versus humans (if known):

$$\text{corrected N(L)OAEC} = \text{inhalatory N(L)OAEC} \times \frac{ABS_{inh\text{-}rat}}{ABS_{inh\text{-}human}}$$

The guidance also recommends that a correction is made for differences in exposure conditions (eg a typical 40 hour working week versus a typical 24 hour/week exposure in animal inhalation experiments). Where data are only available for exposure by the oral route, then the received dose is assumed to be the oral dose unless data are available to indicate a lower efficiency of absorption following exposure by this route. The scaling of the received dose in animals to a human dose has been done differently at different times and by different agencies. Traditionally regulatory agencies have scaled dose in terms of mass – mg/kg – but the pharmaceutical industry has generally scaled by body surface area. The REACH guidance for human health risk assessment indicates that allometric scaling should extrapolate dose according to an overall assumption that equitoxic doses expressed as mg/kg/day scale by body weight to the power 0.75. Where data are derived in an inhalation experiment, the REACH guidance recommends the use of allometric scaling where no adjustment for differential absorption is made but where an adjustment is made to allow for interspecies differences in absorption, no allometric scaling is required. The allometric scaling factors outlined in the guidance are shown below:

**Allometric scaling factors for different species as compared to humans[a]**

| Species | Body weight (kg) | AS factor[b] |
|---|---|---|
| Rat | 0.250 | 4 |
| Mouse | 0.03 | 7 |
| Hamster | 0.11 | 5 |
| Guinea pig | 0.8 | 3 |
| Rabbit | 2 | 2.4 |
| Monkey | 4 | 2 |
| Dog | 18 | 1.4 |

a) assuming the human body weight is 70 kg

b) not applicable when setting an inhalation DNEL based on an inhalation animal study (see APPENDIX R. 8-2)

Given a received dose of 1 mg/kg in rats, the human equivalent dose would be 70 mg, if scaled by body mass, 10.1 mg if scaled by body surface area, or 17.5 mg based on an allometric scaling factor of 4 as indicated in the REACH guidance (if based on oral intake).

Interspecies extrapolation may also be based on pharmacokinetic modelling as recommended by the German Committee on Hazardous Substances (2008), provided sufficient data are available to support the development of a model. Effects can then be assessed in relation to equivalent plasma levels of a carcinogen or its active metabolite.

In the case of occupational toxicology, and cancer in particular, inhalation is the exposure route of primary concern. In scaling inhalation concentrations for the purposes of risk assessment in the workplace, an inhalation volume of 10 $m^3$ is assumed for an 8 hour shift.

In conclusion, it is readily apparent that different approaches to interspecies scaling could result in an order of magnitude difference in risk estimates or in the numerical value assigned to an OEL based on a single data set.

### 2.2.5 Extrapolation between exposure routes

The carcinogenicity of relatively few substances has been investigated in inhalation experiments and most animal carcinogenicity data are available from oral studies. For some substances data are only available for dermal exposure or injection via various routes. For many substances, absorption from the gastrointestinal tract is likely to less efficient than absorption of respirable particles in the lung (but similar for coarser inhaled particles that do not penetrate to the gas exchange region of the lung). Absorption through the skin is highly substance dependent and while the uptake of many substances through the skin is very low, other substances are readily absorbed. The extent to which inhalation risks can be assessed from data derived from

experiments employing other routes of exposure is variable. Generally where substances give rise to tumours remote from the point of contact with a substance, it seems reasonable to assume that similar effects would occur following inhalation. In some circumstances, where tumours are directly associated with the point of contact with the substance, the likelihood of the agent giving rise to tumours elsewhere in the body is highly uncertain. It is also uncertain whether lung carcinogens would necessarily be detected in an assay where lung tissue is not in direct contact with the agent of interest. Recently, the UK Intergovernmental Group on Health Risks from Chemicals (IGHRC) has produced a helpful guidance document on route to route extrapolation which provides advice where such "read across" from one route to another is scientifically acceptable (http://ieh.cranfield.ac.uk/ighrc/cr12[1].pdf).

In most circumstances, the animal dose is scaled to a received human dose in a similar fashion to the scaling of the received dose in inhalation experiments (by mass, body surface area or a function of body surface area). In some circumstances, where sufficient information about metabolism and/or absorption of the substance is available, a more sophisticated approach to scaling may be taken to take account differences in absorption and metabolism following exposure by different routes. This is likely to be particularly important where data are only available for dermal exposure and the absorption and metabolic fate of a substance may be very different from that following inhalation. For oral data, in the absence of specific information about absorption, the IGHRC recommended that for substances of high oral toxicity, absorption of the respirable fraction following inhalation should be assumed to be twice that following ingestion. Absorption of the respirable fraction for substances of low to moderate oral toxicity should be considered to be ten times greater than following ingestion. The scaled human dose can be expressed in terms of an inhaled concentration over a given period of time (ie concentration in $10m^3$ air inhaled over a typical 8 hour shift).

### 2.2.6 Intraspecies variability in susceptibility

Gaylor et al (1993) used $TD_{50}$, a measure of carcinogenic potency (daily dose that causes a tumour type in 50% of the exposed animals that otherwise would not develop the tumour in a standard lifetime) to investigate the reproducibility of cancer rates across experiments, strains, and rodent species. Their estimates of $TD_{50}$ were based on a lognormal distribution. For near-replicate bioassays, approximately 95% of the $TD_{50}$'s were estimated to be within a factor of 4 of the mean. Between strains, about 95% of the $TD_{50}$'s are estimated to be within a factor of 11 of their mean, and the pure genetic component of variability is accounted for by a factor of 6.8. Between rats and mice, about 95% of the $TD_{50}$'s are estimated to be within a factor of 32 of the mean, while between humans and experimental animals the factor was 110 for 20 chemicals. Cancer risk estimates based on the most sensitive rodent species-strain-sex and using interspecies dose scaling based on body surface area appeared to overestimate cancer rates for 20 human carcinogens by about one order of magnitude on the average.

## 2.3 QUANTITATIVE RISK CHARACTERISATION BY LINEAR EXTRAPOLATION

### 2.3.1 Overview

Traditional methods of risk assessment and management have involved the estimation of cancer risks associated with low levels of exposure on the basis of data derived in high dose animal experiments. Where the mode or mechanisms by which a given

substance causes cancer are well understood, it may be possible to develop a mechanistic model in which an exposure-response function is established for each step of the process. In most cases mechanisms are poorly understood and/or quantified and the shape of the exposure response function is unknown, particularly for low levels of exposure. It has been common practice to develop an exposure response function based on high dose experimental data, then to extrapolate from the lowest dose (critical point of departure, POD) for which the exposure response function has been developed. A variety of different approaches have been taken to curve fitting data within the range of observation and extrapolation to lower doses. Where insufficient data are available to support a mechanistic model, a proportional (linear) relationship between risk and dose has generally been assumed at low doses, although the dose-response curve generally is not linear at higher doses. It is generally believed that linear extrapolation is likely to lead to an over-estimation of risk resulting in more stringent exposure control.

The EPA (2005) indicate that linear extrapolation should be used when there is sufficient information about the mode of action to indicate that the dose-response curve is likely to have a linear component below the POD. This includes agents that are DNA-reactive and have direct mutagenic activity, or for which human exposures or body burdens approach doses associated with key precursor events in the carcinogenic process and are likely to lie within the approximately linear, portion of the dose-response curve. Linear extrapolation is also appropriate as a default where the mode of action is not established as it is generally is considered to be a health-protective approach.

If the mode of action of the compound is understood and there are data describing precursor stages, the POD may take account of the dose-response relationships derived for precursor events and it may be possible to link a given precursor response level to a particular tumour response level.

SCOEL have made a preliminary recommendation that quantitative risk assessment should be used to inform the development of OELs at EU level for non-threshold genotoxic carcinogens for which no practical thresholds have been established. Low dose linear extrapolation is already used to inform the setting of OELs in the Netherlands. The German Committee for Hazardous Substances (2008) has recently published guidance on the calculation of cancer risks for the purposes of setting an OEL which recommends the use of low dose linear extrapolation for nonthreshold genotoxic carcinogens where there are insufficient data to support a toxicodynamic approach to modelling. Where genotoxicity is not of predominant importance, the mode of action is predominantly known but there is no established threshold for effects, the German guidance indicates that a sublinear relationship should be assumed.

The EU's Scientific Committees on Health and Environmental Risks, Consumer Products and Emerging and Newly Identified Health Risks have endorsed the use of linear extrapolation for the purposes of cost benefit analysis where appropriate for the purposes of managing the health risks associated with carcinogens.

### 2.3.2 Calculation

The derivation of the POD for linear extrapolation would normally be undertaken by curve fitting the available data and basing the POD on the function giving the best fit to the data. In extrapolating from animal dose data to estimated human dose, corrections are made for differences in metabolic rate and size. A line is drawn from the POD to

the origin, corrected for background. The slope of this line, known as the slope factor, is an upper-bound estimate of risk per increment of dose that can be used to estimate risk probabilities for different exposure levels. Given that the starting dose for extrapolation is itself an estimate, it has been common practice to extrapolate from the lower 95$^{th}$ percentile rather than mid point estimate of the low dose selected as a chosen starting point. If the $LED_{01}$ (lower confidence limit of estimated dose associated with a 1% tumour incidence) is used as the POD, the slope factor is equal to $0.01/LED_{01}$. Risk-specific doses are derived from the slope factor or unit risk to estimate the dose associated with a specific risk level, for example, a one-in-a-million increased lifetime risk.

A variety of models are available for curve fitting the observed data (Table) but in practice the linearised multistage model and low dose linear extrapolation (one hit) models have been most widely used. The low dose linear model is particularly favoured because of its low data requirements, its applicability to a wide variety of different datasets and because it is highly unlikely to give rise to an underestimation of risk (EFSA, 2005). Data may be log-transformed prior to curve fitting using, for example, the logistic or probit models.

| Model | Description |
|---|---|
| Multistage | A mathematical function used to extrapolate the probability of cancer from animal bioassay data, using the form:<br>$P(d) = 1 - e^{-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)}$<br>Where: P(d) = probability of cancer from a continuous, lifetime exposure rate d;<br>$q_i$ = fitted dose coefficients of model; i=0, 1, . . . , k; and<br>k = number of stages selected through best fit of the model, no greater than one less than the number of available dose groups. |
| Linearised Multistage Procedure | A modification of the multistage model, used for estimating carcinogenic risk, that incorporates a linear upper bound on extra risk for exposures below the experimental range. |
| One hit | A dose-response model based on a mechanistic argument that there is a response after a target site has been hit by a single biologically effective unit of dose within a given time period. The form of the model, a special case of the gamma, multistage, and Weibull models, is given by:<br>$P(d) = 1 - e^{(-\lambda d)}$<br>Where P(d) = probability of cancer from lifetime continuous exposure at dose rate d, and<br>$\lambda$ = fitted dose coefficient. |

| Model | Description |
|---|---|
| Gamma (Multi-hit) | A generalization of the one-hit model (see definition) for low-dose extrapolation. The probability P(d) that an individual will respond to lifetime, continuous exposure to dose d is given by<br>$P(d) = \frac{\lambda^k}{\Gamma(k)} \int_0^d t^{k-1} e^{-\lambda t} dt$<br>Where: Γ(k) = the gamma function,<br>k = the number of 'hits' estimated by the model, and<br>λ = fitted coefficient. |
| Logistic | A dose-response model used for low-dose extrapolation, of the form:<br>$P(d) = \gamma + \frac{1-\gamma}{1+e^{-(\alpha+\beta d)}}$<br>Where: P(d) = probability of cancer from lifetime, continuous exposure at dose rate d, and<br>α, β = fitted parameters; and<br>γ = background incidence rate. |
| Probit | Probit Model: A dose-response model of the form:<br>$P(d) = \gamma + (1-\gamma) \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\alpha+\beta d} e^{-\frac{u^2}{2}} du$<br>Where: P(d) = the probability that an individual selected at random will respond at dose d, assuming a normal distribution of tolerances;<br>α, β = fitted parameters; and<br>γ = background response rate. |
| Weibull | A dose-response model of the form:<br>$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta d^{\alpha}})$<br>Where: P(d) = the probability of a tumor (or other response) from lifetime, continuous exposure at dose d until age t (when tumor is fatal);<br>α = fitted dose parameter (sometimes called "Weibull" parameter);<br>β = fitted dose parameter;<br>γ = background response rate. |

| Model | Description |
|---|---|
| Multistage Weibull | A dose-response model for low-dose extrapolation that includes a term for decreased survival time associated with tumor incidence: $P(d,t) = 1 - e^{-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)(t - t_0)^z}$ Where: P(d,t) = the probability of a tumor (or other response) from lifetime, continuous exposure at dose d until age t (when tumor is fatal); $q_i$ = fitted dose parameters, i=0, 1, . . . , k; k = no greater than the number of dose groups - 1; $t_0$ = the time between when a potentially fatal tumor becomes observable and when it causes death; and z = fitted time parameter (also called "Weibull" parameter). |
| Quantal Linear Model | A special case of the Weibull model in which the power term has been set to zero. |

Different expert groups have adopted different estimated incidence levels as their critical point of departure. In conventional cancer bioassays, with approximately 50 animals per group the data are generally sufficient to detect excess cancer risks of between 1 and 10%. In large epidemiological studies, the data may be sufficient to allow detection of cancer risks of less than 1%. The various models commonly used for carcinogens generally yield similar estimates of the POD at response levels as low as 1% (US EPA, 2005). In the past, the POD was most commonly the lower 95% confidence limit on the lowest dose level that can be supported for modelling by the data (EPA, 2005). More recent assessments have used the modelled dose associated with effects in 10 or 25% of the exposed population (Effective dose, $ED_{10}$, $ED_{25}$) or more commonly the lower 95$^{th}$ percentile of these levels ($LED_{10}$, $LED_{25}$) as the POD. In the EU, the calculated dose expected to give rise to tumours in 25% of exposed animals, $TD_{25}$, has been widely used in risk assessment. It has been suggested that estimated dose associated with a cancer risk of 1% above background ($ED_{01}$) provides a more stable estimate of low dose cancer risk than $ED_{10}$ or $ED_{25}$.

Cancer risks may be estimated in terms of “Extra Risk” through adjustments to take account background incidence rates of the same effects to give an estimate of risk associated with dose d only among the fraction of the population not expected to respond to the secondary (background) causes: ER = [P(d)-P(0)/1-P(0)]. For example, if the background rate (P(0)) = 0.8 and the response rate at dose d, P(d) = .9, then ER = (0.9 - 0.8)/(1-0.8) = 0.1/0.2 = 0.5. That is, at dose d, an additional 10% of the population is expected to respond adversely. But since only 20% of the population was expected to be free of adverse effects without the exposure of interest, this 10% represents 50% of the population that would otherwise have been unharmed by this exposure.

**Alternatively cancer risk is more commonly calculated in terms of Additional Risk (Added, Attributable Risk or Risk Difference) which is** calculated difference in risk of a particular condition between those who are exposed and those who are not.

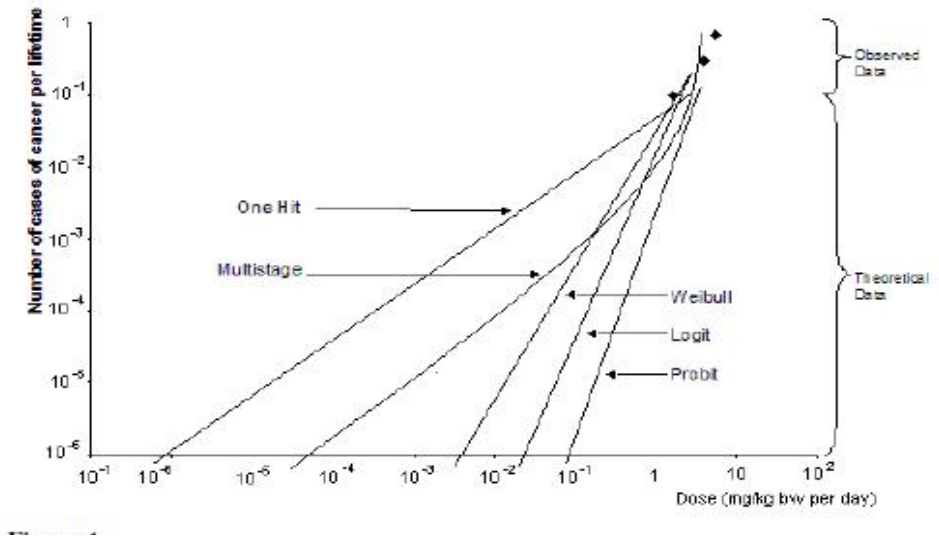
This measure is derived by subtracting the rate (usually incidence or mortality) of the disease among the unexposed persons (Pu) from the corresponding rate among the exposed (Pe), i.e., AR= Pe-Pu. The AR is an absolute measure of the excess risk attributed to exposure.

The US EPA (2005) advise the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) should be calculated where practicable in order to inform decision makers on the degree of uncertainty associated with calculated values.

### 2.3.3 Sources of uncertainty

The main source of uncertainty is in the shape of the exposure-response function and how well linear extrapolation describes risk at low levels of exposure. A variety of methods can be used to estimate $ED_{01}$, $ED_{10}$ or $ED_{25}$ and this can have a substantial impact on estimated cancer risks.

Linear extrapolation is generally believed to lead to over estimation of risk at low levels of exposure but for some substances or types of exposure, it is possible that risks are actually relatively greater at low levels of exposure than would be predicted from high dose data (for example, if there was saturation of the mechanisms leading to carcinogenesis at high dose).




### 2.3.4 Advantages and disadvantages

There are a number of advantages and disadvantages associated with QRA that are not specific to methods based on linear extrapolation. The major advantage of QRA as a tool in setting OELs is that the estimation of the cancer risks associated with differing levels of exposure allows the identification of candidate OELs that are likely to be associated with a meaningful reduction in risk. It is an important tool in cost benefit analysis that can be used in the selection of an OEL that provides the best ratio of health protection versus cost of implementation.

There are a number of major disadvantages to QRA of which the most important is the uncertainty in extrapolating from the high doses used in animal studies to the relatively low doses to which humans are exposed (HPA, 2008; COC 2004). There may be significant nonlinearities in the uptake, metabolism and other biological processes (modes and mechanisms) leading to cancer at low levels of exposure (EFSA, 2005).

Cancer risk estimates based on QRA may give a false impression of precision and the degree of uncertainty varies substantially by substance, depending on the availability of any human data plus the quality and quantity of animal data and our understanding of the biological mechanisms underlying the carcinogenic process for that substance.

SCOEL has advocated the use of linear non-threshold extrapolation for low dose risk assessment for non-threshold genotoxic carcinogens for which there is no or insufficient evidence to underpin a practical threshold. The advantages of linear extrapolation over other methods include ease of use, suitability for extremely limited data sets and reasonable certainty that risks will be over rather than under estimated. One major downside of over-estimation of risk is that stakeholders may be unduly concerned about risks that are for practical purposes negligible.

The lifetime averaging applied to dose estimation in linear extrapolation implies that less-than-lifetime exposure is associated with a linearly proportional reduction of the lifetime risk, regardless of when exposures occur. The US EPA, however, cite published examples where use of a lifetime average daily dose could lead to a two-to fivefold under-estimation or risk and others in which it might overestimate risk. The use of lifetime averaging of exposure leads to considerable uncertainty as to the significance of relatively high exposures occurring within a relatively short period. Although dose-response assessments should evaluate the impacts of less-than-lifetime exposure including precursor effects, reversibility of effects and persistence in the body following exposure, these data are rarely available to be included in an assessment. Similarly data are rarely available that describe the relationship of internal dose to duration of exposure and the impacts of continuous versus intermittent exposure.

## 2.4 QUANTITATIVE RISK ASSESSMENT BASED ON TOXICODYNAMIC MODELLING

### 2.4.1 Overview

Toxicodynamic modelling is based on an understanding of the sequence of events that links exposure to a substance to the end result of cancer. Possible modes of carcinogenic action include mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity leading to repair through cell proliferation, and immune suppression. The aim of toxicodynamic models is to reflect the sequence of key precursor events that lead to cancer and to quantify each stage of that process. The intention is provide a tool for risk estimation that is based on a biological model of carcinogenesis. The German Committee for Hazardous Substances (2008) have recently recommended that a toxicodynamic approach to modelling is employed in risk estimate where data are available to support this approach.

### 2.4.2 Data requirements

Toxicodynamic modelling requires a full understanding of the mode of action underpinned by supporting data. In order to quantitatively model the processes leading

to carcinogenesis, quantitative data are required for the key precursor events of the mode of action. This includes quantification of the relationship between external exposure and internal dose with an understanding of the key steps linking the two and quantification of the processes linking internal exposure to effect.

### 2.4.3 Calculation methods

The modelling process involves identifying the key steps and compartments in the sequence of events linking exposure to cancer and developing a model that describes each step of the process. If a standard model already exists for the agent's mode of action, the model can be adapted for the agent by using agent-specific data to estimate the model's parameters. The EPA cite as, an example, the two-stage clonal expansion model developed by Moolgavkar and Knudson (1981) and Chen and Farland (1991). These models continue to be improved as more information becomes available.

### 2.4.4 Uncertainties

If a model is primarily based on observations made in animals, there will be uncertainties in relation to the relevance to human exposure. There will also be uncertainties in model parameters based on observations made at very different exposure levels, different routes of exposure or over different durations of exposure from those relevant to workplace risk assessment. For example, model parameters may show unexpected relationships with dose or exposure duration.

### 2.4.5 Advantages and disadvantages

Toxicodynamic modeling is potentially the most comprehensive way to account for the biological processes involved in carcinogenesis and can be a useful tool in understanding nonlinear relationships between internal dose and cancer response. One of its main attractions is that risk estimates are underpinned by a plausible and quantified set of biological processes rather than being based simply on an empirical fit of data to a curve with no reference to the underlying biological mechanisms. Toxicodynamic modeling can be used to explore the relationship between tumour development and key precursor events which may help in the identification of practical thresholds or otherwise inform OEL setting. For example, a relatively small change in cell proliferation rates over a specific range may have a large impact on tumour response.

