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EXTRAPOLATING FROM TOXICITY DATA TO OCCUPATIONAL EXPOSURE LIMITS: SOME CONSIDERATIONS*

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Abstract—This paper evaluates procedures relevant to extrapolating from toxicity data in man and animals to Occupational Exposure Limits. It examines effects at or around the 'No Observed Adverse Effect Level' (NOAEL) and the magnitude of safety factors which can be applied in developing occupational exposure limits for non-stochastic effects. The relationship between incidence of stochastic effect and occupational exposure limit is also discussed.

INTRODUCTION

IN THE U.K. the Control of Substances Hazardous to Health (COSHH) Regulations, 1988, describe two classes of occupational exposure limits (OEL): the Maximum Exposure Limit (MEL) and the Occupational Exposure Standard (OES). These relate solely to airborne exposure and are defined in Appendix 1. The regulations further require employers to assess risks due to exposure (from whatever cause) and, where necessary, to prevent or control them. This will often mean setting 'in house' OELs.

Setting an OEL involves two steps:

(i) obtaining and evaluating all the information available on hazard (effect), and in particular, on the dose–effect or dose–response relationship for that hazard; and

(ii) evaluating the risk, or risks, in relation to exposure level and hazard.

The Health and Safety Commission has published guidelines (Appendix 2) which distinguish which limits should be a MEL's and which should be OES's.

Risk criteria for use in this process have been described in an associated paper (ILLING, 1991), and the decision-making sequence is outlined in Fig. 1. Essentially similar sequences can be developed for setting individual workplace standards under COSHH (see ILLING, 1991). This paper addresses the question 'what criteria (yardsticks) are appropriate when deciding how to convert the information available on the dose–effect or dose–response relationship for a chemical into an acceptable OEL'?

A recent paper has set out the criteria used for the parallel exercise, that of setting quantitative acceptable daily intakes (ADIs) of chemicals in food in the U.K. (RUBERY *et al.*, 1990). The ADI is defined in Appendix 1. There are, however, significant

*Opinions expressed in this paper are intended as a contribution to a discussion on these topics. They are not, therefore, statements of HSE policy.

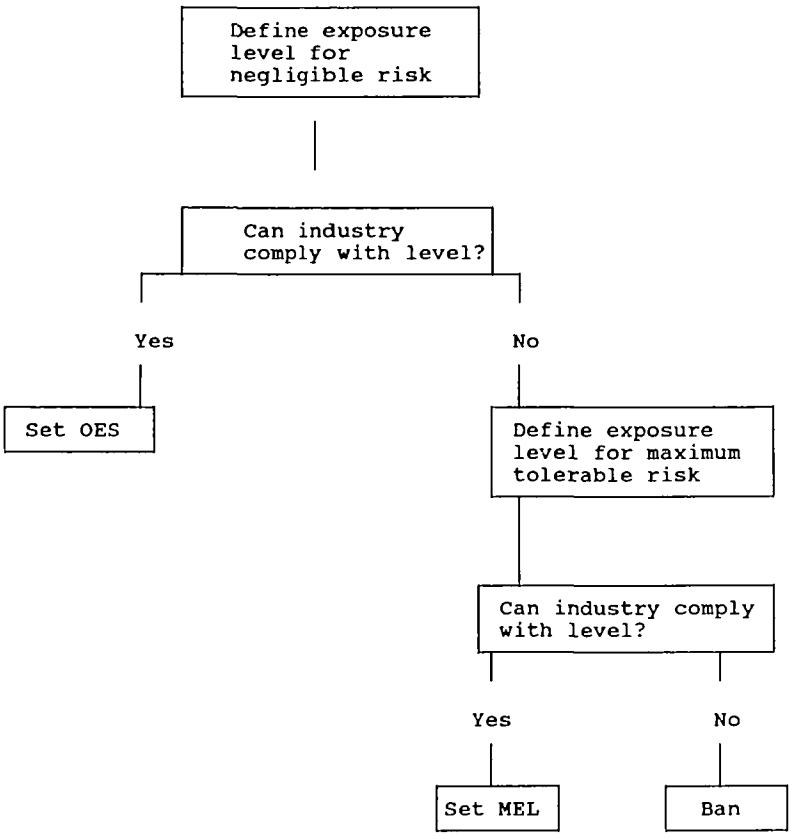

FIG. 1. Decision procedure for setting Occupational Exposure Levels.

differences between the quality and quantity of data available for setting ADIs and OELs.

An OEL has to be set on the basis of the hazard data available, because at present the right to insist on further testing is limited. The data may be of a high quality and adequacy comparable to those required for regulatory schemes (including for setting ADIs), but are more likely to be limited, old and difficult to interpret. Many OEL toxicity assessments include evidence concerning human experience, often not available for pre-marketing regulatory schemes. Thus, in setting an OEL, it is essential to be aware of the quality and type of the information on hazard and exposure, and assessments of this type will usually need revision in the light of new knowledge. As HART and JENSEN (1990) have suggested, no hazard assessment is final.

Also necessary is an understanding of the type of risk ('voluntary' and 'involuntary') and the risk level that is being considered, i.e. 'negligible' (for example, an OES), 'tolerable' (for example, a MEL) or 'unacceptable' (for example, a ban). Definitions are given in Appendix 3.

This paper concentrates on the ways in which often incomplete toxic hazard data, with its uncertainties, can be set against risk criteria. It is intended to stimulate discussion.

STOCHASTIC AND NON-STOCHASTIC EFFECTS

The first distinction to make when assessing toxic hazards is that between 'stochastic' and 'non-stochastic' effects. A 'stochastic' effect is one for which the probability of occurrence, rather than the severity of effect, depends on the absorbed dose (and hence exposure level) and there may be no threshold. The 'non-stochastic' effect is one where the severity varies with the exposure level and for which there may be a threshold (IPCS, 1983). For practical purposes, effects which result from interference in the DNA (e.g. genetically caused cancers) and perhaps (because the vast range of inter-individual variation in threshold) of the immune system (sensitizations) may have to be treated as stochastic effects. For most other toxic effects there is a gradation of response, from, for example, minor, recoverable changes in enzyme levels, through histologically apparent damage of varying severity to irrecoverable organ failure and, potentially, death. Hence they are considered non-stochastic. These latter effects will be examined first as they are the effects most usually needing detailed consideration when setting an OEL.

NON-STOCHASTIC EFFECTS

For these effects it is generally possible to identify various levels of severity of the effect, and a 'no-effect level'. Examples of the levels of severity of effect are given in ILLING (1991). When setting OELs, the meaning of the 'no-effect level' must be clearly understood so it will be further examined here.