The disadvantages of toxicodynamic modelling include the requirement for a relatively detailed understanding of the mode of action of a carcinogen and detailed information about the rates and quantities involved at each step of the process giving rise to cancer. Ideally critical parameters should be estimated from laboratory studies for the individual stages in the process rather than through fitting model parameters on the basis of final tumour outcome. For most substances, this information is unavailable and thus the application of toxicodynamic modelling is limited to a few relatively well investigated substances. Even where information is available, it may be difficult to validate and the extent of between species or between strain variability may be highly uncertain. Where the carcinogenic process is only partially understood it may be possible to develop alternative models that provide an equally good fit to the data within the observed dose range but give very different estimated impacts at low levels of exposure. In addition, if a sufficiently large number of parameters are included, it is possible to develop a plausible model to fit any given dataset and the goodness of fit to observed data is not necessarily informative about model reliability. To this extent,

toxicodynamic modelling may offer no advantage over more straightforward empirical curve fitting. Toxicodynamic modelling is unlikely to become widely applicable to a wide range of substances until methods are developed that allow for the rapid and inexpensive quantification of substance specific key steps in a widely applicable model of carcinogenesis.

## 2.5 QUANTITATIVE RISK ASSESSMENT BASED ON NONLINEAR EXTRAPOLATION

### 2.5.1 Overview

In the absence of mode and mechanistic data and a mechanistic understanding of the process, empirical modelling (curve fitting) may be used to generate the best fit function for the available data. This best fit function can then be used to estimate cancer risks outside of the original dose range. Scaling factors are used to convert from animal data to human equivalent doses. Many different curve-fitting models have been developed but there is insufficient evidence to determine which are most appropriate for use in cancer risk estimation. For a given dataset, several different curves may provide an equally good fit to experimental observations but give widely variable estimates of cancer risk at lower exposure levels.

A nonlinear extrapolation method is most appropriate where there are sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses but with not enough data to support a toxicodynamic model that may be either nonlinear or linear at low
doses.

### 2.5.2 Data requirements

The data requirements are similar to those required for other approaches to cancer risk assessment ie high quality human epidemiological data or multiple dose animal data. In contrast to other quantitative assessment methods, however, there should be sufficient data points (dose levels) to allow a series of models to be tested leading to the identification of the best fit curve.

### 2.5.3 Calculation methods

A variety of models can be used to curve-fit experimental data and in some circumstances the choice of model will be determined by an understanding of the mode/mechanisms leading to carcinogenesis. The US EPA recommend that for cases where the tumours arise through a nonlinear mode of action an oral reference dose or an inhalation reference concentration, or both, should be developed, taking into consideration the factors summarized in the characterization of the POD. The reference value calculations for cancer should be compared with those for other health effects. For effects other than cancer, EPA reference values have traditionally been based on the assumption of biological thresholds, although this assumption is no longer made because of the difficulty of empirically distinguishing a true threshold from a dose-response curve that is nonlinear at low doses.

Quantitative data on precursor events can be used in conjunction with, or instead of, data on tumour incidence to extend the dose-response curve to lower doses, although

rates of molecular events such as mutation or cell proliferation or signal transduction may be difficult to relate to wider tissue changes.

The EPA use an empirical procedure to curve fit data that models incidence (tumours or precursor effects), corrected for background, as an increasing function of dose. Additional judgments and analyses are used when the procedure fails to yield a good model fit. For example, the highest dose may be omitted where it is judged that the highest dose reflects competing toxicity that is more relevant at high doses than at lower doses. Models that include time-to-tumour or time-to-event information may be useful when there are large differences in survival across dose groups

### 2.5.4 Uncertainties

The main source of uncertainty is relation to the appropriateness of the model selected for low dose extrapolation and its likely goodness of fit at exposure levels that are much lower than the observed data range.

### 2.5.5 Advantages and disadvantages

Although this approach appears superficially to be more “scientific” than just drawing a straight line from the POD to the origin, it is subject to relatively greater uncertainties. Given the small number of doses used in rodent cancer bioassays (typically only about 3), several types of function may describe the experimental data equally well but the extrapolation of the different functions to low dose may provide widely variable estimates of risk. In the absence of a clear biological argument to support the use of one type of function as opposed to another, there is a consensus view that the uncertainties arising from nonlinear function are relatively greater than if a simple linear function is used. The US EPA advise that where nonlinear modelling is undertaken, the results of linear extrapolation should be presented for comparison.

## 2.6 MARGIN OF EXPOSURE APPROACH

### 2.6.1 Overview

The MOE approach to managing cancer risks associated with exposure to carcinogens is being adopted by an increasing number of regulatory authorities who are required to develop regulation and guidance intended to protect human health. The MOE approach is being applied to workplace exposure, exposure in food and consumer goods and environmental exposures.

The MOE approach involves establishing a benchmark dose (BMD) for substance and effect – normally the lower $95^{th}$ percentile bound on the estimated dose associated with a 10% response level ($BMDL_{10}$ – benchmark dose low). The MOE is the ratio of the projected level of human exposure (in this case in the workplace) to the benchmark dose. The larger the MOE, the smaller the inferred risk to health. An exposure associated with a small MOE is likely to be of concern and worthy of further investigation and if possible reduction. If the MOE is very large, then no further exposure controls are likely to be required. The MOE approach has primarily been developed for risk assessments based on data from animal experiments, although a similar approach could be also be used where there are human exposure-response data available from epidemiological studies.

The BMD approach has been developed particularly by Crump (1984, 1995) and the EPA (1995). Within the EU level the MOE approach has been adopted by the European Food Safety Panel (EFSA, 2009) and was used to assess the level of concern associated with exposures to aflatoxins (2007), ethyl carbamate (2007) and PAHs (2008). This was in line with the earlier adoption of the MOE approach by the international Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006). More recently the EU's Scientific Committees on Health and Environmental Risks, Consumer Products and Emerging and Newly Identified Health Risks have also endorsed the MOE approach. They have also however endorsed the use of linear extrapolation for the purposes of cost benefit analysis and where appropriate the use of the "Threshold of Toxicological Concern".

The MOE approach is also being used by Member States in some areas of regulation but not necessarily for occupational exposure. In the UK, the Department of Health (DH) expert committee COT have advocated the use of an MOE approach for risk management but ALARP remains the preferred approach for workplace exposures. The Environment Agency for England and Wales is starting to use an MOE approach in some of its work.

### 2.6.2 Data requirements

The MOE approach requires a good toxicological database from which a benchmark dose can be developed. The MOE approach also requires an understanding of relevant levels of human exposure. Ideally experimental data should be available from lifetime carcinogenicity studies in at least two species over a range of doses with excess tumour incidences occurring at more than one dose level in each species.

### 2.6.3 Methods

Conventional mathematical models are used to obtain dose-response curves for modelled toxicological endpoints without the assumption of linearity in the low-dose region (although the way in which BMDs are interpreted during the assessment of risks associated with low levels of exposure may effectively involve linear extrapolation from high dose experiments). Where the underlying nature of the relationship between exposure and response is not well understood, several different models should be used to calculate BMD in order to avoid introducing bias, although assuming a particular type of a relationship. The use of multiple models gives rise to a range of different BMD values by model type, although normally these values would be similar.

The US EPA have assembled a suite of standard models that they recommend for use in developing a BMD and made these available within a software package that can be freely downloaded from the internet (BMDS). BMDS allows entry of dose and incidence data into worksheet and calculation of the BMD and BMDL using the model suite available: multistage, multistage cancer, gamma, logistic, log-logistic, probit, log-probit, Weibull and the Quantal Linear Model. The software default is to calculate $BMD_{10}$, but it is possible to select any target incidence eg calculation of $TD_{25}$. The outputs from the model include information on goodness of fit.

BMDS uses the Pearsons chi-squared test to determine goodness of fit for modelled curves. The test establishes how well the theoretical distribution on which the fitted curve is modelled described the observed data. The chi-square statistic is calculated by finding the difference between each observed and theoretical frequency for each possible outcome, squaring them, dividing each by the theoretical frequency, and

taking the sum of the results. A second important part of determining the test statistic is to define the degrees of freedom of the test: this is essentially the number of observed frequencies adjusted for the effect of using some of those observations to define the "theoretical frequencies". The US EPA (2006) recommend a minimum goodness of fit p value of 0.1 for model acceptance.

The comparison of different models and selection of the model for BMD calculations can be based on the Akaike Information Criterion: a tool for model selection that determines how well the data support each model. In practice a number of unrelated models (eg logistic and probit) may provide a similar goodness of fit for an individual data set.

### 2.6.4 Sources of uncertainty

The benchmark dose can be calculated using different models which may make a significant difference to value selected. There are uncertainties in the determination of BMD associated with the selection of the most appropriate model.

### 2.6.5 Advantages and Disadvantages

The MOE approach to risk management offers a number of benefits:

> It is relatively easy to communicate risks in terms of exposures being controlled to a small fraction of a benchmark dose that has been calculated to give rise to a 10% risk in an experimental study.
>
> It avoids the uncertainties associated with extrapolation from high dose study data to dose levels that are orders of magnitude smaller and the false sense of precision that may be conveyed when cancer risks are calculated by extrapolation from study data.
>
> It avoids the requirement to make assumptions about the shape of the dose response function at exposure levels below those for which observational data exist. In practice there is a tendency to treat the exposure-response function as linear.

The requirement to understand how human exposure arises can be a major barrier to implementation of the MOE approach in some circumstances. For example, for the purposes of risk management for human health risks arising from contaminated soils, the potential for human exposure to carcinogenic contaminants can be highly uncertain. In contrast, it is usually relatively straightforward to measure exposure to contaminants in workplace air, although the assessment of exposure by skin contact and/or inadvertent ingestion is more uncertain. For substances and industries where these routes of exposure are likely to be significant in comparison to exposure in workplace air, this may lead to difficulties in determining an appropriate MOE for exposures in air. In addition to uncertainty about how much exposure occurs by different routes, there may also be uncertainty as to the extent of absorption and metabolic fate associated with different exposure routes.

Disadvantages of the MOE approach include uncertainty about the interpretation of the MOE under different circumstances. For example, in assessing risks associated with exposure to substance in workplace air, a larger MOE is likely to be required where the

benchmark dose has been established in an animal feeding experiment than where it has been established in a study of workers exposed via inhalation

Using $BMDL_{10}$ as the basis for calculating an MOE may not be appropriate for small data sets as the statistically derived 95% lower confidence limit on the dose-response curve may be substantially lower than the median estimate of $BMD_{10}$.

There are likely to be difficulties where the calculated MOE falls on the boundary between being or not being of concern and the ranking also implies a level of precision that may not exist in the source data used in the calculation of BMD. It seems likely that a smaller MOE would be acceptable for workplace exposure than for involuntary exposures experienced in the wider environment.

A further important disadvantage for the purposes of regulation is that the MOE approach does not lend itself to the quantification of potential impacts. Given the requirement for regulatory impact analysis and the desirability of demonstrating that proposed regulation will lead to a net benefit, it is important to be able to quantify the health benefits of a proposed measure and, for non threshold genotoxic carcinogens, this is likely to require the application of quantitative risk assessment.

### 2.6.6 Other comments

Despite the important conceptual difference in approach to standard setting based on a MOE or QRA approach, there may be little practical difference in the outcome of the two approaches. Given that QRA most commonly employs linear extrapolation from an identified lower benchmark dose, an environmental limit based on a calculated cancer risk of $10^{-5}$ is likely to be similar to that based on the calculated dose associated with a 10% cancer risk and an MOE of 10000. In adopting an MOE approach for regulatory purposes, it would be appropriate to provide guidance on the calculation of benchmark dose. This should define both the models to be employed and the criteria by which the benchmark dose should be selected from several candidate values.

## 2.7 $T_{25}$

### 2.7.1 Overview

The $T_{25}$ (or $TD_{25}$) is the chronic dose rate that would result in 25% of exposed animals developing tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life-time of that species. $T_{25}$ has been used within the European Union for setting specific concentration limits for carcinogens in relation to labelling of preparations (formulations). Dybing et al (1997) proposed the use of $T_{25}$ as a simple index of carcinogenic potency for use in carcinogen classification systems. They reported that calculated $T_{25}$ values of a set of 113 US National Cancer Institute/National Toxicology Program (NC/NTP) carcinogens showed excellent correlation (correlation coefficient 0.96, $P < 0.0001$) with the carcinogenic potency index $TD_{50}$ of Peto et al (1984). The mean of $T_{25}$ values for 51 transspecies, multiple common site NCI/NTP carcinogens were 10-fold lower than those for 62 NCI/NTP single species, single site carcinogens. For these 113 carcinogens, the mean $T_{25}$ values were approximately 3-fold lower for agents that were also mutagenic in Salmonella compared to the non-mutagenic agents.

### 2.7.2 Data requirements

The data requirements are essentially the same as for the calculation of a benchmark dose to support a MOE based risk assessment.

### 2.7.3 Calculation method

Calculation involves curve fitting the data and estimating the $T_{25}$ on the basis of the curve that gives the best fit to the data. A number of software packages exist for curve fitting (for example, the EPA's BMDS) and the use of different packages will lead to small differences in the estimated value of $TD_{25}$. Alternatively, Sanner et al (2001) describe the calculation of $T_{25}$ as a simple proportion of the dose giving rise to an incidence of tumours in an experiment that is closest to 25% (for example $T_{25}$ = 83.3% of the dose giving rise to a tumour incidence of 30% or 125% of the dose giving rise to a tumour incidence of 20%). If several different $T_{25}$ values can be calculated from the available data, the lowest available value is selected for the purposes of risk assessment.

The $T_{25}$ is most commonly reported without being rescaled to a human equivalent dose and may be used in risk assessment without rescaling. Various scaling factors have been used by different agencies to convert to human equivalent doses for the purposes of extrapolation to low dose exposure. Sanner et al (2001) discussed the use of the dose-descriptor $T_{25}$ as a basis for quantitative risk characterisation of non-threshold carcinogens. For the purposes of risk estimation, $T_{25}$ should be converted to the corresponding human dose descriptor (expressed in mg per kg body-weight per day), $HT_{25}$, by dividing it with the appropriate interspecies scaling factor based on comparative metabolic rates. The predicted human dose should be based on available exposure data. The human life-time cancer risk can be estimated using linear extrapolation by dividing predicted exposure levels with the coefficient ($HT_{25}$/0.25). The method is essentially that has been subsequently adopted for the derivation of DMELs under REACH.

### 2.7.4 Advantages and disadvantages

The $T_{25}$ is a simple concept to communicate, relatively simple to calculate and is associated with a relatively high level of confidence as it falls well within range of original data. Sanner et al (2001) claim that risk estimates derived using this method show excellent agreement with results from computer-based extrapolation methods such as the linearised multistage model and the benchmark method using $LED_{10}$. Estimates of the dose associated with a $10^{-5}$ cancer risk derived from $T_{25}$ for 33 three substances were between 0.9 and 2.3 times those derived using the linearised multistage model. The simple calculation method proposed by Sanner et al (2001) is, however, less of an advantage now than it was at the time their paper was published. The BMDS programme is readily available for free download and can be readily run on a personal computer.

$T_{25}$ has already been used for risk evaluation in the EU and represents a familiar quantity. $BMD_{10}$ and $BMD_{05}$ have however, been more widely used in recent risk assessments that have taken an MOE approach. Given that $T_{25}$ and BMD values are generated through curve fitting, it follows that $T_{25}$ is not numerically equivalent to 2.5 times $BMD_{10}$ or 5 times $BMD_5$. Currently both $T_{25}$ and BMDs are used as PODs for linear extrapolation, for example, in the derivation of DMELs, which could give rise to

small differences in estimated risk level, although the impact is no greater than the uncertainty arising from the use of different methods for interspecies scaling.

## 2.8 DERIVED MINIMUM EFFECT LEVEL (DMEL)

### 2.8.1 Overview

The REACH Regulation is intended to reduce exposure to hazardous chemicals including carcinogens. Under REACH, carcinogens are likely to become subject to "restrictions" on use and suppliers will have to apply for "authorisation" in order to supply a carcinogen for specified uses until a replacement technology or substance is in place. The authorisation and restriction of carcinogens will take account of socio-economic factors. While the REACH regulation is intended to lead to the eventual phase out of carcinogens from use, it also allows for the identification of tolerable levels of exposure for nonthreshold carcinogens based on Derived Minimum Effects Levels (DMELs) which are comparable to the Derived No Effects Levels (DNELs) that are to be an important tool in control of exposure to substances with a threshold of effect.

### 2.8.2 Calculation

The guidance for REACH indicates that for non-threshold carcinogens, the BMDL is the most appropriate starting point for the calculation of a derived minimum effect level (DMEL). Expert judgement and a weight evidence approach are advised for the selection of an appropriate BMDL where several alternatives exist. Two approaches to developing a DMEL are suggested: either the estimation of the exposure associated with a $10^{-5}$ (or $10^{-6}$) cancer risk based on the BMDL and a scaling factor of 10000, or an approach based on $T_{25}$ and a scaling factor of 25000. Both methods are based on the "large assessment factor" that has been used by EFSA. The assessment factors suggested in the REACH guidance for calculation of a DMEL (ECHA, 2008) are listed below.

| Assessment factor | | Default value |
|---|---|---|
| Interspecies | Differences in metabolic rate per body weight | AS* |
| | Remaining differences | 2.5 |
| Intraspecies | General population | 10 |
| Dose-response | Issues related to the reliability of the source data including extrapolation from LOAEL and severity of effect | 10 (BMDL is not a NOAEL) |
| Quality of whole database | Issues related to completeness and consistency of available data | 1 |
| | Issues related to the reliability of alternative data | 1 |
| Nature of carcinogenic process | | 10 |

*species specific allometric scaling factor

In comparison, the calculation of a DNEL is based on an observed no adverse effects level in animals (NOAEL) and a series of assessment factors to allow for interspecies differences and intraspecies differences in susceptibility to effects (Table).

| Assessment factor – accounting for differences in: | | Default value systemic effects | Default value local effects |
|---|---|---|---|
| Interspecies | - correction for differences in metabolic rate per body weight | AS[a, b] | – |
| | - remaining differences | 2.5 | 1[f]<br>2.5[g] |
| Intraspecies | - worker | 5 | 5 |
| | - general population | 10[c] | 10[c] |
| Exposure duration | - subacute to sub-chronic | 3 | 3[h] |
| | - sub-chronic to chronic | 2 | 2[h] |
| | - subacute to chronic | 6 | 6[h] |
| Dose-response | - issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect | 1[d] | 1[d] |
| Quality of whole database | - issues related to completeness and consistency of the available data | 1[d] | 1[d] |
| | - issues related to reliability of the alternative data | 1[e] | 1[e] |

[a] AS = factor for allometric scaling (see Table R. 8-3)
[b] Caution should be taken when the starting point is an inhalation or diet study
[c] Not always covering for very young children; see text for deviations from default
[d] See text for deviations from default
[e] Special consideration needed on a case-by-case basis
[f] for effects on skin, eye and GI tract via simple destruction of membranes
[g] for effects on skin, eye and GI tract via local metabolism; for effects on respiratory tract
[h] for effects on respiratory tract.

### 2.8.3 Sources of Uncertainty

The permitted use of either $TD_{25}$ or $BMD_{10}$ as a starting point for linear extrapolation to a risk of $10^{-5}$ gives rise to a slight uncertainty as $TD_{25}/25000$ will not normally be numerically equivalent to $BMD_{10}/100000$, although the difference may in practice be small in comparison to other sources of uncertainty.

### 2.8.4 Advantages and disadvantages

The calculation of a DMEL is relatively straightforward and the adoption of REACH is intended to harmonise the approach to managing chemical risks across the EU.
The DMEL approach implies a risk acceptance criteria of a lifetime cancer risk of $10^{-5}$ which is considerably smaller than the risk levels associated with existing OELs for carcinogens within the EU, individual EU states or elsewhere in the world. The methodology developed in the REACH guidance for the derivation of tolerable levels of exposure, implies a much lower level of tolerable risk than has been traditionally accepted in the workplace for both carcinogens and noncarcinogens (see box below).

**Comparison of DNEL for 1,1,1 Trichloroethane with published exposure limits**

8 hour TWA: ACGIH TLV = 350 ppm and UK WEL = 100 ppm

**NOEL in humans** (behavioural effects/eye irritation 250 ppm)
Allow x 5 for intraspecies variation, **DNEL = 50 ppm**

**NOEL in rats** (kidney lesions) 300 mg/kg/day in long term experiments (ingestion)
Allow interspecies scaling factor of x4 (REACH guidance), equivalent intake for 70 kg adult would be 5250 mg
= intake from exposure to 525 $mgm^{-3}$ as 8 hour TWA
Allow x 2.5 for interspecies variation, x5 for intraspecies variation, x5 for differences in exposure route
**DNEL = 8.4 mgm-3 = 1.4 ppm**

## 2.9 THRESHOLD OF TOXICOLOGICAL CONCERN

### 2.9.1 Overview

The threshold of toxicological concern (TTC) is defined by the EU Scientific Committees (2008) as the threshold human exposure for daily uptake of a chemical below which there is no appreciable risk to human health. The approach identifies a safe level of exposure for chemicals based on their chemical structure and the known toxicity of substances which share similar structural characteristics (SCCP, 2008). The TTC is used within the EU in relation to oral exposure to food contact materials and genotoxic impurities in pharmaceuticals. Its use is being explored in relation to other sources of exposure to carcinogens including medical devices, industrial chemicals and chemicals in the environment.

### 2.9.2 Data requirements

The TTC approach requires sufficient data to be available to be able to demonstrate an absence of measurable risk to health at the TTC. Ideally the data should be derived from human epidemiological studies. If only animal data are available, there should be sufficient supporting data to demonstrate relevance to human health risk assessment and also to support dose extrapolation to human exposure.

### 2.9.3 Calculation method

The existence of a TTC requires statistical evidence of an absence of a significant risk to health, essentially the no observed adverse effects level (NOAEL). A series of “assessment factors” (also termed uncertainty factors) are then used to derive an exposure guideline at which no adverse effects would be expected. This approach has been enshrined in the guidance for chemical risk assessment for the purposes of implementing the new EC guidance on Registration, Evaluation and Authorisation of Chemicals (REACH), but has also been widely used by regulatory authorities elsewhere. Examples include the derivation of minimal risk levels by ATSDR and reference doses by the US EPA. Uncertainty factors are allowed for interspecies and

interindividual variability in susceptibility to an agent, possible differences in potency and effects following exposure by different routes, less than lifetime exposure to an agent in the experimental or epidemiological study. Where dose information is based on animal data, different agencies have used different scaling factors to account for species differences in metabolic rate.

In practice the TTC concept has mostly been used where the potential levels of exposure to carcinogens are extremely low (eg 0.5 ppb in food) such that even in the absence of detailed toxicological information, there is a high level of certainty that the cancer risks associated with a compound of relatively high potency would be extremely small.

### 2.9.4 Sources of uncertainty

It is difficult to reliably detect the presence or absence of an excess risk of cancer in workers or in an animal experiment at low levels of exposure where the expected incidence rate is low. The sensitivity of a study to detect excess risks at low levels of exposure will depend on the study size.

If the TTC is based on human data, there are likely to be considerable uncertainties in the underlying exposure data. Under estimation of exposure (eg assuming regulatory compliance) could lead to the TTC being established at a relatively low level. If the investigation of exposure-response relationships has been limited to considering fairly broad bands of exposure with arbitrarily defined boundaries, the absence of excess cancer risk in a particular group does not necessarily mean that there would be an absence of risk at the highest exposure level within that group. If the TTC is based on animal data, there may be a substantial gap between levels of exposure at which tumours are observed and the apparent no effects level.

### 2.9.5 Advantages and disadvantages

This approach is simple and easy to use but for many substances there are insufficient robust data that could be used to confidently identify a TTC. There are few substances for which there are sufficient human data to be able to confidently derive a TTC below which no significant cancer risk would be expected. However, like the MOE discussed earlier, it is very useful as a pragmatic tool in food risk assessment where there may be many unavoidable contaminants present in very low, even trace amounts, and a degree of reassurance is required by the general public. The no observed effects level (NOEL) for cancers in an animal experiment would not normally be considered a suitable starting point for human risk assessment for genotoxic carcinogens because of the relatively small numbers of animals (usually 50 of either sex) in each dose group. It is arguable that cancers might have been observed at lower levels of exposure, had a greater number of animals been used.

If sufficient data are available to establish a TTC, the numbers of people exposed above the TTC and the extent to which the TTC is exceeded can be used to inform the prioritisation of control measures by regulators or industry. For a proposed control measure such as an OEL, a limited cost benefit analysis can be conducted through consideration of the numbers of exposed individuals who would be exposed to more than the TTC without the measure versus the number exposed with the measure. The approach does not, however, enable direct calculation of the number of cancer cases avoided. Some estimate of the potential number of cases avoided could be made

based on the incidence of cancer associated with current/historical levels of exposure and the likely impact of the proposed measure in reducing exposure levels.

The TTC approach has clear advantages in respect to communication of risk and in the establishment of an appropriate level of control. The demonstration that a given level of exposure does not give rise to an observed cancer risk in humans is considerably more reassuring for many people that the concept of controlling exposure to a level that is much lower than that associated with effects in animals. The TTC can be readily justified to industry as a reasonable level to control exposures to. In addition, given that the TTC may be at a much higher level than any control limit based on animal data, the application of the TTC approach may mean that over stringent and expensive control measures can be avoided.

## 2.10 PRACTICAL THRESHOLD

### 2.10.1 Overview

Some genotoxic carcinogens appear to have a practical threshold below which there is no observable increase in cancer risk. The concept is very similar to that of Threshold of Toxicological Concern but the supporting evidence for a practical threshold is subtly different from that required to underpin a TTC.

A practical threshold can be established where there are mode/mechanistic data that indicate that the development of cancer only occurs subsequent to some other pathological change. For example, the development of nasal cancer following exposure to formaldehyde is a secondary consequence of developing nasal irritation and an OEL set to prevent nasal irritation will also protect against cancer. SCOEL have recently proposed an IOELV for formaldehyde based on eye irritation which occurs at a lower level than nasal irritation and thus affords a greater level of protection to exposed workers.

A practical threshold may also be based on toxicokinetic considerations. For example, saturation of a specific metabolic pathway may lead to a substance passing into general circulation that is normally largely inactivated by metabolism or it may lead to the formation of carcinogenic metabolites. Provided exposures are controlled to levels below which such saturation occurs, then cancer would not be expected to develop. Similarly a substance may be metabolised to substances that are naturally present in the body and no excess cancer risk would be anticipated, provided that normal endogenous levels of these substances are not substantially exceeded. Vinyl acetate, for example, produces tumours at the site of application in rodents after exposure by inhalation or the oral route. It is hydrolysed to formaldehyde and acetic acid instantaneously on contact which are both endogenous compounds of $C_1$-metabolism by folic acid. Provided that endogenous levels of these substances remain within normal bounds, no excess cancer risk would be expected (Bolt and Huici-Montagud 2008).

SCOEL have advocated the identification of practical thresholds as a tool for use in the setting of OELs for genotoxic carcinogens where there are sufficient mechanistic and/or toxicokinetic data. It seems probable that the number of substances for which practical thresholds can be established will increase with increasing understanding of carcinogenesis and the mechanisms by which individual substances cause cancer.

### 2.10.2 Data requirements

This approach is only appropriate for carcinogens for which it is possible to demonstrate that at low levels of exposure the substance is completely metabolised to harmless metabolites and such that the target organ is effectively unexposed to the carcinogen or that cancer only occurs as a secondary response to an earlier pathological change. Sufficient data are required to establish the exposure level associated with saturation of the low dose metabolic pathway or the threshold level of exposure associated with the pathological change that may eventually lead to cancer.

Ideally the demonstration of a practical threshold would be based on human data. If only animal data are available, there would be an additional requirement to demonstrate relevance to human exposure.

### 2.10.3 Calculation method

The data manipulation required to demonstrate the existence of a practical threshold is likely to depend on the substance. If cancer follows an earlier pathological change for which a threshold exists, an analysis of relevant epidemiological or experimental data would be required to establish a no effects level or lower benchmark dose. The setting of an OEL would have to take account of whether the source data were from animal or human experience and the relevance of the study exposure conditions to workplace exposure (route, duration, magnitude). If the practical threshold results from toxicokinetic considerations, then modelling would be required to establish the levels of exposure leading to metabolic processes giving rise to significant systemic exposure to the carcinogen itself or carcinogenic metabolites. Confident determination of a toxicokinetic threshold is likely to require a substantial quantity of experimental data.

### 2.10.4 Sources of uncertainty

The sources of uncertainty in identifying a practical threshold include the impact of study size on the apparent no effects level of exposure for a precursor pathological condition or giving rise to the toxicokinetic pathways that may result in carcinogenesis.

### 2.10.5 Advantages and disadvantages

The advantages of a practical threshold are similar to those of TTCs in terms of risk communication and management. In addition, a practical threshold may be more strongly underpinned by evidence than a TTC giving greater reassurance about the level of control required and a better balance between the cost and type of control measures versus potential cancer risk. It is also possible to calculate the number of individuals whose exposure would be reduced below the practical threshold in order to inform cost benefit analysis. The approach does not provide information about the benefits, if any, of reducing exposure levels but only to levels above the threshold. Given that there will be a distribution of exposures around mean levels; however, it would be possible to estimate the impacts of reducing mean exposure in terms of the increased proportion of workers will exposure levels below the practical threshold. Another factor to be taken into account is the slope of the dose response curve, if a precursor pathological event is used as a point of departure for OEL setting. If the dose response curve is very steep, then a larger uncertainty factor may be appropriate.

## 2.11 ALARP

### 2.11.1 Overview

The “as low as reasonable practicable” (ALARP) approach has been traditionally used for managing the risks associated with exposure to carcinogens and a wide range of other types of risk within the UK. This approach makes no attempt to quantify risk levels but focuses on the means and measures that are available and suitable for minimising exposures and the associated risks. The approach requires identification of appropriate technical measures and consensus as to balance of socio-economic costs of implementing control measures versus the risk of disease or injury. There is an implicit acceptance of some unspecified level of risk to health which is believed to be outweighed by the economic and social benefits of the continued use of the substance. The ALARP approach has been applied across a wide range of regulatory activities in the UK but has been championed by the Health and Safety Executive (HSE) and scientifically underpinned by the independent UK expert committees, the Committee on Carcinogenicity of Chemicals on Food, Consumer Products and the Environment and the Committee on Mutagenicity of Chemicals on Food, Consumer Products and the Environment (www.advisorybodies.doh.gov.uk/pdfs/mut0702.pdf).

### 2.11.2 Data requirements

In principle an ALARP approach could be applied in the absence of any data. In practice, exposure measurements are required to demonstrate that exposures are well controlled and remain well controlled.

### 2.11.3 Calculation method

The application of ALARP does not in itself require calculations to be undertaken. In practice, however, an ongoing review of exposure levels is required to prevent any long term upwards drift in exposure. The application of ALARP requires agreed good practice in order to ensure that exposures are controlled to the standard implied by ALARP.

### 2.11.4 Advantages and disadvantages

The ALARP approach is pragmatic and simple to implement. It avoids regulators and industry being drawn into long complex discussions involving difficult science and a large number of uncertainties thus enabling relatively rapid implementation of protective measures. It is relatively straightforward to develop and police “best practice” in order to ensure that the risks to workers’ health are controlled, although the extent of protection conferred by “best practice” will be uncertain. The ALARP approach can also be implemented in the absence of high quality toxicological data and detailed understanding of exposure-response relationships.

The major short coming in ALARP is that in the absence of risk quantification, it is impossible to demonstrate that the benefits arising from implementation of the control measures outweigh the costs. Cancers typically take years to develop and therefore there will a substantial time gap between the implementation of exposure reduction measures and any associated reduction in cancer cases. If control measures are inadequate, it will be several years before it becomes apparent that cancer rates in exposed workers have either not declined to background rates or even increased. In the absence of effects quantification, the choice of an appropriate level of control is to

some extent arbitrary and it will unclear as to whether the adopted level of control will be adequate for the protection of health.

The “as reasonably practicable” element of ALARP implies that some account should be taken of cost and therefore that ALARP would not necessarily lead to the best possible control measures being implemented. In the absence of effects quantification, however, it may be difficult to establish whether costs were excessive. In addition, regulators may find themselves hostage to the views of industry who may have low threshold at which costs are perceived as excessive.

The ALARP approach takes no account of potency and provides no means for comparison between substances that would enable regulatory authorities or industry to identify priority substances or exposures for improved measures for exposure control.

An unintended outcome of the use of the ALARP approach for managing workplace risks in the UK is that workplace exposure limits may not be set for substances of known high hazard where risks are uncertain. UK workplace exposure limits (WELs) are set at levels believed to represent “no risk” to workers’ health. Where risks are uncertain and not quantified, it is not possible to determine a level of exposure that gives rise to an “acceptable” risk. The HSE have withdrawn a number of workplace exposure limits that were believed to be inadequately protective and have not set WELs for many substances for which the level of exposure representing “no risk” has not been established. Unfortunately the majority of people interpret the absence of a WEL to indicate an absence of hazard.

The ALARP approach will not be sufficient for the purposes of REACH. Under REACH, industry will be required to phase out the use of carcinogens and other “substances of very high concern” or present a socio-economic case to support their continued use. The development of a socio-economic case will require effects quantification.

# 3 REVIEW RISK CRITERIA USED IN THE MANAGEMENT OF WORKPLACE RISKS

## 3.1 INTRODUCTION

This section reviews the risk acceptance criteria that are applied in the control of workplace and other types of risk in the EU, its member states and elsewhere, with specific reference to carcinogens. The final part of this section considers how approaches to risk quantification and management may affect risk tolerance. For example, the use of cost-benefit analysis to inform the setting of OELs or other types of exposure limit may lead to a much high level of risk tolerance than where straightforward quantitative risk criteria are applied.

## 3.2 CRITERIA CURRENTLY APPLIED IN CONSIDERATION OF WORKPLACE RISKS WITHIN THE EU AND ELSEWHERE

The setting of OELs at EU level is informed by recommendations made by the Scientific Committee on OELs (SCOEL). Although SCOEL recommend that the setting of OELs for nonthreshold genotoxic carcinogens should be informed by quantitative risk assessment, they do not provide guidance on risk acceptability. The actual level at

which OELs are set at EU level is subject to agreement between the EC and representatives of employers and employees through the operation of consultation with the Advisory Committee on Safety and Health at Work (ACSH). In this way the socioeconomic costs and benefits of setting OELs can be account of in the development of an appropriate OEL. The quantitative estimates of excess cases of cancer at various levels of exposure and produced by SCOEL are used as part of the basis on which these latter discussions can take place.

In the guidance on the derivation of DMELs developed by ECHA for the purposes of the implementation of REACH, it is indicated that although there is no formal definition of "tolerable risk" within the EU, a lifetime cancer risk of $\leq 10^{-5}$ is generally considered to be indicative of a tolerable risk in the context of workplace exposure. The suggested approach to calculating a DMEL actually leads to the derivation of an exposure level with a MOE of 10000 in comparison to $BMDL_{10}$ or 25000 in comparison with $TD_{25}$, rather than strictly an exposure level associated with a calculated $10^{-5}$ cancer risk. The EU has, however, been previously reported to define acceptable risk less as being only 1000 times lower than the $T_{25}$ (Seeley et al, 2001), ie an estimated cancer risk of 2.5 x $10^{-4}$.

The European Agency for Safety and Health at Work (European Risk Observatory, 2009) reported that only 2 EU countries have a formal numerical definition of "acceptable risk".

Under most regulatory regimes within the EU, OELs are agreed between regulator (government) and representatives of employers and employees and in some countries such as Germany, the insurance industry is also involved. Italy differs from other regimes in that OELs (for substances for which IOELVs or BOELVs have not been established) are agreed between unions and employers in individual industry sectors. Several countries have recently reviewed their system for setting to OELs and in the Netherlands this has led to major change in regime with OELs for most substances being determined at individual company level. This is essentially what will result for most substances under the REACH regulation. Although regulatory OELs are primarily health-based, in most EU countries that set their own OELs, they also take account of the feasibility of implementation. OELs for carcinogens are likely to be set at level that is achievable in the majority of workplaces and the level of protection to health varies substantially between substances. OELs are not generally expressed in terms of specific levels of risk but are instead described in qualitative terms referring to minimisation of cancer risk. Historically only the EU and the Netherlands have set OELs for genotoxic carcinogens that related to specified risk levels whereas other member states have based their limits on technical feasibility (Seeley et al, 2001). A number of EU countries use the American Conference of Governmental Industrial Hygienists Threshold Limit Values (TLVs) as a basis for their national OELs. TLVs are intended to be entirely health-based and not take account of practicability. The level of protection offered by TLVs for different substances is, however, extremely variable and there is likely to have been some implicit consideration of existing exposure levels (and thus feasibility of control measures) in their determination.

QRA is currently used to inform the setting of OELs for genotoxic carcinogens in the Netherlands. An additional risk of cancer of $>10^{-4}$ per substance per year is considered as the target level (one extra death from cancer each year per million exposed employees). OELs may be set at higher levels if it is not technically feasible to reduce exposures to the target level. OELs for these substances are reviewed every 4 years in

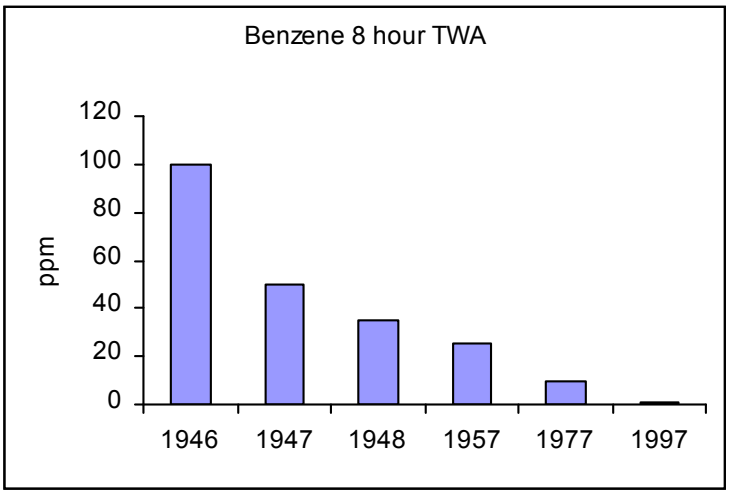
order to assess whether any additional measures are available to further reduce exposure.

In Poland, risk levels for OELs of between $10^{-3}$ and $10^{-5}$ have been deemed socially acceptable. For an individual substance, the decision making body chooses one of two proposed OELs based on risk levels of $10^{-3}$ and $10^{-5}$.

In Germany OELs for substances where no threshold of effect has been established were traditionally based on technical feasibility and represented levels of exposure that should be readily achievable using available measures and good practice. Risk was only indirectly considered as part of the decision process as the costs of implementation of the OEL had to be balanced against the potential number of cases of illness leading to compensation that may result from a given level of exposure. The MAK did, however, have a system for classifying occupational carcinogens into 5 classes; the first three based on hazard and the last two based on risk (Greim and Reuter, 2001). Germany has recently developed a risk based approach to deriving OELs for carcinogens based on quantified risks. Three risk bands are identified (high, medium and low) and these are linked to substance-independent control measures that are graded according to risk band. The upper limit (tolerable) (additional) cancer risk for workplace exposure, 8 hours/day, 240 days/year over 40 years was set at 4:1000 and the lower limit (acceptable risk) was set at 4:100,000, to be achieved by 2018. An interim target of 4:10,000 to be achieved by 2013 has also been set. In deriving these limits, the risks of a fatal work accident (3:1000 to 4:10,000, depending on occupation) and of a non-smoking adult developing lung cancer (about 4:1000) were taken into account (Wriedt, 2008).

In the UK, there is no numerical definition of acceptable risk levels in the workplace and a general reluctance to quantify acceptable risk. In considering the tolerability of risk arising from nuclear power plants, the HSE (1992) has indicated that the upper bound for risk tolerability in relation to death from workplace exposures is $10^{-3}$. Although more recent guidance (eg HSE, 2001) has avoided explicitly quantifying tolerable risk, $10^{-3}$ is still implicitly regarded as the upper bound of tolerability for lifetime risks of mortality arising from workplace causes. The 2001 guidance also implies however that the tolerable risk for death from cancer is likely to be lower than for death from other causes because of the specific dread that is associated with cancer. For environmental exposures, a lifetime cancer risk of $10^{-5}$ has been widely used in the setting of index doses for the purposes of setting guideline values for soil contaminants and the use of a benchmark dose and MOE approach to risk assessment (Defra, 2008).

ACGIH does not have a formal definition of risk acceptability and close inspection of their TLVs indicates the values for individual substances are associated with greatly varying levels of risk. For some carcinogens, TLVs have been set at levels at which the no excess risk of cancer has been observed in human or in animal studies. Other TLVs have been set at levels where no excess risk expected on the basis of modelling. A number of TLVs have been set at a low level without explicit explanation of why that particular concentration was selected. In general the level of risk associated with TLVs increases with time since the TLV was set or last revised, although this trend is not consistent across all substances (see bar chart below). It should be borne in mind however, that although the ACGIH are the most widely used US OELs, they have no regulatory status in the US. Many of the regulatory limits set by OSHA have been set on a cost-benefit basis (see below).




In the US, regulatory Permissible Exposure Levels (PEL) are set by the Occupational Safety and Health Administration (OSHA). Prior to 1980, the lack of demonstrable exposure thresholds for the toxic effects of carcinogens was interpreted to mean that no workplace exposure standard, however low, could assure that "no employee will suffer material impairment of health." Workplace standards for carcinogens were set as low as was deemed to be technically feasible at reasonable cost. A proposed 1 ppm standard for workplace exposure to benzene, however, was challenged in court, eventually leading to a Supreme Court decision that required OSHA to demonstrate that the chemical posed a "significant risk" before issuing a standard. Unless the risk is significant (a lifetime risk of one in a thousand), the material could not considered a "toxic material" or "harmful physical agent" and its presence could not be said to meaningfully lead to an unhealthy workplace.. However, a subsequent Supreme Court decision on cotton dust ruled that OSHA may set a level as protective of health as feasible, even if a less stringent one has a more favourable cost-benefit ratio (The Commission on Risk Assessment and Risk Management, 1996). More recently (2009), the Court of Appeals upheld the 5 $ugm^{-3}$ PEL for hexavalent chrome which is associated with a cancer risk of about risk of about 1-4.5% risk for 45 years exposure at work as opposed to about 0.21-0.91% associated with a 1 $ugm^{-3}$ PEL. The court endorsed OSHA's analysis of economic feasibility which determined that a 1 $ugm^{-3}$ PEL would be economically infeasible for electroplating job shops and that these shops could not be expected to absorb the costs to comply (Metal finishing, 2009).

## 3.3 RISK CRITERIA FOR ENVIRONMENTAL, FOOD, DRINKING WATER AND CONSUMER PRODUCTS

There is a general consensus that risks arising from involuntary exposures to substances in air, water and food; arising from environmental pollution are less tolerable than risks arising from workplace exposure which are to some extent voluntary. The management of risks associated with nonwork exposure to carcinogens in the EU is split between various bodies. The European Food Safety Agency (EFSA) is responsible for providing advice on dietary exposure to carcinogens. The Directorate-General for Health and Consumer Protection is advised by three committees on issues relating to non-food exposures to hazardous substances:

The Scientific Committee on Consumer Products (SCCP)
The Scientific Committee on Health and Environmental Risks (SCHER)

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)

Although the Scientific Committee (SC) of the EFSA has recommended the application of the MOE approach as a harmonised methodology for assessing the risk of genotoxic and carcinogenic substances, it also emphasizes its overall aim to keep the exposure to those substances at the lowest level possible, regardless of the MOE. In the Committee's view, it is for the risk manager to decide if the magnitude of the MOE is acceptable, and if further action is needed taking into consideration additional aspects, such as the feasibility of removing the substance from the food supply. In general a MOE ≥10000 based on $BMDL_{10}$ would be of low concern from a public health point of view. In addition, however, substances which are both genotoxic and carcinogenic should not be deliberately added to food and feed at any point in the food chain. The same also applies for substances which may leave residues that could have both genotoxic and carcinogenic properties (e.g. pesticides).

SCCP, SCHER and SCENIHR do not appear to have developed advice on tolerable risk levels. Their guidance allows for different approaches to risk assessment and management to be taken in different cases in order to optimise the costs and benefits. By implication, risk tolerability is likely to vary under different circumstances, particularly where different types of risk are balanced against each other.

The European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) has published a "Guideline on the Limits of Genotoxic Impurities" (EMEA, 2005) that recommends the use of TCC for defining acceptable limits of genotoxic impurities in drug substances.

For non-threshold genotoxic carcinogens, the guideline indicates that a TTC of 1.5 ug/day for an intake in pharmaceuticals corresponding to a lifetime cancer risk of $10^{-5}$ is appropriate for substances with structural alerts for a lifetime cancer risk of $10^{-6}$ (Kroes et al, 2004). A higher level of intake may be acceptable where a patient is being treated for a life threatening condition, has a limited life expectancy or is exposed to far greater quantities of the substance in question from other sources (eg in food).

Separately the REACH Regulation is also intended to limit non-work exposure to carcinogens. In the guidance developed by ECHA for the purposes of the implementation of REACH, it is indicated that a lifetime cancer risk of $\leq 10^{-6}$ is generally considered to be indicative of a tolerable risk for the general population. This is consistent with the EFSA MOE recommendation.

The UK COC has suggested the following ranking for consumer and environmental exposures for benchmark doses based on animal data. Given that a higher level of risk may be acceptable in the workplace where exposure is (to some extent) voluntary than in the wider environment, it is possible that a smaller MOE might be acceptable or tolerable for workplace exposures.

| MOE | Interpretation |
|---|---|
| <10,000 | May be a concern |
| 10,000-1,000,000 | Unlikely to be a concern |
| >1,000,000 | Highly unlikely to be a concern |

If an MOE approach was used for human data, it would seem likely that a smaller MOE would be acceptable, given the lower levels of uncertainty in the data.

## 3.4 RELATIONSHIP BETWEEN METHODS OF RISK ASSESSMENT AND RISK CRITERIA

If cost benefit analysis is used as a major tool in decision making and the level at which the OEL is set is related to the number of lives saved versus cost, then the implied level of risk acceptability might be considerably higher than the $10^{-5}$ lifetime cancer risk embodied in REACH. For example, if only 1000 workers are exposed to a substance across the entirety of EU and the typical pattern of use meant that these workers were not repeatedly exposed day after day, then the number of deaths avoided by reducing the OEL to from a level associated with a $10^{-4}$ cancer risk to a level associated with a $10^{-5}$ cancer risk would not be expected to have any appreciable impact on cancer deaths arising from use of that substance. It has been noted in the past that OELs based on socio-economic factors and technical feasibility were higher than those based more closely on acceptable risk levels (Seeley et al, 2001).

If an ALARP approach is taken to risk management, risks would be managed to a “low level” but in practice this is likely to represent a much higher exposure concentration than that associated with a $10^{-5}$ cancer risk. A “low level” could be perceived in terms of the risk associated with exposure to the substance being no greater than the wider background rate of mortality from work-related causes (approximately $10^{-3}$ as a lifetime risk).

In summary the use of a MOE or QRA approach to risk management is unlikely to have a substantial influence on perceived risk acceptability. Other approaches to risk management which do not involve explicit description of risks in quantitative terms, however, will have an effect on implied risk acceptability. It is likely that an ALARP or CBA approach to setting an OEL would lead to a higher OEL being set than using MOE or QRA (depending on the risk acceptance criteria applied). The use of an apparent or practical threshold to underpin an OEL could also have an indirect effect on the level of risk incorporated into an OEL. If the OEL is based on human data, little or no allowance may be made for interindividual differences in susceptibility which could give rise to the implicit acceptance of a greater level of risk than associated with an OEL based on an ALARP or CBA approach and considerably more risk than associated with an OEL based on an MOE or QRA approach. Under these circumstances, however, there are likely to be insufficient data to justify lowering the OEL.

## 3.5 DISCUSSION AND CONCLUSIONS

Risk tolerability varies widely in different situations. Higher levels of risk are likely to be tolerated in the workplace than for wider population exposure. In addition, risk tolerability depends to some extent on current exposure levels and feasibility of reducing them. This however, is a product of history and it is arguable that those in the workplace should be afforded a level of protection that is no less than that of the general population.

There is no societal agreement on the level of calculated cancer risk that is considered acceptable. There is also no consensus as to whether or how judgement of risk acceptability might take account of uncertainties in the database. It is not clear whether

a calculated risk of one in a thousand is more or less acceptable depending on the uncertainties in the risk estimate. Most people have difficulty in understanding risk in such statistical formats and risk estimates are difficult to communicate. It is human nature to focus on the 0.1% risk of getting cancer from a given exposure level versus the 99.9% risk of not getting cancer.

OELs have generally been set at levels that are believed to be achievable and there are substantial variations in the effectiveness of exposure control and levels of exposure to carcinogens in different industry sectors.

Guidance produced by ECHA for the derivation of DMELs suggests that a lifetime cancer risk of $10^{-5}$ should be regarded as tolerable for workplace exposure to chemicals and we have asked by the Commission to consider $10^{-5}$, $10^{-6}$ and $10^{-7}$ as the potential criteria for acceptable risk. These are considerably lower levels of risk than currently regarded as tolerable for workplace exposures in some member states such as the UK and the Netherlands. In the Netherlands, for example, an annual risk of $10^{-4}$ is considered acceptable, which is slightly greater than the risk of dying in a road traffic accident in the UK. The benefits of setting OELs that based on $10^{-6}$ or $10^{-7}$ cancer risks over an OEL based on a $10^{-5}$ cancer risk are dubious. It is unlikely that sufficient workers would be exposed to a substance across Europe for this reduction in risk to lead to any avoided cases.

It is worth noting that for substances which do have a threshold of effect, the guidance produced by ECHA for the derivation of DNELs for workplace exposures would give rise to values that are typically one or more orders of magnitude smaller than for existing exposure limits for that substance. This probably reflects how knowledge of exposure conditions has influenced the setting of OELs. If it is known that people are widely exposed to a substance without apparently showing adverse effects, then there will be a reluctance to set an OEL to further reduce exposure levels. In contrast, if adverse effects are widespread, then the OEL should be set at a level intended to drive real improvements in exposure control.

It would seem desirable to harmonise the process by which OELs are derived at EU level with the intended process under REACH. This is likely to give rise to difficulties, however, given that DMELs may be 10-1000 times smaller than existing OELs for carcinogens. Socio-economic considerations are likely to play an important role in the determination of risk tolerability for individual carcinogens.

# 4 CASE STUDIES

## 4.1 INTRODUCTION

This chapter reviews the potential application of quantitative risk assessment in the development of OELs for some representative genotoxic carcinogens for which OELs have already been set in some EU countries. Candidate OELs have been calculated on the basis of a level of exposure associated with a $10^{-5}$ cancer risk for workplace exposure over 40 years (equivalent to an exposure level associated with a MOE of 10,000 based on $BMD_{10}$). For each substance, a comparison is provided of candidate OELs developed using different quantitative risk assessments and existing OELs based on other criteria. For most of the substances, there are a number of published risk estimates available. In some cases these are different risk estimates based on a

single dataset whereas in other cases, different groups have used different datasets as the basis for their risk estimation.

## 4.2 ACRYLAMIDE

### 4.2.1 Overview

The EU-RAR (2002) and DECOS (2006) concluded that acrylamide is a proven carcinogen in animals. No excess of cancers has been detected in workers exposed to acrylamide, but this may reflect the limited power of the epidemiological investigations to detect small excess cancer risks. The main known health effect of concern in exposed workers is neurotoxicty.

Rats exposed to acrylamide by the oral route in two studies showed increased tumours at several sites including mesotheliomas in the tunica vaginalis of the testes, mammary gland fibroadenomas, thyroid follicular-cell ademomas (EU-RAR). There were inconsistencies between the two studies in the sites at which statistically-significant excess tumours occurred. Most of the tumour types observed were potentially related to disturbed endocrine function. Both studies reported the tunica vaginalis mesotheliomas, although a significant increase was only found in one study, at doses as low as 0.5 mg/kg/day (EU-RAR).

### 4.2.2 Risk estimate calculated by DECOS

DECOS (2006) derived a cancer risk estimate for acrylamide based on the results of the oral studies in rats as no inhalation studies were available. Their analysis was based on the incidence of tunica vaginalis mesotheliomas in male rats (Johnson et al, 1986; Friedman et al, 1995).

The incidence rate of tumours at a given dose ($I_{dose}$) is defined as:

$I_{dose} = (I_e - I_c)/( Dx(Xpo/L)x(Xpe/L)x(\text{days per week}/7))$

Where $I_e$ is the incidence in the exposed animals, $I_c$ is the incidence in the unexposed animals, D is the daily dose (mg/kg/day), Xpo and Xpe the exposure and experimental period respectively and L is the standard lifetime of the animal species (assumed as 1000 days for rats).

In estimating the additional risk of cancer in humans on the basis of animal data, DECOS assumed that there were no differences between experimental animals and humans with respect to toxicokinetics, mechanism of tumour induction, target susceptibility etc. Using the estimated tumour incidence of 0.5 per mg/kg/day, the additional risk was calculated as $I_{dose}$ x (40/75 years) x (48/52 weeks) x (5/7 days) x ($10m^3$) x (70 kg bw)$^{-1}$ which equates to 2.5 x $10^{-2}$ per $mgm^{-3}$ for 40 years exposure. This equates to a risk of $4x10^{-3}$ for 40 years exposure at work to 0.160 $mgm^{-3}$ and 4 x $10^{-5}$ for 40 years exposure to 0.0016 $mgm^{-3}$. If an interspecies scaling factor of 4 is used to translate from rat to humans (not included in the DECOS calculation), the implied DMEL associated with a $10^{-5}$ cancer risk would be 0.0001 $mgm^{-3}$.

### 4.2.3 US EPA risk estimate

The US EPA has developed a cancer risk estimate for environmental exposure based on one of the rat studies (Johnson et al, 1986) identified by the EU-RAR, using a

linearised multistage procedure. The implied workplace exposure concentration associated with a $10^{-5}$ cancer risk (0.00008 $mgm^{-3}$) is comparable with a DMEL based on the DECOS risk estimate. Cancer risks were calculated on the combined incidence of CNS, mammary and thyroid glands, uterus, oral cavity tumours in rats exposed to acrylamide in drinking water. The risk estimates were based on the data for female rather than male rats as there were significantly increased tumour incidences at a greater number of sites than in the males. Human equivalent doses were calculated using a factor of 7.05 was used (the cube root of the ratio of human to rat body weights, or 70 kg/0.2 kg).

.

| Risk Level | Concentration – lifetime exposure in ambient air | Working lifetime exposure at work |
|---|---|---|
| $10^{-4}$ (1 in 10,000) | 0.08 $\mu gm^{-3}$ | 0.77 $\mu gm^{-3}$ |
| $10^{-5}$ (1 in 100,000) | 0.008 $\mu gm^{-3}$ | 0.08 $\mu gm^{-3}$ |
| $10^{-6}$ (1 in 1,000,000) | 0.0008 $\mu gm^{-3}$ | 0.01 $\mu gm^{-3}$ |

### 4.2.4 Glycidamide

A number of authors have suggested that glycidamide – a genotoxic metabolite of acrylamide – plays an important role in the carcinogenic action of acrylamide. In a review of the carcinogenicity of acrylamide in rats, Dourson et al (2008) concluded that the mutagenic mode of action of glycidamide is likely to determine low-dose-response to acrylamide whereas growth stimulation is likely to occur at higher doses. Using the probit model, they calculated a health-protective, linear cancer slope factor of 0.030 $(mg/kg\text{-}day)^{-1}$for the low dose part of the dose-response curve associated with possible mutagenicity. The implied workplace exposure concentration (8 hour TWA) associated with a $10^{-5}$ cancer risk would be $4.56x10^{-6}$ $mgm^{-3}$ for 40 years exposure at work (assuming equivalent absorption following oral administration or inhalation). Dourson et al (2008) developed a reference Dose (RfD) in the range of 0.05-0.02 mg/kg-day (equivalent to 1.4-3.5 mg/day for a 70 kg adult or a workplace exposure concentration of 0.14-0.35 $mgm^{-3}$) for the part of the dose-response curve associated with the growth stimulation.

Paulsson et al (2001) evaluated rat and mouse experimental data using a multiplicative model in which the incremental cancer risk is proportional to dose and background incidence. The dose associated with a doubling of incidence in mice was about 20-50 mg/kg/day compared with 500 mg/kg/day in rats and they concluded that mice are about 10 times more sensitive per administered dose of acrylamide than rats. When *in vivo* doses of acrylamide and the metabolite glycidamide, as inferred from levels of haemoglobin adducts, were examined in rats and mice after exposure to acrylamide, the adduct levels from glycidamide were, per administered dose of acrylamide, approximately 3-10 times higher in mice than in rats, consistent with the apparently greater susceptibility of mice to acrylamide. By contrast, the US EPA procedure of scaling dose by body surface area would suggest that rats should be about twice as sensitive as mice to carcinogenic chemicals.

### 4.2.5 Cancer risk estimates for dietary exposure to acrylamide

Most recent evaluations of acrylamide carcinogenicity have been made in relation to dietary exposure.

Shipp et al (2006) reported that the assessment of noncancer endpoints for acrylamide using benchmark models and the methods published by the US EPA resulted in a reference dose (RfD) of 0.83 ug/kg/day based on reproductive effects, and 1.2 µg/kg/day based on neurotoxicity. The equivalent workplace exposure concentrations based on a 40 year working lifetime would be 0.056 and 0.08 $mgm^{-3}$. Shipp et al (2006), however, considered thyroid tumours in male and female rats as the only endpoint relevant to human health and estimated a POD using the multistage model. They used data from two studies: Johnson et al (1986) and Friedman et al (1995). Because the mode of action of acrylamide in thyroid tumour formation is not known, they conducted both linear and nonlinear low-dose extrapolations under the assumption that glycidamide or acrylamide, respectively, were the active agent. The human equivalent dose was calculated on the levels of acrylamide and glycidamide haemoglobin adducts observed in rats and in humans following oral exposure to acrylamide. The RfD was estimated to be 1.5 µg/kg/day based on the use of the area under the curve (AUC) for acrylamide haemoglobin adducts (ie a time-integrated measure of adduct formation) and the assumption of nonlinearity. The equivalent workplace exposure concentration would be 0.1 $mgm^{-3}$. Assuming a linear mode of action at low doses, the dose of acrylamide associated with a $10^{-5}$ cancer risk was estimated as $9.5 \times 10^{-2}$ µg/kg/day based on the use of the AUC for glycidamide adduct data. The equivalent workplace exposure concentration would be 0.006 $mgm^{-3}$.

Allen et al (2005) explored the use of *in vivo* genotoxicity data from experiments in mice and rats in risk assessment for acrylamide using three modelling approaches: Poisson regression of counts of genetic effects per cell; dynamic modelling of the time-course of micronucleus production and loss as a function of exposure; and categorical regression of sets of genetic toxicity experiments. Modelled benchmark doses and predicted response rates for predetermined doses for acrylamide data base suggested that the findings of studies of genetic damage were not consistent or congruent with the thyroid tumour endpoints observed in two long-term bioassays in rats. Poisson model analysis of somatic cell chromosome aberrations and sister chromatid exchanges showed extremely small effects at the doses at which tumours have been reported in animals. The percent increase in micronucleated cells was also much smaller than the percent increase in tumours and the categorical regression generated BMDs for effects on somatic cells that were greater than the maximum doses used in the cancer assays. They concluded that the acrylamide may not act by a genotoxic mechanism and that a nonthreshold approach to risk assessment might not be appropriate.

### 4.2.6 SCOEL recommendation

SCOEL concluded that the uncertainties surrounding the risk of cancer and genotoxicity (in particular heritable mutations) in workers exposed to acrylamide prevented derivation of a health-based OEL. They categorised acrylamide as a genotoxic carcinogen, for which the existence of a threshold cannot be sufficiently supported at present.

SCOEL were unable to develop a reasonable quantitative cancer risk assessment for humans because of the lack of reliable human data combined with the significant influence of species-specific factors for the cancers observed in rats (testicular mesotheliomas, mammary tumours, glial cell tumours, thyroid tumours and adrenal phaeochromocytomas). This makes meaningful quantitative extrapolations to humans almost impossible.

SCOEL considered it important that any regulation that may be established for acrylamide should also be protective against the development of neurotoxicity, given that there is a wealth of evidence for acrylamide-induced neurotoxicity in workers. Based on biological monitoring of the haemoglobin adduct of acrylamide (*N*-2-carbamoyl-ethyl-valine), a NOAEL for neurotoxicity of 0.5 nmol adduct/g globin has been reported with respect to neurotoxicity in occupationally exposed persons. The adduct level based on these studies of 0.5 nmol/g globin would correspond to an airborne exposure of about 0.1 $mg.m^{-3}$ or 0.035 ppm (8-hour TWA).

### 4.2.7 Discussion and conclusions

The use of cancer risk estimates based on animal studies in which acrylamide was administered in drinking water implies that a DMEL for workplace exposure, based on a $10^{-5}$ lifetime cancer risk arising from 40 years exposure at work, would be of the order of 0.0001 $mgm^{-3}$. Other approaches to interspecies scaling and risk estimation give rise to calculated OELs associated with a $10^{-5}$ cancer risk that range from 0.00008 $mgm^{-3}$ to 0.006 $mgm^{-3}$. The difference in the risk estimates presented by different authors is largely related to differences in the estimation of human equivalent doses, the inclusion of different tumour endpoints in the analysis and in the animal studies included in the analysis. The Friedman et al study was not available at the time when the EPA derived their risk estimate (1988). There is considerable uncertainty as to the mechanisms by which acrylamide may cause cancer and some evidence that cancer risks calculated from animal tumour data may have been substantially over-estimated. In contrast to the estimated concentrations of acrylamide associated with a $10^{-5}$ cancer risk, SCOEL have recommended a limit of 0.1 $mgm^{-3}$ to protect against neurotoxicity. The current UK WEL is 0.3 $mgm^{-3}$ set to prevent neurotoxicity and until 2001, the ACGIH TLV was 0.3 $mgm^{-3}$ based on reported NOELs for neurotoxicity in animals of animals at 0.014 and 0.1 mg/kg/day. A proposed TLV of 0.03 $mgm^{-3}$ to protect against carcinogenicity was withdrawn (ACGIH, 2005). The basis of the proposed 0.03 $mgm^{-3}$ is not outlined in the 2005 criteria document.

| Candidate OEL $mgm^{-3}$ | Comments |
|---|---|
| 0.0001 | DMEL ($10^{-5}$ cancer risk) based on the DECOS calculation |
| 0.00001 | Exposure level associated with $10^{-6}$ cancer risk based on DMEL |
| 0.000001 | Exposure level associated with $10^{-7}$ cancer risk based on DMEL |
| 0.00008 | $10^{-5}$ cancer risk based on USEPA risk function, scaled for workplace exposure |
| 0.006 | $10^{-5}$ cancer risk based on Shipp et al (2000) risk function, scaled for workplace exposure (interspecies extrapolation based on plasma concentrations) |
| 0.000005 | $10^{-5}$ cancer risk based on Dourson et al (2008) risk function, scaled for workplace exposure |
| 0.1 | SCOEL recommendation based on neurotoxicity |

The candidate OELs based on cancer risk estimates are orders of magnitude smaller than the OEL recommended by SCOEL. The absence of clear evidence of an excess cancer risk in workplace studies suggests that either existing levels of exposure are exceedingly small or that the cancer risks in occupationally exposed humans are very much lower than implied by the animal data. It seems highly unlikely that the introduction of an OEL based on a $10^{-5}$ cancer risk estimate would lead to any public health benefit in the form of avoidable cancers. The benefits of setting OELs based on cancer risk estimates of $10^{-6}$ and 10-$^{7}$ would be even smaller. It is worth noting, however, that an OEL based on neurotoxicity would control estimated lifetime cancer risks to less than $10^{-3}$ (for working lifetime exposure) if the animal modelling were predictive of human cancer risk.

## 4.3 BENZENE

### 4.3.1 Risk Estimates

A number of authoritative bodies and authors have developed risk functions for benzene based on human epidemiological studies. The US EPA, WHO (2000) and ACGIH (2001)have based their risk estimates on analysis undertaken by Crump (1994, 1996) of published studies of the Pliofilm workers who reportedly had fewer reported co-exposures to other potentially carcinogenic substances in the workplace that might confound risk analysis for benzene, than other cohorts. Differences in the unit risk estimates published by different groups stem largely from differences in the exposure estimates and the type of dose-response model used. Crump (1992, 1994) presented 96 unit risk calculation analyses by considering different combinations of the following factors: (1) different disease endpoints, (2) additive or multiplicative models, (3) linear/nonlinear exposure-response relationships, (4) two different sets of exposure measurements (Crump and Allen [1984] vs. exposure estimates by Paustenbach et al. [1992]) and (5) cumulative or weighted exposure measurements. The unit risk estimates range from 8.6 x $10^{-5}$ to 2.5 x $10^{-2}$ at 1 ppm (3200 $\mu g/m^3$) of benzene air concentration. The corresponding concentrations associated with a $10^{-5}$ cancer risk for 40 years exposure in workplace air are 0.012 to 3.56 $mgm^{-3}$. Crump reported that multiplicative risk models described the data better than additive models and cumulative exposures better than weighted exposures. Dose response relationships were essentially linear when the Crump and Allen (1984) exposure matrix was used but

for the Paustenbach et al (1992) exposure matrix, the data were best-fitted by a quadratic model.

The US EPA considered that linear extrapolation was most appropriate for low doses in the absence of a full understanding of the biological mechanism(s) of benzene-induced leukaemia. When a linear model was employed, the choice of cancer unit risk estimates narrowed to a range between $7.1 \times 10^{-3}$ and $2.5 \times 10^{-2}$ at 1 ppm ($2.2 \times 10^{-6}$ to $7.8 \times 10^{-6}$ at 1 µg/m$^3$ of benzene in air), depending on which exposure measurements were used, i.e., Crump and Allen (1984) or Paustenbach et al. (1993). Crump and Allen's exposure estimates were greater for the early years (1940s) than the Paustenbach estimates whereas the Paustenbach et al exposure matrix considered short-term high level exposure, background concentrations and dermal absorption which gave rise to calculated exposure levels that were 3-5 higher than earlier estimates. The US EPA risk estimates indicate that 40 years exposure to a concentration of between 0.012 and 0.043 mgm$^{-3}$ would be associated with a $10^{-5}$ cancer risk.

The WHO (2000) based their risk estimate for benzene on the calculation of Crump (1994). The WHO risk estimate indicates that 40 years exposure to 0.016 mgm$^{-3}$ in workplace air would be associated with a $10^{-5}$ cancer risk. The WHO gave preference to models giving equal weight to concentration and duration of exposure, although a concentration-dependent model gave a better fit to the Paustenbach exposure data.

In a more recent study of benzene-exposed petroleum workers, Glass et al (2006) reported that leukaemia risk was significantly increased for the subjects with greater than 16 ppm years cumulative exposure (equivalent to a 40 year working lifetime exposure to 0.4 ppm; odds ratio 51.9, 95% confidence interval 5.6-477). The choice of cut-point and reference group had a marked effect on the odds ratios. Previously Glass et al (2003) showed that the risk of leukaemia was increased at cumulative exposures above 2 ppm-years (equivalent to working lifetime exposure to 0.05 ppm) and with intensity of exposure of highest exposed job over 0.8 ppm. Risk increased with higher exposures; for the 13 case-sets with greater than 8 ppm-years cumulative exposure, the odds ratio was 11.3 (95% confidence interval = 2.85-45.1). If 2 ppm.years is taken as a threshold for carcinogenicity and allowing an assessment factor of 5 for interindividual differences (REACH guidance), then 0.01 ppm (0.017 mgm$^{-3}$) might represent an appropriate DMEL. It would probably be appropriate to add an additional factor to allow for uncertainties in the detection of a threshold of effect, even in relatively large studies and also to allow for the impact of grouping workers by exposure level on the apparent threshold.

The EU Binding Occupational Exposure Limit of 1 ppm for benzene (=3.2 mgm$^{-3}$) is considerably higher than potential candidate health based OELs based on a $10^{-5}$ lifetime cancer risk as estimated by the US EPA or WHO. It is also considerably higher than the DMEL based on a possible threshold for carcinogenic effect reported by Glass et al (2003, 2006). The BOELV is based on the LOAEL for haematoxic effects in animals (10 ppm) and reported chromosomal effects (induction of sister chromatid exchange and micronuclei) in humans and animals exposed to concentrations of between 1 and 10 ppm. The criteria document also discusses a possible limit of 0.5 ppm which would "reduce the range of best estimated lifetime risks down to 0.25-3.3 additional leukaemia cases per 1000 exposed to 0.5 ppm, corresponding to an exposure of 20 ppm-years." The tabulated risks in the criteria document suggest that the adopted 1 ppm limit is associated a lifetime leukaemia risk of between 0.5 and 6.6 per 1000 workers. SCOEL did not adopt the 0.5 ppm proposal because the risk

assessment did not explicitly take account the possible influence of target cell toxicity and was therefore considered to be conservative.

The ACGIH TLV of 0.5 ppm (TWA) was set at level at which no excess risk has been reported in epidemiological studies or on the basis of workplace experience (which might imply a level of tolerable risk of 1% or greater). In an analysis of the Pliofilm data, the ACGIH concluded that the risk of leukaemia due to occupational exposure was no greater than for people without occupational exposure, whereas an excess lifetime risk existed at 1 ppm or greater. The ACGIH acknowledge that these data have been analysed by a number of groups who have come to differing conclusions about the exposure response relationship.

### 4.3.2 Comparison of OELs

Despite the relative abundance of human data for benzene in comparison to that available for other substances, there is considerable uncertainty in the estimation of cancer risks which is largely related to the choice of model employed. It is impossible to ascertain the role of technical feasibility in driving the choice of OEL value in the determination of the BOELV or TLV. The existing BOELV is at the top end of the wide range of reported estimates of the workplace concentration associated with a $10^{-5}$ lifetime cancer risk with most estimates being 10-100 times lower than the BOELV. The estimated concentrations associated with a $10^{-6}$ or $10^{-7}$ risk would be 10 or 100 times smaller than the concentration associated with a $10^{-5}$ risk. The choice of cancer risk function could lead to a more than 100-fold difference in the proposed OEL, if the OEL were to be based on a pre-determined risk criterion.

| Candidate OEL $mgm^{-3}$ | Comments |
|---|---|
| 3.2 | SCOEL BOELV Based on haematoxic effects in animals and reported chromosomal effects in humans; estimated cancer risk between 0.5 and 6.6 $x10^{-3}$ |
| 1.6 | ACGIH TLV – an exposure level believed to have no associated risk of excess cancer |
| 0.12-3.56 | Exposure concentration associated with a $10^{-5}$ cancer risk for 40 years exposure at work based on analysis of Crump (1992, 1994) |
| 0.012-0.356 | Exposure concentration associated with a $10^{-6}$ cancer risk for 40 years exposure at work based on analysis of Crump (1992, 1994) |
| 0.0012-0.0356 | Exposure concentration associated with a $10^{-7}$ cancer risk for 40 years exposure at work based on analysis of Crump (1992, 1994) |
| 0.012-0.043 | Exposure concentration associated with a $10^{-5}$ cancer risk for 40 years exposure at work based on US EPA risk estimate |
| 0.016 | Exposure concentration associated with a $10^{-5}$ cancer risk for 40 years exposure at work based on WHO (2000) risk estimate |
| 0.017 | DMEL based on apparent threshold for cancer in humans reported by Glass et al (2006) and an assessment factor of 5 |

## 4.4 ETHYLENE OXIDE

### 4.4.1 Risk estimates

Ethylene oxide (EO) is a widely used chemical intermediate that is also formed endogenously as a result of cytochrome P450-mediated metabolism of ethylene, which is ubiquitous in the environment and also arises in the body through normal physiological processes such as methionine oxidation and lipid peroxidation. There is considerable uncertainty as to the carcinogenic potential of EO in humans. A number of groups have attempted to establish exposure-response relationships linking exposure EO cancer or precursor events that indicate an elevated cancer risk. Teta et al (1999), for example, presented a meta-analysis of the findings from 10 unique EO study cohorts from five countries, comprising nearly 33,000 workers, and over 800 cancers. They reported no overall increase in risk of cancer or of brain, stomach or pancreatic cancers. The findings for leukaemia and non-Hodgkin's lymphoma (NHL) were inconclusive. Exposure response modelling was undertaken for two studies with the requisite attributes of size, individual exposure estimates and follow up using a variety of plausible alternative assumptions. A point of departure analysis, with various margins of exposure, was also undertaken. The two data sets both yielded similar leukaemia risk estimates that were orders of magnitude lower than prior animal-based predictions under conservative, default assumptions, with risks of the order of $10^{-6}$ or lower for exposures in the low ppb range.

The IPCS (2003) reviewed the toxicity of EO and established a risk estimate based on studies in laboratory animals, because of limitations of the available epidemiological data and evidence that the metabolism and mode of action of EO in humans and laboratory animals are not qualitatively different. Data suitable for analysis of exposure–response were available from two studies in F344 rats (Lynch et al., 1984a,b; Snellings et al., 1984; Garman et al., 1985; Garman & Snellings, 1986) and one in B6C3F1 mice (NTP, 1987). In F344 rats, there were dose-related increases in the incidence of mononuclear leukaemias, peritoneal mesotheliomas, and brain tumours. In mice, the incidence of lung carcinomas, malignant lymphomas, uterine adenocarcinomas, mammary adenocarcinomas and adenosquamous carcinomas, and Harderian cystadenomas was increased. The concentration of EO causing a 5% increase in tumour incidence over background ($TC_{05}$) for each data set was calculated by first fitting the multistage model to the dose–response data using GLOBAL82 (Howe & Crump, 1982). No adjustment was made to take account of interspecies differences. A chi-square lack of fitness test was performed for each model fit. A P-value less than 0.05 indicates a significant lack of fit. Calculated concentrations of EO causing a 5% increase in the incidence of individual tumours over background in rats ranged from 2.2 $mgm^{-3}$ to 31.9 $mgm^{-3}$. $TC_{05}$s in mice ranged from 6.7 $mgm^{-3}$ to 22.7 $mgm^{-3}$ (see table overleaf)

| Study protocol | Tumour incidence | $TC_{05}$ ($mgm^{-3}$) | LCL on $TC_{05}$ ($mgm^{-3}$) | Chi-square | df | *P*-value |
|---|---|---|---|---|---|---|
| Male rats exposed to 0, 92, or 183 mg EO/$m^3$, 7 h/day, 5 days/week* | Incidence of mononuclear cell leukaemia: 24/77, 38/70, 30/76 | 12.5 | 5.1 | 3.5 | 1 | 0.06 |
| | Incidence of peritoneal mesothelioma: 3/78, 9/79, 21/79 | 14.4 | 6.1 | 0 | 0 | – |
| | Incidence of brain mixed cell glioma: 0/76, 2/77, 5/79 | 31.9 | 18.3 | 0 | 1 | 1.0 |
| Male and female rats exposed to 0, 18.3, 60.4, or 183 mg EO/$m^3$, 6 h/day, 5 days/week* | Incidence of mononuclear leukaemia in males: 13/97, 9/51, 12/39, 9/30 | 6.0 | 3.1 | 2.2 | 2 | 0.34 |
| | Incidence of mononuclear leukaemia in females: 11/116, 11/54, 14/48, 15/26 | 2.2 | 1.5 | 0.58 | 2 | 0.75 |
| | Incidence of peritoneal mesothelioma in males: 2/97, 2/51, 4/39, 4/30 | 10.8 | 5.6 | 0.78 | 2 | 0.68 |
| | Incidence of primary brain tumours in males: 1/181, 1/92, 5/85, 7/87 | 17.5 | 10.8 | 1.6 | 2 | 0.50 |
| | Incidence of primary brain tumours in females: 1/188, 1/94, 3/92, 4/80 | 31.0 | 16.1 | 0.45 | 2 | 0.80 |
| Male and female mice exposed to 0, 92, or 183 mg EO/$m^3$, 6 h/day, 5 days/week* | Incidence of lung carcinoma in males: 6/50, 10/50, 16/50= | 10.2 | 4.1 | 0 | 0 | – |
| | Incidence of lung carcinoma in females: 0/49, 1/48, 7/49 | 19.8 | 10.3 | 0.34 | 2 | 0.84 |
| | Incidence of malignant lymphoma in females: 9/49, 6/48, 22/49 | 12.2 | 6.3 | 3.5 | 1 | 0.06 |
| | Incidence of uterine adenocarcinoma: 0/49, 1/47, 5/47 | 22.7 | 11.4 | 0.07 | 2 | 0.97 |
| | Incidence of mammary adenocarcinoma and adenosquamous carcinoma in females: 1/49, 8/48, 6/49 | 10.4 | 6.0 | 3.0 | 1 | 0.08 |
| | Incidence of Harderian cystadenoma in males: 1/43, 9/44, 8/42 | 6.7 | 4.2 | 2.0 | 1 | 0.16 |
| | Incidence of Harderian cystadenoma in females: 1/46, 6/46, 8/47 | 9.1 | 5.5 | 0.30 | 1 | 0.58 |
| | Incidence of lung carcinoma in males: 6/50, 10/50, 16/50= | 10.2 | 4.1 | 0 | 0 | – |

* Exposure concentration adjusted to allow for continuous exposure in calculation of $TC_{05}$

The IPCS compared the calculated tumorigenic potencies developed based on animal studies compared with risks of haematological cancers reported in epidemiological studies in populations occupationally exposed to EO. They concluded that the risks predicted based on the most sensitive outcome in rats (mononuclear cell leukaemia in female F344 rats) were consistent with the confidence intervals of the SMRs observed for both leukaemias overall and all haematopoietic neoplasms in males in the cohort study by Stayner et al. (1993).

Based on the $BMCL_{05}$ of 1.5 $mgm^{-3}$for mononuclear leukaemia in female rats, the implied concentration associated with a $10^{-5}$ cancer risk based on linear extrapolation would be 0.0003 $mgm^{-3}$ for continuous exposure over a lifetime and 0.003 $mgm^{-3}$ for 40 years exposure at work. Allowing for differences in inhalation volumes between humans and rats would give a workplace DMEL of 0.001 $mgm^{-3}$.

Using the BMDS software to calculate $BMD_{10}$ for the same dataset gives estimated workplace concentrations associated with a $10^{-5}$ cancer risk that are not significantly different from those based on the IPCS BMD: 0.003 and 0.007 $mgm^{-3}$, scaling for working lifetime exposure but not scaling for interspecies differences. Notably, none of the curves give a good fit to the data. The implied DMEL would be 0.001 $mgm^{-3}$.

| | **$BMD_{10}$ $mgm^{-3}$** | **$BMDL_{10}$ $mgm^{-3}$** | **p** | **Concentration associated with $10^{-5}$ cancer risk* $mgm^{-3}$** | **DMEL $mgm^{-3}$** |
|---|---|---|---|---|---|
| Gamma | 24.9 | 17.3 | 0.7498 | 0.00341 | 0.003 |
| Logistic | 47.9 | 37.6 | 0.2486 | 0.00655 | 0.007 |
| loglogistic | 20.0 | 12.7 | 0.7802 | 0.00274 | 0.003 |
| Logprobit | 19.5 | 4.27 | 0.4178 | 0.00267 | 0.003 |
| Multistage | 24.9 | 17.3 | 0.7498 | 0.00341 | 0.003 |
| probit | 44.8 | 35.4 | 0.2929 | 0.00613 | 0.001 |
| Weibull | 24.9 | 17.3 | 0.7498 | 0.00341 | 0.005 |
| Quantal linear | 24.9 | 17.3 | 0.7498 | 0.00341 | 0.003 |

*scaled for 40 years exposure at work versus 70 years lifetime exposure, no interspecies scaling

Previous to the IPCS review, Austin and Sielken (1988) had investigated the variability in risk assessment results for EO that could be derived using the multistage dose-response model and a single animal study. Risk estimates depended on the method used to characterize risk, the health endpoint selected, the use of confidence intervals, and the method used to equate animal and human exposure levels. The selection of the most conservative option at each stage in the risk estimation process resulted in the estimated virtually safe dose being characterized as 0.005 ppb. If the most likely rather than most conservative option was chosen at each stage of the risk estimation process, the estimated virtually safe dose was 1300 ppb.

Also previous to the IPCS review, Beliles and Parker (1987) had analysed the results of two rat inhalation bioassays with EO. Brain tumours were selected as the relevant endpoint because adverse effects on the nervous system arising from EO exposure were found consistently across species. Two methods, time-exposure concentration product and area under the plasma concentration-time curve (AUC), were used as a basis for calculating effective dose. Two mathematical risk extrapolation models, the probit and the multi-stage, were used to estimate the cancer risk for daily exposures to EO of 1.8 µg/liter over a working lifetime. The use of AUC as a basis for dose from a daily exposure of 1.8 µg/liter over a working lifetime gave a higher risk rates (90-142/10,000 workers) than the cumulative exposure. Based on this risk estimate, a workplace DMEL associated with a $10^{-5}$ cancer risk would be 0.013 $mgm^{-3}$.

Subsequent to the IPCS review, Kirman et al (2004) reported that a quadratic dose-response model provided the best overall fit to the epidemiology data in the range of observation which was consistent with the anticipated mode of action linking EO exposure to the development of leukaemia (and therefore risk). They presented cancer dose-response assessments based on human and animal data using three different assumptions for extrapolating to low doses: (1) risk is linearly proportionate to dose; (2) there is no appreciable risk at low doses (margin-of-exposure or reference dose approach); and (3) risk below the point of departure continues to be proportionate to

the square of the dose. In their opinion, the weight of evidence for EO supports the use of a nonlinear assessment and exposures to concentrations below 37 $\mu gm^{-3}$ are not likely to pose an appreciable risk of leukaemia in human populations. The quantification of risks at lower levels of exposure using the quadratic estimates of cancer potency and alternative points of departure provided risk estimates that 3.2- to 32-fold lower than derived using linear estimates of cancer potency. Given that a small linear component for the dose-response relationship at low concentrations could not be conclusively ruled out, a unit risk value of $4.5 \times 10^{-8}$ per $\mu gm^{-3}$ was derived for environmental exposure to EO, with a range of $1.4 \times 10^{-8}$ to $1.4 \times 10^{-7}$ per $\mu gm^{-3}$ reflecting the uncertainty associated with a theoretical linear term at low concentrations. The implied workplace exposure concentration associated with a $10^{-5}$ cancer risk is 2.1 $mgm^{-3}$ for 40 years exposure (range 0.68-6.8 $mgm^{-3}$).

The US EPA (2006) has published a draft cancer risk assessment for EO. Their analysis of the human data concluded that for environmental exposure, the estimated extra cancer risk based on lymphohaematopoietic cancer in males is $9.0 \times 10^{-4}$ per $ugm^{-3}$ and the extra risk based on breast cancer incidence in females is $5.0 \times 10^{-4}$ per $ugm^{-3}$. The implied workplace concentrations associated with a $10^{-5}$ cancer risk are 0.001 $mgm^{-3}$ and 0.002 $mgm^{-3}$ respectively based on a 40 year working lifetime.

Valdez Flores et al (in press) were highly critical of the EPA analysis and have re-analysed epidemiological data for over 19000 EO-exposed workers from studies of hospital sterilisation workers (Steenland et al, 2004) and manufacturing workers (Swaen et al, 2009). None of the Standardised Mortality Rates (SMRs) for any combination of the 12 cancer endpoints and 6 groups of workers examined were statistically greater than one and no evidence of a positive cumulative dose response relationship was found. This implies that the evidence for carcinogenicity in humans is relatively weak. Cox model estimates of the concentration corresponding to a $10^{-6}$ environmental cancer risk were greater 1 ppb, approximately 1500 times higher than the EPA estimates. (The implied workplace concentration associated with a $10^{-5}$ cancer risk would be about 0.1 ppm or 0.182 $mgm^{-3}$). The authors attributed this difference in risk estimate to:

1) The use of specific data for individual workers rather than summary odds data and mortality rather than incidence data (x 150);
2) Direct evaluation of extra risks of $10^{-6}$ rather than linear extrapolation from an extra risk of $10^{-2}$ (x1.6);
3) Use of effect concentrations (EC) rather than the lower 95$^{th}$ percentile of the EC (x2).
4) Assessment of extra risk at age 70 rather than 85 (x2.3)
5) Correct implementation of EPA's guidelines for Age Dependent Adjustment Factors (x 1.66).

Other groups have examined how dose-response information for precursor events to cancer could be used to derive an OEL. Experimentally, EO has revealed only weak mutagenic effects *in vivo*, which are confined to higher doses. EO reacts with DNA to form N7-(2-hydroxyethyl)guanine adducts (N7-HEG) that can be used as biomarkers of exposure and potential cancer risk. In rats, sub-acute EO exposures of the order of 1 ppm (1.83 $mgm^{-3}$) cause DNA adduct levels (HOEtG) of the same magnitude as produced by endogenous EO (Thier and Bolt, 2000). Endogenous background levels of HOEtG in DNA of humans are comparable to those that are produced in rodents by repetitive exogenous EO exposures of about 10 ppm (18.3 $mgm^{-3}$). Thier and Bolt (2000) concluded that long-term human occupational exposure to low airborne

concentrations of EO, at or below current occupational exposure limits of 1 ppm (1.83 $mgm^{-3}$), would not produce unacceptable increased genotoxic risks based on the experimental findings of van Sittert et al (2000). This is virtually identical to the level of workplace exposure that the analysis published by Flores Valdez et al suggests is associated with a $10^{-5}$ cancer risk. In the future, biomonitoring may prove a useful tool in managing the cancer risks associated with workplace EO exposure. Marsden et al (2007) used a highly sensitive LC-MS/MS assay with a limit of detection of 0.1 fmol of N7-HEG on column, to establish background levels of N7-HEG (1.1-3.5 adducts/$10^8$ nucleotides) in tissues of rats. Following intraperitoneal administration of a single dose or three daily doses of EO (0.01-1.0 mg/kg), N7-HEG adducts generally increased with dose, except at the lowest concentration where total N7-HEG levels were no different from that detected in control animals.

In addition to assessing the direct carcinogenic risk associated with EO, the IPCS also discussed the genetic risk to the offspring of humans exposed to EO based on induced dominant visible mutations in mice. Using the parallelogram approach and additional quantitative data on somatic mutations (*Hprt* in splenocytes) in mice and in an occupationally exposed human population (*HPRT*), it was estimated that exposure for one working year (1800 hours) to 1.8 mg EO/$m^3$ would lead to an incremental risk of $4 \times 10^{-4}$ above background that a disease with dominant inheritance would be transferred to the offspring, not taking account of recessive mutation, dominant lethal mutations, or heritable translocations As a basis for comparison with the potency estimates for cancer, the $BMC_{05}$ for this effect would be 46 $mgm^{-3}$ (IPCS, 2003). If the exposure-response function is assumed to be linear between zero and $BMC_{05}$, and no interspecies scaling is applied, then the predicted workplace concentration associated with a $10^{-5}$ risk of inherited genetic damage would be 0.050 $mgm^{-3}$ ( for exposure for 40 hours a week for 40 years).

### 4.4.2 Conclusions

Both epidemiological and animal data are available for EO. Different groups have calculated very different excess cancer risks based on the available data (see table overleaf). Overall, there are clear disparities in the findings of different animal experiments and between the findings of animal experiments and the epidemiological studies. The use of different software packages, different data sets and approaches to calculation has given rise to orders of magnitude differences in cancer risk estimates. A DMEL of 0.001 $mgm^{-3}$ based on the IPCS analysis seems unreasonably protective given that workplace exposure to 1.83 $mgm^{-3}$ is not believed to give rise to genotoxic risks that are elevated above those associated with endogenous EO. Existing OELs for EO are at the top end of the range of candidate values and about 1000x greater than most candidate OELs that are based on most estimates of the concentration associated with a $10^{-5}$ cancer risk. If the OEL were to be based on the estimated concentration associated with a $10^{-6}$ or $10^{-7}$ cancer risk, it would be 10 or 100 times lower than an OEL based on a $10^{-5}$ cancer risk.

| Candidate OEL mgm$^{-3}$ | Comments |
|---|---|
| 0.003 | Estimated concentration associated with a $10^{-5}$ cancer risk based on IPCS analysis of the incidence of mononuclear leukaemia in female rats as reported by IPCS with no scaling for interspecies differences |
| 0.001 | DMEL based on IPCS analysis of the incidence of mononuclear leukaemia in female rats ($10^{-5}$ cancer risk) |
| 0.0001 | Estimated concentration associated with a $10^{-6}$ cancer risk based on DMEL for leukaemia in female rats |
| 0.00001 | Estimated concentration associated with a $10^{-7}$ cancer risk based on DMEL for leukaemia in female rats |
| 0.003-0.007 | Based on BMDS analysis of the incidence of mononuclear leukaemia in female rats as reported by IPCS with no scaling for interspecies differences, but allowing scaling for 40 years exposure at work versus 70 years lifetime exposure |
| 0.0003-0.0009 | DMEL based on BMDS analysis of the incidence of mononuclear leukaemia in female rats |
| 0.013 | DMEL based on incidence of brain tumours in rats and cancer risk estimate of Beliles and Parker 1987 |
| 2.27 | Virtually safe level identified by Austin and Sielken (1988) |
| 2.1 (range 0.68-6.8) | Workplace exposure concentration associated with $10^{-5}$ cancer risk for 40 year working lifetime, based on human epidemiological data and risk function developed by Kirman et al (2004) |
| 0.001 | Based on draft US EPA (2006) cancer risk assessment |
| 0.182 | Valdez Flores (in press) |
| 1.83 | Based on endogenous formation of HOEtG in DNA, workplace exposure concentration at which no increased genetic risk is believed to exist (Thier and Bolt, 2000) |
| O.05 | Based on $BMD_{05}$ for genetic risk to offspring calculated by IPCS |
| 9.2 | UK WEL; no safe level identified; level industry could comply with |
| 1.8 | ACGIH TLV Based on absence of adverse effects observed at 10 ppm. |

## 4.5 PROPYLENE OXIDE

### 4.5.1 Introduction

Propylene oxide (PO) is a weakly DNA-reactive genotoxic agent and animal inhalation studies have demonstrated that it is a nasal carcinogen. Studies in humans have failed to demonstrate an excess cancer risk specifically associated with PO in workers also co-exposed to EO. Investigations of DNA adducts and sister chromatid exchange in exposed workers have, however, demonstrated that PO is genotoxic. PO also has nongenotoxic effects (glutathione depletion and cell proliferation) that are anticipated to augment its DNA-reactive and non-DNA-reactive genotoxicity. These biological events are believed to be similar in humans and rodents (Sweeney et al, 2009).

### 4.5.2 Risk estimates

In inhalation experiments in rodents, no-observed-adverse-effect levels (NOAELs) of 100 and 200 ppm have been established for nasal tumours. Available evidence on mode-of-action suggests that cancer induction by PO at the site of contact in rodents is characterized by a practical threshold. Sweeney et al (2009) derived human toxicity reference values for potential carcinogenic effects of PO based on nasal tumours identified in rodent studies and specified uncertainty factors. The 95% lower confidence limit on the dose producing a 10% increase in additional tumour risk ($LED_{10}$) was calculated using rat and mouse data sets. The analysis of the rat data was based on an internal measure of dose (plasma concentrations of PO integrated over time; AUC) based on Physiological Based Pharmacokinetic (PBPK) modelling. The analysis of the mouse data was based on continuous external concentrations. The human reference values derived from the rat and mouse $LED_{10}$ values and a composite uncertainty factor of 100 were 0.7 and 0.5 ppm PO, respectively. The composite uncertainty factor took account of inter-species differences in susceptibility and in metabolism. Sweeney et al also derived a noncancer reference value, 0.4 ppm, based on non-neoplastic nasal effects in rats.

Nilsson et al (1991) estimated a carcinogenic potency factor of 0.001 per mg/kg/day for PO in humans by inhalation. Although less data were available for PO than for EO, PO appeared to yield a rather uniform alkylation pattern in various tissues and Nilsson et al concluded that PO is probably detoxified at a rate which does not vary widely in various mammalian species, including man. For these reasons, Nilsson et al (1991), determined that the surface-based
extrapolation model for estimation of the human equivalent dose may not be appropriate and provided their own lower risk estimate. The workplace exposure concentration associated with a $10^{-5}$ cancer risk would be 0.067 $mgm^{-3}$.

The US EPA cancer risk estimate based on the incidence of nasal tumours in rats gives a slightly higher estimation of risk than Nilsson et al. The workplace exposure concentration associated with a $10^{-5}$ cancer risk would be 0.029 $mgm^{-3}$. The US EPA assumed 50% pulmonary absorption for the absorption of propylene oxide in the respiratory tract of rats, consistent with the absorption efficiency observed for epichlorohydrin.

### 4.5.3 REACH

There are several possible routes for derivation of a DMEL for PO based on the animal data used in the US EPA assessment. Given that a dose of 400 mg/kg/day in rats was associated with 20% cancer risk, linear extrapolation leads to the inference that a dose of 200 mg/kg/day would be associated with a 10% cancer risk, although no tumours were observed in rats at that level of exposure. If an allometric scaling factor of x4 is used to scale from rats to humans, the implied human equivalent dose would be 50 mg/kg/day. Based on a scaling factor of 10,000, the estimated dose associated with a $10^{-5}$ cancer risk would be 0.005 mg/kg/day. The equivalent exposure in 10 $m^3$ air over 8 hour shift, 5 days/week for 40 years of a 75 year lifetime, would give an OEL of 0.092 $mgm^{-3}$.

The best estimate of $BMD_{10}$ derived using BMDS is 295 mg/kg (see table below). If an allometric scaling factor of x4 is used to scale from rats to humans, the implied human equivalent dose would be 73.75 mg/kg/day. Based on a scaling factor of 10,000, the estimated dose associated with a $10^{-5}$ cancer risk would be 0.007 mg/kg/day. The

equivalent exposure in 10 $m^3$ air over 8 hour shift, 5 days/week for 40 years of a 75 year lifetime, would give an OEL of 0.136 $mgm^{-3}$.

| Model | BMD $mgm^{-3}$ | BMDL $mgm^{-3}$ | Ch-sq | p |
|---|---|---|---|---|
| Gamma | - | | | |
| Logistic | 391 | 324 | 0 | 0.9996 |
| loglogistic | 382 | 304 | 0 | 1 |
| Logprobit | 376 | 295 | 0 | 0.9997 |
| Multistage | 311 | 244 | 2.82 | 0.2438 |
| Probit | 382 | 313 | 0 | 0.9996 |
| Weibull | 384 | 307 | 0 | 1 |
| Quantal Linear | 295 | 182 | 5.63 | 0.0599 |

Alternatively, if the lowest observed effect level of 30 ppm for nasal irritation in rats is treated as a practical threshold (assumes cancer follows nasal irritation), it is possible to calculate a DNEL. Allowing for difference in breathing volume and weekly exposure duration (x 0.67), combined with an interspecies uncertainty factor of 2.5 and an intraspecies uncertainty factor of 5 would give a DNEL of 1.6 ppm (3.9 $mgm^{-3}$) for workplace exposure.

### 4.5.4 SCOEL

SCOEL (2009) have determined that the carcinogenicity of propylene oxide is characterised by a practical threshold (Bolt & Huici-Montagud, 2008). They have proposed an OEL based on the (i) no observed SCE effect in workers below 2 ppm exposure, (ii) an only-minimal local glutathione depletion in rats at 5 ppm, and (iii) an LOAEL for local changes at the rat nasal epithelium at 30 ppm. SCOEL have also proposed a short-term limit intended to avoid a glutathione depletion within the nasal epithelium, which could eventually make this target more susceptible for PO-induced toxicity.

### 4.5.5 Conclusions

Estimates of exposure level associated with a $10^{-5}$ lifetime cancer risk or MOE of 10,000 in comparison with $BMD_{10}$ vary according to how the exposure-response is modelled and also how human equivalent exposure concentrations are estimated. Calculated OELs based on a $10^{-5}$ cancer risk/MOE of 10,000 range from about 0.001 to 0.01 $mgm^{-3}$ (see table overleaf). If nasal irritation is assumed to represent a practical threshold for carcinogenesis, then an OEL of >1 $mgm^{-3}$ could be supported. Estimated exposure concentrations associated with a $10^{-6}$ or $10^{-7}$ cancer risk would be 10-100 times smaller than those associated with a 10-5 lifetime risk.

SCOEL (2009) have proposed a health-based OEL of 1 ppm (2.41 $mgm^{-3}$) and a STEL of 5 ppm (9.15 $mgm^{-3}$) for propylene oxide. In the UK, no safe level of exposure to PO was identified and the current WEL is based on industrial hygiene measurements that indicate that 5 ppm (=12 $mgm^{-3}$) was an exposure concentration that could be readily achieved in UK chemical industry. This value was identified as being 6 times lower than the level producing minimal respiratory tract damage in rodents (30 ppm).

| Candidate OEL $mgm^{-3}$ | Comments |
|---|---|
| 0.96 -1.6 | Reference values for humans proposed by Sweeney et al (2009) |
| 0.067 | Concentration associated with a $10^{-5}$ cancer risk for 40 years workplace exposure based on risk estimate of Nilsson et al |
| 0.029 | Concentration associated with a $10^{-5}$ cancer risk for 40 years workplace exposure based on US EPA risk estimate |
| 0.136 | DMEL based on $BMD_{10}$ for tumours in rats |
| 0.0136 | Estimated concentration associated with a 10-6 cancer risk based on DMEL |
| 0.00136 | Estimated concentration associated with a $10^{-7}$ cancer risk based on DMEL |
| 3.9 | DNEL based on nasal irritation in rats |
| 2.41 | SCOEL recommendation |

## 4.6 BIS(CHLOROMETHYL)ETHER (BCME)

### 4.6.1 Risk estimates

Studies of workplace exposure to BCME have demonstrated a link with lung cancer but provide insufficient data for the purposes of risk assessment. The US EPA cancer risk function for BCME is based on the occurrence of respiratory tract tumours in male Sprague-Dawley rats in an inhalation experiment (Kuschner et al, 1975). The EPA calculated the human equivalent dose from the animal dose, assuming surface area equivalence. The animal dose was calculated from the air concentration (0.1 ppm or 0.479 $mgm^{-3}$), an assumed breathing rate (0.283 $m^3$/day) for 500g rats (assumed), and from the number of exposures in each group.

| Dose Number of 6-hour, 0.1-ppm Exposures | Human Equivalent (mg/kg/day) | Tumour Incidence |
|---|---|---|
| 0 | 0 | 0/240 |
| 10 | 0.000270 | 1/41 |
| 20 | 0.000541 | 3/46 |
| 40 | 0.00105 | 4/18 |
| 60 | 0.00184 | 4/18 |
| 80 | 0.00347 | 15/34 |
| 100 | 0.00373 | 12/20 |

The US EPA developed a cancer risk function using a linerarized multistage procedure. Their results are shown below:

| Risk Level | Concentration life time exposure in ambient air | Equivalent concentration for 40 years exposure in workplace air* |
|---|---|---|
| $10^{-4}$ (1 in 10,000) | $1.6x10^{-3}$ µgm$^{-3}$ | $1.53x10^{-5}$ mgm$^{-3}$ |
| $10^{-5}$ (1 in 100,000) | $1.6x10^{-4}$ µgm$^{-3}$ | $1.53x10^{-6}$ mgm$^{-3}$ |
| $10^{-6}$ (1 in 1,000,000) | $1.6x10^{-5}$ µgm$^{-3}$ | $1.53x10^{-7}$ mgm$^{-3}$ |

Using BMDS to analyse the same dataset and estimating the exposure concentration associated with a $10^{-5}$ cancer risk based on linear extrapolation from $BMD_{10}$ provided similar estimates of the concentration associated with a $10^{-5}$ cancer risk for workplace exposure over 40 years. The data was best fitted by a logistic model. The implied DMEL based on $BMD_{10}$ and a MOE of 100000 would be 0.0000006 mgm$^{-3}$.

| Model | $BMD_{10}$ ppm.years | BMDL ppm.years | p | Workplace concentration (mgm$^{-3}$) associated with $10^{-5}$ cancer risk based on BMD and 16000 hours lifetime exposure | DMEL – no US EPA HEC interspecies scaling |
|---|---|---|---|---|---|
| Cancer – linear multistage | 1.70 | 1.08 | 0.90 | $3.84x10^{-7}$ | $1.84x10^{-6}$ |
| Gamma | 1.61 | 1.06 | 0.88 | $3.64x10^{-7}$ | $1.74x10^{-6}$ |
| Logistic | 2.82 | 2.44 | 0.08 | $6.37x10^{-7}$ | $3.05x10^{-6}$ |
| Loglogistic | 1.60 | 1.06 | 0.85 | $3.63x10^{-7}$ | $1.73x10^{-6}$ |
| LogProbit | 1.51 | 1.04 | 0.81 | $3.41x10^{-7}$ | $1.63x10^{-6}$ |
| Probit | 2.57 | 2.21 | 0.18 | $5.81x10^{-7}$ | $2.78x10^{-6}$ |
| Weibull | 1.65 | 1.07 | 0.89 | $3.72x10^{-7}$ | $1.78x10^{-6}$ |
| Quantal Linear Model | 1.13 | 0.87 | 0.63 | $2.56x10^{-7}$ | $1.22x10^{-6}$ |

Using BMDS to estimate $T_{25}$ provides estimates of $T_{25}$ that are variable fractions of $BMD_{10}$. (see table overleaf).The implied DMEL based on $T_{25}$ and a MOE of 250000 would be 0.0000003 mgm$^{-3}$ – half the value based on $BMD_{10}$.

| | $T_{25}$ ppm.years | $T_{25L}$ ppm.years | p | $BMD_{10}$ as fraction $T_{25}$ | $BMDL_{10}$ as fraction $T_{25}L$ |
|---|---|---|---|---|---|
| Gamma | 3.17 | 2.57 | 0.8752 | 50.78% | 39.79% |
| Logistic | 40.67 | 36.69 | 0.0798 | 6.93% | 6.64% |
| loglogistic | 31.23 | 24.98 | 0.8501 | 69.27% | 66.39% |
| Logprobit | 29.82 | 23.79 | 0.8056 | 51.37% | 42.62% |
| Multistage | 33.45 | 27.10 | 0.9032 | 50.55% | 43.59% |
| probit | 38.80 | 34.72 | 0.1799 | 66.17% | 63.63% |
| Weibull | 32.33 | 26.12 | 0.889 | 50.90% | 41.09% |
| Quantal linear | 30.85 | 23.68 | 0.6315 | 36.62% | 36.62% |
| Simple linear | 73.53 | | | 40% | |

In comparison, if the data are entered into Excel and simple linear extrapolation is performed then:

Tumour risk (based on the animal data) = 0.0845 x ppm.hours

The $T_{25}$ calculated on this basis is 73.5ppm.years. For 16,000 hours exposure, this implies that the concentration associated with a $10^{-5}$ cancer risk is $3.54x10^{-8}mgm^{-3}$ (no interspecies scaling); based on the EPA human equivalent dose, the exposure concentration associated with a $10^{-5}$ cancer risk would $2.68\ x10^{-8}mgm^{-3}$, based on the REACH guidance, the DMEL associated with a $10^{-5}$ cancer risk would be $2.33\ x10^{-8}mgm^{-3}$. If the $T_{25}$ calculated on the basis of logistic regression were used instead, the DMEL concentrations would be 55% of that based on the $BMD_{10}$.

### 4.6.2 Conclusions

There are extremely few data on which to base on OEL. Candidate OELs based on the limited available animal data and a $10^{-5}$ cancer risk are extremely low and well below measurable levels (see table below). The choice of calculation method makes a significant difference to the OEL recommendation in terms of percentage difference, but much less significant difference in terms of practical application. Estimated concentrations associated with a $10^{-6}$ or $10^{-7}$ cancer risk would be 10 or 100 times lower than those associated with a $10^{-5}$ cancer risk. In the absence of an identifiable threshold for lung cancer risk, the UK WEL has been set at 12 $mgm^{-3}$ identified as an achievable level of control.

| Candidate OEL $\mu gm^{-3*}$ | Comments |
|---|---|
| 0.002 | Based on US EPA cancer risk estimate |
| 0.0006 | DMEL based on $BMD_{10}$, no interspecies scaling |
| 0.0003 | Based on $BMD_{10}$, EPA scaling |
| 0.0006 | MOE approach based on $BMDL_{10}$ |
| 0.00001 | DMEL based on $TD_{25}$ derived using BMDS |
| 0.00002 | DMEL based on $TD_{25}$ (linear derivation) |
| 0.00004 | Simple linear extrapolation no interspecies scaling |

*Estimated workplace concentrations associated with a $10^{-5}$ cancer risk, based on respiratory tract cancers in male rats

## 4.7 TRICHLOROETHYLENE

### 4.7.1 Review of carcinogenicity

A large number of studies have been conducted in trichloroethylene-exposed workers but these have generally lacked the power to reliably detect a presence or absence of excess of cancers. Typically workers have been exposed to a mixture of solvents, and exposures to trichloroethylene have been poorly characterised. Other studies have had insufficient follow-up time to be certain of detecting an effect or have examined only small numbers of workers. A review by Wartenberg *et al* (2000) concluded that among occupational cohorts with the most rigorous exposure assessment, there was evidence of cancer risks for kidney cancer and a more recent meta-analysis undertaken by Kelsh *et al* (2005) reported consistent evidence for increased risks of kidney cancer in trichloroethylene-exposed workers. There is also some less consistent evidence that trichloroethylene is associated of an excess risk of cancer of the liver and biliary tract and of non-Hodgkin lymphoma (WHO, 2000; COC 1996). The COC noted that a clear distinction between primary and secondary cancers of the liver had not been made in all studies. Moore and Harrington-Brock (2000) concluded that chemically-induced mutation is unlikely to be a key event in the induction of human tumours by trichloroethylene or its metabolites, chloral hydrate, dichloroacetic acid or trichloroacetic acid. All these chemicals only display genotoxicity at high doses. They found some evidence, however, that *S*-(1,2-dichlorovinyl)-l-cysteine is a more potent mutagen but were unable to draw definitive conclusions as to whether trichloroethylene was likely to induce tumours in humans via a mutagenic mode of action. Caldwell and Keshava (2006) reported that studies of S-(1,2-dichlorovinyl) -l-cysteine have revealed a number of different possible cell signalling effects that may be related to kidney tumorigenesis at lower concentrations than those leading to cytotoxicity. They also concluded that studies of the trichloroethylene metabolites dichloroacetic acid (DCA), trichloroacetic acid (TCA) , and chloral hydrate suggest that both DCA and TCA are involved in TCE-induced liver tumorigenesis and that many DCA effects are consistent with conditions that increase the risk of liver cancer in humans. They also reported that studies of S-(1,2-dichlorovinyl) -l-cysteine have revealed a number of different possible cell signalling effects that may be related to kidney tumorigenesis at lower concentrations than those leading to cytotoxicity.

SCOEL have concluded that exposure to high peak concentrations of trichloroethylene at work over several years is associated with an excess risk of renal-cell carcinomas (Bolt, 2008). Experimental investigations have determined that a local metabolic activation via the glutathione-dependent pathway and renal beta-lyase is involved and tumour development is preceded by renal toxicity.

In long-term inhalation experiments in animals, trichloroethylene induced hepatocellular tumours in some strains of mice and was also associated with lesions of the lung. The COC (1996), however, did not consider the lesions observed in mouse lungs to be unequivocal tumours from the evidence reported and suggested that they might instead represent localised irritant reactions in the lung. No excess of tumours was observed in one series of experiments in rats and hamsters exposed to trichloroethylene by inhalation (HSE, 1982). Renal tumours were however observed in other experiments in rats following exposure to 600 ppm for 7 hours per day, 5 days per week for two years (Maltoni *et al*, 1986).

It has been suggested that the development of liver tumours in mice is linked to the metabolism of trichloroethylene to trichloroacetic acid, which has been shown to cause

peroxisome proliferation and sustained cell proliferation in mice. In other species, including humans, the extent to which trichloroethylene is metabolised to trichloroacetic acid is much smaller and human hepatocytes have been shown not to undergo peroxisome proliferation in response to trichloroacetic acid. It has therefore been concluded that the findings in mice are of limited relevance to humans (EU RAR, 2002, COC, 1996). In a separate review, Bull (2000) concluded that although low-level exposure to trichloroethylene is not likely to induce liver cancer in humans, higher exposures could affect sensitive populations. It was suggested that sensitivity could arise from different metabolic capacities for trichloroethylene or its metabolites or result from certain chronic diseases that have a genetic basis.

The development of lung tumours/lesions is also thought to be mouse specific and related to the build up of chloral hydrate in Clara cells in the lining of the lung as a result of trichloroethylene metabolism. In contrast human lung cells have a negligible capacity to metabolise trichloroethylene to the chlorate (EU RAR; Green 2000).

There is uncertainty about the mechanisms by which trichloroethylene induces kidney tumours in rats and the potential relevance to humans; given the species and gender differences in the susceptibility of animals (EU RAR; Lash *et al*, 2000; COC, 1996).

### 4.7.2 Published risk estimates

Several groups have used animal data to model human cancer risk factors. The outcome of such modelling is obviously dependent on which set of animal data is selected and the model used for analysis.

Using a linearised multistage model, a WHO working group calculated unit risk factors of $9.3 \times 10^{-7}$ per $ugm^{-3}$ based on the occurrence of pulmonary adenomas and carcinomas in mice reported by Maltoni *et al* (1988) and $4.3 \times 10^{-7}$ per $ugm^{-3}$ for Leydig-cell testicular tumours in rats (Maltoni *et al*, 1986). The development of Leydig cell tumours in rats was identified as the most sensitive endpoint and the WHO (2000) calculated that lifetime exposure to 23 $\mu gm^{-3}$ in ambient air is associated with a $10^{-5}$ cancer risk. The equivalent exposure concentration for a 40 year working lifetime would be 0.22 $mgm^{-3}$.

The EC Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity (2000) estimated that the systemic lifetime dose that would give rise to tumours in 25% of exposed animals ($TD_{25}$) was 130 mg/kg/day based on lymphomas observed in a mouse inhalation study (Henschler *et al*, 1980, 1984). The corresponding $TD_{25}$ based on kidney tumours in rats (Maltoni *et al*, 1986, 1988) was 5607 mg/kg/day. A DMEL for workplace based on the T25 for lyphomas in mice calculated by the EC Specialised Experts would be 0.052 $mgm^{-3}$ (allowing an allometric scaling factor of 7).

Clewell and Andersen (2004) used a physiologically-based pharmacokinetic (PBPK) model to estimate target tissue doses for the three principal animal tumours associated with trichloroethylene exposure: liver, lung, and kidney. Their approach was based on the observation that carcinogenicity appeared to be associated with increased cell proliferation due to receptor interaction or cytotoxicity and that most tumours represent an increase in the incidence of a commonly observed, species-specific lesion. The lowest PODs (lower bound estimates of the exposure associated with 10% tumour incidence) for lifetime human exposure to TCE were obtained for mouse liver tumours, assuming a mode of action primarily involving the mitogenicity of the metabolite trichloroacetic acid (TCA). The associated linear unit risk estimate for mouse liver

tumours is 1.5 x $10^{-6}$ for lifetime exposure to 1 µgm$^{-3}$ in ambient air. The equivalent workplace concentration associated with a $10^{-5}$ cancer risk for 40 years exposure at work would be 0.064 mgm$^{-3}$. However, these risk estimates ignore the evidence that the human is likely to be much less responsive than the mouse to the carcinogenic effects of TCA in the liver. A margin-of-exposure (MOE) approach was deemed to be more appropriate. Applying an MOE of 1000, environmental exposures below 66 µgm$^{-3}$ in ambient air (equivalent for 0.63 mgm$^{-3}$ at work for working lifetime exposure) were considered unlikely to present a carcinogenic hazard to human health. A DMEL based on the same benchmark dose would be 0.063 mgm$^{-3}$(allowing an MOE of 10,000 equivalent to a risk of $10^{-5}$) or the same as if the cancer risk estimate had been used directly.

The US EPA (2001) developed a number of cancer risk estimates based on both human and animal data in their draft toxicological review of trichloroethylene and these vary by several orders of magnitude. None of these risk estimates has been considered sufficiently reliable for adoption and incorporation into the Integrated Risk Information System (IRIS) database. The US EPA suggested users choose a single slope factor from among those it describes as appropriate for the population of interest and mode of exposure, but provided little guidance for making this choice.

| **Species** | **Data** | **POD mg/kg/day** | **Slope factor (mg/kg/day)$^{-1}$** | **Dose associated with $10^{-6}$ cancer risk mg/kg/day*** |
|---|---|---|---|---|
| Human studies | Liver cancer | | | |
| | Finnish cohort | 1.4 | $7x10^{-2}$ | $1.4x10^{-5}$ |
| | Kidney cancer | | | |
| | Finnish cohort | 0.05 | $2x10^{0}$ | $5x10^{-7}$ |
| | German cohort | 5 | $2x10^{-2}$ | $5x10^{-5}$ |
| | Non-Hodgkin's lymphoma | | | |
| | Finnish cohort | 0.014 | $7x10^{0}$ | $1.4x10^{-7}$ |
| | New Jersey cohort | 0.25 | $4x10^{-1}$ | $2.5x10^{-4}$ |
| Mouse studies | Liver cancer | | | |
| | Mechanism based model | Not applicable | $8x10^{-4}$ | $1.25x10^{-3}$ |
| | Mechanism based model | Not applicable | $8x10^{-2}$ | $1.25x10^{-3}$ |
| | Linear extrapolation | 0.5-3.1 | $3x10^{-3}$-$2x10^{-1}$ | $0.5\text{-}3.1x10^{-5}$ |
| | Nonlinear extrapolation | 0.5-3.1 | Not applicable | ($3x10^{-4}$) |
| | Lung cancer | 1.4-4.8 | Not applicable | Not calculable |
| Rat studies | Kidney cancer | 33 | $3x10^{-4}$ | $3.3x10^{-3}$ |
| | Testicular cancer | 25 | Not indicated | ($8x10^{-4}$) |

*environmental exposure

Based on the US EPA compilation of risk estimates, Lewandowski and Rhomberg (2005) identified the most appropriate interim unit risk for low-level inhalation exposure as 9 x $10^{-7}$ per µgm$^{-3}$ in ambient air. The associated concentration in workplace air associated with a lifetime cancer risk of $10^{-5}$ would be 0.02 ppm (0.11 mgm$^{-3}$) for 40 years exposure at work.

### 4.7.3 Derivation of a risk-based OEL

The table overleaf shows estimated workplace concentrations associated with a $10^{-5}$ cancer risk for forty years exposure in the workplace. An extremely wide range of potential values can be derived using published risk estimates from 0.0001 to >22 mgm$^{-3}$. Most estimates are less than 0.1 mgm$^{-3}$. Estimated concentrations associated with a $10^{-6}$ or $10^{-7}$ cancer risk would be 10 or 100 times lower than those associated with a $10^{-5}$ cancer risk.

| $10^{-5}$ cancer risk $\mu gm^{-3}$ | Source of estimate |
|---|---|
| 9.6 | US EPA draft - humans liver |
| 0.34 | US EPA draft - humans kidney – two studies |
| 33.5 | |
| 0.1 | US EPA draft – humans NHL – two studies |
| 1.7 | |
| 33.5-838 | US EPA draft -mouse Liver – various calculation methods |
| 22356 | US EPA draft - rat kidney |
| 105 | Lewandowski and Rhomberg (2005) |
| 64 | Clewell and Andersen (2004) |
| 220 | WHO (2000) rat Leydig-cell tumours |
| 52 | DMEL based on EU T25 - Mouse lung lymphomas |

There is no clear mechanism for selecting one of the projected values associated with a $10^{-5}$ cancer risk as opposed to another, although the data for kidney cancer in humans is probably the most relevant for risk assessment, implying that an appropriate OEL based on cancer risk estimation would be less than 0.04 $mgm^{-3}$.

The current UK WEL is 550 $mgm^{-3}$ (TWA) and 820 $mgm^{-3}$ as a 15 minute short-term exposure limit (STEL). The critical effect was identified as central nervous system toxicity with a steep dose response curve. The WEL was set to prevent impairment of performance and was based on very limited human data. The ACGIH TLV for trichloroethylene was in set 1993 and is 269 $mgm^{-3}$ as an 8 hour TWA with a 15 minute STEL of 537 $mgm^{-3}$. It is not listed as a suspected human carcinogen and the TLV was set to control subjective complains such as headaches, fatigue and irritability. The level at which the TLV was set was based on industrial experience and limited experimental data.

SCOEL are consulting on a health-based OEL of 10 ppm (55 $mgm^{-3}$) which is based on the avoidance of nephrotoxicity which they regard as a necessary precursor to kidney cancer. This proposed OEL based on a “practical threshold” for carcinogenicity is considerably higher than any candidate OEL based on estimated cancer risks of $10^{-5}$.

In conclusion, there is evidence to support the existence of a practical threshold for carcinogenicity in humans. An OEL based on the practical threshold would be expected to control cancer risks to less than $10^{-5}$ for lifetime exposure, although risk estimates based on mathematic modelling rather than mechanistic considerations would suggest that the proposed OEL is associated with a much higher level of cancer risk.

# 5 ADVANTAGES AND DISADVANTAGES OF USING QUANTITATIVE RISK CRITERIA IN SETTING OEL

## 5.1 ADVANTAGES

Major advantages of risk quantification are that it can inform cost benefit analysis to enable the setting of OELs at levels providing maximum health benefit versus socio-economic costs and it would enable the appropriate prioritisation of control measures.

## 5.2 DISADVANTAGES

The major disadvantage in using risk estimation as a tool in setting OELs is the high level of uncertainty in risk estimation combined with the false sense of precision that is conveyed by any numerical expression of risk.

Different methods of risk estimation can give rise to order of magnitude differences in calculated risks. Differences in risk estimation arise from the selection of different pivotal studies, differences in extrapolating from animal studies to human exposure and the use of different risk estimation models and curve fitting software. Although most methods of risk estimation for low levels of exposure are based on linear extrapolation from an index dose, different authorities have recommended different PODs corresponding to the modelled dose at which 1, 5, 10 or 25% of animals would be expected to show tumours on the basis of the curve that gives the best fit to the observed data, or the lower 95$^{th}$ percentile confidence limit on those estimated doses. Given that the modelled doses giving rise to tumours in 1, 5, 10 or 25% of animals do not scale linearly and the 95$^{th}$ lower confidence bound can be substantially lower than the median estimate, this immediately introduces an order of magnitude difference into risk estimates. Different authorities have also taken different approaches to the estimation of human equivalent doses from animal data and in whether dose is scaled according to a 40 year working lifetime versus a 70 or 75 year total lifespan or whether dose is simply scaled by considering the duration of the working week versus the dosing regime used in an experimental assay. Differences in the approach to dose scaling can also lead to order of magnitude differences in risk estimates. The adoption of common methods for risk estimation would reduce the variability of risk estimates based on an agreed single data set (e.g. through the adoption of the DMEL methodology, although this does not provide a unique specification of how the calculation should be performed). However, reducing the variability of risk estimates does not necessarily mean that the risk estimate is more reliable.

The uncertainties in risk estimation mean that the use of quantitative risk analysis might not lead to appropriate prioritisation or appropriate balance of apparent risk versus cost of control measures.

Risk estimates are difficult to communicate, particularly if expressed in terms of lifetime cancer risks and there is no widely accepted definition of tolerable risk. The guidance for REACH indicates that a $10^{-5}$ cancer risk would be tolerable in relation to workplace exposure. This however is a much lower level of risk than that associated with most current OELs for carcinogens. It is also likely that the application of cost-benefit analysis to inform the setting of OELs for carcinogens would lead to considerably greater risks being considered tolerable.

### 5.3 OTHER COMMENTS

The MOE approach provides quantified approach without assumptions of curve fit at low levels of exposure.

# 6 RECOMMENDATIONS

There is considerable variability in the mechanisms by which carcinogens cause cancer and in their toxicity. It would therefore be appropriate for SCOEL or other OEL setting bodies to use different approaches to the setting of OELs that take account of the mode/mechanisms leading to cancers and the huge variability in our knowledge of actual human exposure and dose response relationships. Even the division into genotoxic and non-genotoxic carcinogens is an over-simplification which, although useful as a simple division of occupational carcinogens for identifying further risk management measures, may lead to misplaced understanding of the more complex biology underlying both these terms. The greatest problem in setting OELs for many substances is the extremely limited data on which to base the OEL. This leads to a requirement for a flexible approach to setting OELs with a heavy reliance on expert judgement. QRA should play a role in the decision-making process where there are sufficient data to support QRA and good evidence that no threshold of effect is likely. It is however important that QRA merely informs the process and does not become the single criterion for setting an OEL at a given level. It also needs to be recognised QRA can only be undertaken where there are sufficient data to support QRA. There are many substances for which the available data cannot be used to develop quantitative risk estimates using any of the available methodologies. In developing a common approach to the use of QRA in setting OELs, a number of factors must be considered and these are discussed below.

QRA provides a mechanism for estimating the benefits that would arise from the imposition of OELs at different levels in terms of potential cancer deaths avoided, although the uncertainties in estimated benefits must be clearly stated. It should not be applied where risk estimates are based on animal data for tumour types not observed in humans or the mechanism leading to tumour development is clearly species specific (eg prolactin related tumours in rats). The uncertainties in risk estimates derived from animal data are such that while QRA may usefully inform the OEL decision process, it would be inappropriate to set OELs at pre-determined levels of risk, solely on the basis of animal data. Even where risk estimates are based on good human data, if the underlying mechanisms leading to carcinogenicity are not understood, then the use of different modelling approaches can lead to very different risk estimates. The current state of scientific knowledge is not adequate to determine which of the available risk estimates is likely to provide the most reliable indication of risk. It is uncertain that the implicit assumption of no threshold of effect for all genotoxic carcinogens is appropriate as DNA does have a considerable capacity for repair. For a number of better studied carcinogens, it has become apparent that the mechanisms leading to carcinogenicity are triggered by exposures to levels of a substance that exceed the body's ability to metabolise the substance by a particular route or lead to levels of a naturally occurring endogenous substance that significantly exceed background levels in the absence of exposure. Where such thresholds of effect are identified, then it is desirable to use them as a basis for setting an OEL. The unintended consequence of adopting this kind of mechanistic approach, is that QRA is most likely to be used in the OEL decision process for substances where the carcinogenic process is not understood and

exposure-response functions are based on uncertain data. Risk estimates developed using QRA for these substances may incorporate substantial (orders of magnitude) uncertainties.

It is clearly beneficial to consider the relationship between exposure and cancer risk in setting OELs as carcinogens have very variable potencies. The cancer risk associated with a given level of exposure as mg/m$^3$ or ppm may vary from negligible to more than 10% depending on the substance. This implies a requirement to use quantitative or semi-quantitative risk assessment to inform the OEL-setting process. Ranking by $T_{25}$ or $BMD_{10}$ provides a mechanism for doing this and both $T_{25}$ and $BMD_{10}$ can be linked into QRA if desired (see sections 2.6 and 2.7). The reliability of estimated $T_{25}$ or $BMD_{10}$ values and the extent to which QRA can be used is however is limited by data availability. For many substances, the information that is available from experimental and/or epidemiological studies may be almost nonexistent or highly contradictory and it may not be possible to develop a meaningful estimate of $T_{25}$ or $BMD_{10}$. Even where data are available, the level of uncertainty in the data may lead to uncertainties in these estimated values of more than an order of magnitude.

Given the variable nature, quantity and quality of data available for different substances, it is not possible to recommend a single approach to quantitative risk assessment for workplace exposures. Where possible, quantitative modelling should take account of the biological processes linking exposure to cancer and these are likely to vary on a substance-by-substance basis. It is also possible that with increasing knowledge of modes/mechanisms for many occupational carcinogens, “practical thresholds” (ie levels of exposure below which mechanistic considerations indicate carcinogensis is unlikely) will be demonstrated for a significant proportion of carcinogens. In these cases, it is likely to be appropriate to control exposure to below the practical threshold rather than to a much lower level based on a no threshold assumption. This is an approach that has been adopted by SCOEL where adequate data have been available.

Provided that a threshold cannot be established, cancer risk estimates should be based on human epidemiological data where there are sufficient data to develop exposure-response relationships over a wide range of exposures. If the available human data are inadequate for the development of exposure-response relationships, the risk assessment process should still take account of the available data, in considering the plausibility of risk estimates based on animal studies. The paucity of human data for many carcinogens, means that it is likely that for the foreseeable future it will be necessary to use animal data in setting OELs for occupational carcinogens. It would therefore seem sensible to reduce some of the variability in the quantitative risk assessment process by adopting an agreed EU approach to issues such as scaling animal dose to human exposure levels in the workplace. The guidance recently developed for the purposes of REACH would seem a sensible starting point (ECHA, 2008). The guidance includes the approach to be taken species to species and route to route scaling and scaling to allow for differences in duration of exposure (see section 2.8 above).

The REACH guidance does not provide a comprehensive guide to developing exposure-response relationships and risk estimates for carcinogens and it would be desirable to develop further guidance to ensure that a consistent approach is taken to risk estimation the development of OELs. Ideally exposure-response relationships and risk estimates should be based on toxicological mode/mechanistic where available. Where toxicological mode/mechanistic data are not available, a range of models can

be employed as described in section 2.3 above. These models should be tested with the data in order to select the one giving the best fit to the data. The USEPA software package BDMS provides a convenient tool for testing a range of widely used models as discussed in section 2.6, but does not include an exhaustive range of potential models. The REACH guidance suggests that either $T_{25}$ or $BMD_{10}$ may provide an appropriate starting point (POD) from which risks at lower exposure levels may be estimated on the basis of linear extrapolation (section 2.8). Other authorities have suggested that $BMD_1$ would give a more stable estimate (section 2.3). Under most circumstances, however, $BMD_{10}$ is within or close to the range of observed data, which provides an indication of reliability. Given that risk estimates based on $T_{25}$ will differ from those based on $BMD_{10}$ to a varying extent depending on the dataset, it would be desirable to specify which of the two quantities provides the most appropriate POD (section 2.8).

Recent regulatory discussions have promoted the use of $BMD_{10}$ and MOE to inform regulation rather than traditional cancer risk estimates (section 2.6). Although the two approaches are based on different philosophies, in practical terms, setting an OEL based on a $BMD_{10}$ and an MOE of 10,000 in concordance with recent risk management practice will give the same numerical value as setting an OEL based on more traditional risk assessment in which a lifetime cancer risk of $10^{-5}$ is calculated using linear extrapolation and $BMD_{10}$ as a POD.

Current OELs for carcinogens are typically set at risk levels that greatly exceed the $10^{-5}$ target set out in the REACH guidance, if quantitative risk assessment is to be believed. Even taking account of factors within the QRA process that introduce a bias towards risk over-estimation, OELs for many widely used carcinogens may have been set at levels that greatly exceed those associated with a $10^{-5}$ lifetime cancer risk. In practice, however, there may be little or no evidence of an increased cancer risks. It would seem desirable to consider the actual number of cancers likely to be avoided in the process of setting an OEL rather than simply applying a blanket level of “tolerable risk” as this could lead to the imposition of OELs that will have no health benefit. The work carried out within the other work packages of this project will inform on the number of cancers that might be avoided by the imposition of different risk management measures including OELs which could be an important tool in prioritising the substances of concern and the risk management measures to be applied. However, in order to develop reliable estimates of benefit, it will be necessary to have a reliable estimate of the number of the workers within the EU who are exposed to that substance and the current exposure levels. Some relevant historic information is available from the CAREX database and this could be updated using data generated as part of industry’s response to the REACH regulations. Undertaking this procedure to calculate the numbers of cancers prevented where there was reliance on animal data to establish risk could lead to estimates with high uncertainty. It is clearly important that confidence intervals are not only provided for all estimates but also taken account of within the OEL setting process. There are likely to be circumstances under which the confidence limits are so wide that risk estimates are not helpful to the decision making process. Where confidence limits are very wide, then it would important not to place undue weight on the estimated health benefits in the OEL decision process.

The approach taken to setting OELs for occupational carcinogens including when and how qualitative risk assessment is to be used should be underpinned by specific guidance that explains when and why any approach should be used. Such guidance needs to provide the criteria when certain defined quantitative methods are appropriate. Given the current evidence base as described in the main body of this review, these criteria will be necessarily judgement-based and should be based on the

consensus view of a wider group experts than those involved in this project. The likelihood is that not all criteria would need to be fulfilled for QRA to be appropriate and that the guidance should be there to assist, but not constrain, the work of an expert OEL-setting committee. The criteria must reflect a basic understanding of the toxicological mode/mechanism relevant to humans and a reliable understanding of exposure-response relationship. This latter could be from measured, estimated or modelled data. In cases where the basic criteria for using QRA are not fulfilled a more pragmatic approach is justified.

Bolt (2008) has outlined the way in SCOEL attempts to set out some ground rules for dealing with genotoxic and non-genotoxic carcinogens in fairly general terms. This approach has been further developed by Bolt and Huici-Montagud (2008), and has been endorsed as the SCOEL approach. As reviewed above, SCOEL in their OEL-setting work have tackled a number of genotoxic and non-genotoxic carcinogens and recommended OELs based on a number of approaches discussed above, including QRA. It is thus quite possible that a number of qualitative and quantitative approaches could be adopted provided that there is an agreed framework to inform the selection of an appropriate methodology for different substances. The table overleaf is based on the review undertaken for this project rather than the existing SCOEL documents and provides a suggested framework for the use of QRA in setting OELs that takes account of data availability. In our view, development of the exact criteria for using quantitative risk assessment would best be achieved through a workshop involving SCOEL members and a number of invited experts. The workshop could discuss a position paper based on the information within this Work Package.

| Data availability | Steps towards determining an OEL |
|---|---|
| Good human epidemiological data; good understanding of mechanisms underlying carcinogenesis | Review mechanistic information to establish whether threshold is likely to exist; use mechanistic information to establish threshold level of exposure in humans if possible or to inform QRA based on human epidemiological data. If no threshold apparent, use QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, establish health benefits in terms of cancers avoided across EU at each exposure level. If threshold identified, use as basis of OEL taking account of uncertainty in data. |
| Good human epidemiological data; poor understanding of mechanisms underlying carcinogenesis | Use epidemiological data to establish exposure response relationships, examine evidence for a threshold, undertake QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, establish health benefits in terms of cancers avoided across EU at each exposure level. If threshold identified, use as basis of OEL taking account of uncertainty in data. If no threshold established, review results of QRA taking account of uncertainties in model estimates. If data not adequate to reliably establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, use comparison of cancer incidence under different exposure regimes (eg low to high groups) to estimate number of cancers avoided by the imposition of an OEL at different levels. |
| Limited human data, good quality animal data, good understanding of mechanisms | Examine mechanistic information to confirm carcinogenic process is relevant to humans and to determine whether there is a threshold for effect. If threshold exists, establish equivalent human exposure level and use as basis of OEL. In absence of a threshold and undertake QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, |

| Data availability | Steps towards determining an OEL |
|---|---|
| | establish health benefits in terms of cancers avoided across EU at each exposure level. Review results of QRA taking account of uncertainties of model estimates and plausibility in terms of findings of workplace studies. |
| Very limited or no human data, good quality animal data | Consider potential mechanisms underlying carcinogenic process and likely relevance to humans and also whether a threshold of effect is likely. In absence of a threshold, undertake QRA to establish exposure levels associated with $10^{-3}$, $10^{-5}$, $10^{-6}$ and $10^{-7}$ lifetime cancer risks, establish health benefits in terms of cancers avoided across EU at each exposure level. Review results of QRA taking account of uncertainties of model estimates and plausibility in terms of findings of workplace studies. If no and/or lowest effects levels are identified and there are good arguments to support a threshold model, base OEL on no and/or lowest effects levels with appropriate scaling factors to take account of uncertainties |
| Very limited or no human data, poor quality animal data | QRA will give rise to highly uncertain results and should not be used as main rationale underlying an OEL. Given that it is desirable to set an OEL in order to ensure that excessive exposures are avoided, it may be appropriate to determine a generic low level of exposure that is applied as an OEL for suspected carcinogens where the data are inadequate to assess relative potency compared with other carcinogens. If there are data that allow some estimate of potency relative to other carcinogens, it might be possible to set an OEL on the basis of comparison with OELs for other similar substances. If cancers have been reported in exposed workers, OELs should be set at lower levels than the likely levels of exposure associated with cancers. |

At this stage we consider that it is possible to state a number of guiding principles that the workshop should take account of:

1. The extent to which the results of QRA are taken into account in setting OELs should reflect the certainty of the data. Considerably more reliance should be placed on the results of QRA based on well-conducted studies in humans rather than on animal data. Considerably greater credence should be given to the results of QRA undertaken for well established human carcinogens than for animal carcinogens for which there are no data to suggest an excess cancer risk in exposed workers

2. The extent to which animal data are taken into account should reflect study quality and the whether it is likely that the toxicological mechanisms leading to cancer and reported tumours could reasonably be expected to be relevant to humans.

3. Health impact assessment should be used as a tool to inform the setting of OELs, which would be consistent with the requirement to undertake regulatory impact analysis in the development of regulation within the EU. Where possible the number of cases avoided within the EU as a result of imposing OELs at different

levels should be estimated together with an indication of the timescale over which these benefits would accrue, taking account of foreseeable changes in patterns of use. The workshop should also consider how health impact assessment might be approached where it is not possible to use QRA or there are insufficient epidemiological data to estimate the number of cases avoided.

4. There is a need to determine a minimum dataset that satisfies a number of criteria including relevance to human exposure, data quality, dosing regime and cancer response for QRA to be used for genotoxic carcinogens. There is also a need develop a clear set of options that can be employed where it is not appropriate to use QRA. To a great extent, some of these possible approaches are addressed in current SCOEL procedures (Bolt and Huici-Montagud, 2007). Other options might include consideration of analogous substances, for example, for RCF a worst case cancer risk estimate could be based on risk estimates for chrysotile.

There are considerations which go beyond the direct issue of setting OELs for carcinogens in this Report and which are no doubt considered by the Commission along with social partners. As an example, in determining the level of risk that might be associated with exposure to a substance at the OEL, it would be appropriate to consider the risks of other work-related deaths. This approach has been taken by Germany in helping to define acceptable and tolerable risk. Given the dread and suffering associated with cancer, it would seem sensible to reduce cancer risks below the risk levels associated with other work-related causes of death. It is, however, arguable that it is difficult to justify reducing the risks to levels that are several orders of magnitude lower than those associated with other causes of work-related deaths. It is also relevant that if the OEL represents an upper bound of exposure, then actual exposures and risks will be much lower, particularly in the modern European economy where worker mobility means that it is unlikely that individuals would be exposed over a 40 year working lifetime.

With the large number of recognised human carcinogens still in existence in the workplace and with increasing focus on regulatory impact assessment, quantitative risk assessment can play an important role in estimating the health benefits (cancer reduction or elimination) associated with different candidate OELs as part of the decision-making process.

# 7 REFERENCES

ACGIH (2001) TLV Criteria Documents for acrylamide, benzene. American Conference of Governmental Industrial Hygienists Threshold Limit Values

ACGIH (2005) TLV Criteria Documents for acrylamide. American Conference of Governmental Industrial Hygienists Threshold Limit Values

Allen B, Zeiger E, Lawrence G, Friedman M, Shipp A. Dose-response modeling of in vivo genotoxicity data for use in risk assessment:some approaches illustrated by an analysis of acrylamide. Regul Toxicol Pharmacol. 2005 Feb;41(1):6-27.

Austin SG, Sielken RL Jr. Issues in assessing the carcinogenic hazards of ethylene oxide. J Occup Med. 1988 Mar;30(3):236-45.

Beliles RP, Parker JC. Risk assessment and oncodynamics of ethylene oxide as related to occupational exposure. Toxicol Ind Health. 1987 Sep;3(3):371-82.

Bolt HM. The Concept of “Practical Thresholds” in the Derivation of Occupational Exposure Limits for Carcinogens by the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Union. 2008 Genes and Environment; 30:114-119

Bolt HM, Huici-Montagud A. Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. Arch Toxicol. 2008 Jan;82(1):61-4.

Bull RJ (2000) Mode of action of liver tumor induction by trichloroethylene and its metabolites, trichloroacetate and dichloroacetate. Environmental Health Perspectives: 108 Suppl 2;241-59

Caldwell JC, Keshava N. Key issues in the modes of action and effects of trichloroethylene metabolites for liver and kidney tumorigenesis. Environ Health Perspect. 2006 Sep;114(9):1457-63.

Chen C, Farland W. Incorporating cell proliferation in quantitative cancer risk assessment: approaches, issues, and uncertainties. Prog Clin Biol Res. 1991;369:481-99.

Clewell HJ, Andersen ME Applying mode-of-action and pharmacokinetic considerations in contemporary cancer risk assessments: an example with trichloroethylene.. Crit Rev Toxicol. 2004 Sep-Oct;34(5):385-445.

COC (2004) Guidance on a strategy for the risk assessment of chemical carcinogens

COC/COM (1996) Report of the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, Department of Health

Commission on Risk Assessment and Risk Management (1996) www.riskworld.com/nreports/1996/risk_rpt/html/nr6aa042.htm

Crump, K. S. (1995). Calculation of benchmark doses from continuous data. Risk Anal. 15, 79–89.

Crump KS. Risk of benzene-induced leukemia predicted from the Pliofilm cohort. Environ Health Perspect. 1996 Dec;104 Suppl 6:1437-41.

Crump KS. Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health. 1994 Jun;42(2):219-42.

Crump KS. An improved procedure for low-dose carcinogenic risk assessment from animal data. J Environ Pathol Toxicol Oncol. 1984 Jul;5(4-5):339-48.

Crump K, Allen B. Quantitative estimates of risk of leukemia from occupational exposure to benzene. Unpublished report prepared for the Occupational Safety and Health Administration, 1984.

DECOS (2006) Acrylamide: Health-based occupational cancer risk values. Health Council of the Netherlands; publication no. 2006/05OSH

Defra (2008) Guidance on the legal definition of contaminated land http://www.defra.gov.uk/environment/quality/land/contaminated/documents/legal-definition.pdf

Dourson M, Hertzberg R, Allen B, Haber L, Parker A, Kroner O, Maier A, Kohrman M. Evidence-based dose-response assessment for thyroid tumorigenesis from acrylamide. Regul Toxicol Pharmacol. 2008 Dec;52(3):264-89.

Dybing E, Sanner T, Roelfzema H, Kroese D, Tennant RW.T25: a simplified carcinogenic potency index: description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity.Pharmacol Toxicol. 1997 Jun;80(6):272-9.

EC Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity (2000)

ECHA (2008) Guidance on information requirements and chemical assessment: Chapter R.8: Characterisation of dose (concentration) – response for human health. European Chemicals Agency

EFSA (2009) Scientific opinion: use of the benchmark dose approach in risk assessment. Guidance of the Scientific Committee. The EFSA Journal 1150, 1-72

EFSA (2005) A harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. The EFSA Journal 282, 1-31

EMEA (2005) Guideline on risk management systems for medicinal products for human use. European Medicines Agency. EMEA/CHMP/96268/2005

EU RAR 2002 Acrylamide

EU RAR (2004) European Risk Assessment Report. Trichloroethylene, 1st Prioirty List, vol. 31, EUR 21057EN (ecb.jrc.it) – check data

European Risk Observatory (2009) Exploratory survey of Occupational Exposure Limits (OELs) for Carcinogens, Mutagens and Reprotoxic substances (CMRs) at EU Member

States level http://osha.europa.eu/en/riskobservatory/teaser/Exploratory_survey_Occupational_Exposure_Limits

Friedman MA, Dulak LH, Stedham MA. A lifetime oncogenicity study in rats with acrylamide. Fundam Appl Toxicol. 1995 Aug;27(1):95-105.

Garman RH, Snellings WM, Maronpot RR. Frequency, size and location of brain tumours in F-344 rats chronically exposed to ethylene oxide. Food Chem Toxicol. 1986 Feb;24(2):145-53.

Garman RH, Snellings WM, Maronpot RR. Brain tumors in F344 rats associated with chronic inhalation exposure to ethylene oxide. Neurotoxicology. 1985 Spring;6(1):117-37.

Gaylor DW, Chen JJ, Sheehan DM. Uncertainty in cancer risk estimates. Risk Anal. 1993 Apr;13(2):149-54.

German Committee on Hazardous Substances (2008) Guide for the quantification of cancer risk figures after exposure to carcinogenic hazardous substances for establishing limit values at the workplace.

Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR, Fritschi L, Adams GG, Bisby JA,

Manuell R. Leukemia risk associated with low-level benzene exposure. Epidemiology. 2003 Sep;14(5):569-77.

Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR. The health watch case-control study of leukemia and benzene: the story so far. Ann N Y Acad Sci. 2006 Sep;1076:80-9.

Green T (2000) Pulmonary toxicity and carcinogenicity of trichloroethylene: species differences and modes of action. Environmental Health Perspectives;108 Suppl 2:261-4.

Greim H, Reuter U. Classification of carcinogenic chemicals in the work area by the German MAK Commission: current examples for the new categories. Toxicology. 2001 Sep 14;166(1-2):11-23. 2001

Howe RB, Crump K. GLOBAL82: A computer program to extrapolate quantal animal toxicity data to low doses, KS Crump and Company, Inc, Ruston LA 1982

Henschler D, Elsasser HM, Romen W, Elder E (1984) Carcinogenicity study of trichloroethylene with and without epoxide stabilisers, in mice. Journal of Cancer Research and Clinical Oncology: 104: 149-156

Henschler D, Romen W, Elsasser HM, Reichert D, Eder D, Radwan Z (1980) Carcinogenicity study of trichloroethylene by long term inhalation in 3 animal species. Archives of Toxicology 69; 291-299

HPA 2008 Benzo[a]pyrene: Use of excess lifetime cancer risk estimates. Health Protection Agency Clarification Note Series Note 1

HSE (1982) Toxicity review 6: Trichloroethylene. Health and Safety Executive, HMSO.

HSE (1992) The tolerability of risk from nuclear power stations. Health and Safety Executive, HMSO

HSE (2001) Reducing risks, protecting people: HSE's decision making process. Health and Safety Executive.

JECFA (2006) Sixty fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO/IPCS Safety evaluation of certain contaminants in food. WHO Food Additives Series 55.

Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA, Mast RW. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl Pharmacol. 1986 Sep 15;85(2):154-68.

Kelsh MA, Weingart M, Mandel JH, Mink PJ, Alexander DD, Basu R, Goodman M (2005) A meta-analysis of occupational trichloroethylene exposure and selected cancers. Annals of Epidemiology:15; 632

Kirman CR, Sweeney LM, Teta MJ, Sielken RL, Valdez-Flores C, Albertini RJ, Gargas ML. Addressing nonlinearity in the exposure-response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. Risk Anal. 2004 Oct;24(5):1165-83.

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Würtzen G Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol. 2004 Jan;42(1):65-83.

Kuschner M, Laskin S, Drew RT, Cappiello V, Nelson N. Inhalation carcinogenicity of alpha halo ethers. III. Lifetime and limited period inhalation studies with bis(chloromethyl)ether at 0.1 ppm. Arch Environ Health. 1975 Feb;30(2):73-7.

Lash LH, Parker JC, Scott CS. Modes of action of trichloroethylene for kidney tumorigenesis. Environ Health Perspect. 2000 May;108 Suppl 2:225-40.

Lewandowski TA, Rhomberg LR (2005) A proposed methodology for selecting a trichloroethylene inhalation unit risk value for use in risk assessment. Regulatory Toxicology and Pharmacology;41:39-54

Lynch DW, Lewis TR, Moorman WJ, Burg JR, Gulati DK, Kaur P, Sabharwal PS. Sister-chromatid exchanges and chromosome aberrations in lymphocytes from monkeys exposed to ethylene oxide and propylene oxide by inhalation. Toxicol Appl Pharmacol. 1984 Oct;76(1):85-95.

Lynch DW, Lewis TR, Moorman WJ, Burg JR, Groth DH, Khan A, Ackerman LJ, Co Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. Toxicol Appl Pharmacol. 1984 Oct;76(1):69-84.

Maltoni C, Lefemine G, Cotti G, Perino G (1988) Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. Annals of the New York Academy of Sciences;534:316-42.

Maltoni C, Lefermine G, Cotti G (1986) Experimental research on trichloroethylene carcinogenesis. In Archives of research on Industrial carcinogenesis (eds: Maltoni C, Mehlman MA) 5; 1-393. Princeton Scientific, Princeton, NJ cited by EU RAR

Manuell R. Leukemia risk associated with low-level benzene exposure. Epidemiology. 2003 Sep;14(5):569-77.

Marsden DA, Jones DJ, Lamb JH, Tompkins EM, Farmer PB, Brown K. Determination of endogenous and exogenously derived N7-(2-hydroxyethyl)guanine adducts in ethylene oxide-treated rats. Chem Res Toxicol. 2007 Feb;20(2):290-9. Epub 2007 Jan 31.

Metal finishing Metal finishing; May 2009; 17-8www.metalfinshing.com).

Moolgavkar SH, Knudson AG Jr. Mutation and cancer: a model for human carcinogenesis. J Natl Cancer Inst. 1981 Jun;66(6):1037-52.

Moore MM, Harrington-Brock K (2000) Mutagenicity of trichloroethylene and its metabolites: implications for the risk assessment of trichloroethylene. Environmental Health Perspectives 108 Suppl 2:215-23

Nilsson R, Molholt B, Sargent EV. Quantitative assessment of a human carcinogenic potency for propylene oxide. Regul Toxicol Pharmacol. 1991 Dec;14(3):229-44.

Paulsson B, Granath F, Grawé J, Ehrenberg L, Törnqvist M. The multiplicative model for cancer risk assessment: applicability to acrylamide. Carcinogenesis. 2001 May;22(5):817-9. Erratum in: Carcinogenesis 2001 Sep;22(9):1577.

Paustenbach DJ, Price PS, Ollison W, Blank C, Jernigan JD, Bass RD, Peterson HD. Reevaluation of benzene exposure for the Pliofilm (rubberworker) cohort (1936-1976). J Toxicol Environ Health. 1992 Jul;36(3):177-231.

Peto R, Pike MC, Bernstein L, Gold LS, Ames BN. The TD50: a proposed general convention for the numerical description of the carcinogenic potency of chemicals in chronic-exposure animal experiments. Environ Health Perspect. 1984 Dec;58:1-8.

Sanner T, Dybing E, Willems MI, Kroese ED. A simple method for quantitative risk assessment of non-threshold carcinogens based on the dose descriptor T25. Pharmacol Toxicol. 2001 Jun;88(6):331-41.

SCCP (2008) Use of the Threshold of Toxicological Concern (TTC) approach for the safety assessment of chemical substances. Draft Opinion of the Scientific Committees:The Scientific Committee on Consumer Products (SCCP), The Scientific Committee on Health and Environmental Risks (SCHER) The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); SCCP/1171/08

Seeley MR, Tonner-Navarro LE, Beck BD, Deskin R, Feron VJ, Johanson G, Bolt HM. Procedures for health risk assessment in Europe. Regul Toxicol Pharmacol. 2001 Oct;34(2):153-69. Review.

Shipp A, Lawrence G, Gentry R, McDonald T, Bartow H, Bounds J, Macdonald N, Clewell H, Allen B & Van Landingham C 2006 Acrylamide: review of toxicity data and

dose–response analyses for cancer and noncancer effects. *Critical Reviews in Toxicology* **36** 481–608

Snellings WM, Weil CS, Maronpot RR. A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. Toxicol Appl Pharmacol. 1984 Aug;75(1):105-17.

Stayner LT, Dankovic DA, Smith RJ, Gilbert SJ, Bailer AJ. Human cancer risk and exposure to 1,3-butadiene--a tale of mice and men. Scand J Work Environ Health. 2000 Aug;26(4):322-30.

Steenland K, Stayner L, Deddens J. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med. 2004 Jan;61(1):2-7.

Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med. 2009 Jun;51(6):714-23.

Sweeney LM, Kirman CR, Albertini RJ, Tan YM, Clewell HJ, Filser JG, Csanády G, Pottenger LH, Banton MI, Graham CJ, Andrews LS, Papciak RJ, Gargas ML. Derivation of inhalation toxicity reference values for propylene oxide using mode of action analysis: Example of a threshold carcinogen. Crit Rev Toxicol. 2009;39(6):462-86.

Teta MJ, Sielken RL Jr, Valdez-Flores C. Ethylene oxide cancer risk assessment based on epidemiological data: application of revised regulatory guidelines. Risk Anal. 1999 Dec;19(6):1135-55.

Thier R, Bolt HM. Carcinogenicity and genotoxicity of ethylene oxide: new aspects and recent advances. Crit Rev Toxicol. 2000 Sep;30(5):595-608.

US EPA (2001) Draft Trichloroethylene health risk assessment: synthesis and characterization. oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=4580

US EPA (2005) Guidelines for carcinogen risk assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283US EPA (2006) Evaluation of the Carcinogenicity of Ethylene Oxide http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157664

US EPA (2000) Carcinogenicity assessment for benzene http://www.epa.gov/ncea/iris/subst/0276.htm

US EPA (1994) Carcinogenicity assessment for propylene oxide http://www.epa.gov/ncea/iris/subst/0403.htm

van Sittert NJ, Boogaard PJ, Natarajan AT, Tates AD, Ehrenberg LG, Törnqvist MA. Formation of DNA adducts and induction of mutagenic effects in rats following 4 weeks inhalation exposure to ethylene oxide as a basis for cancer risk assessment. Mutat Res. 2000 Jan 17;447(1):27-48.

Wartenberg D, Reyner D, Scott CS (2000) Trichloroethylene and cancer: epidemiologic evidence.Environmental Health Perspectives;108 Suppl 2:161-76.

Wriedt H (2008) The future German system for setting OELs for carcinogens. Working Party Chemicals at the Workplace, Luxembourg, 16th April 2008.

WHO (2000) Air quality guidelines for Europe. World Health Organization

**HEAD OFFICE:**

Research Avenue North,
Riccarton,
Edinburgh, EH14 4AP,
United Kingdom
Telephone: +44 (0)131 449 8000
Facsimile: +44 (0)131 449 8084

Tapton Park Innovation Centre,
Brimington Road, Tapton,
Chesterfield, Derbyshire, S41 0TZ,
United Kingdom
Telephone: +44 (0)1246 557866
Facsimile: +44 (0)1246 551212

Research House Business Centre,
Fraser Road,
Perivale, Middlesex, UB6 7AQ,
United Kingdom
Telephone: +44 (0)208 537 3491/2
Facsimile: +44 (0)208 537 3493

Brookside Business Park,
Cold Meece,
Stone, Staffs, ST15 0RZ,
United Kingdom
Telephone: +44 (0)1785 764810
Facsimile: +44 (0)1785 764811

**Email: iom@iom-world.org**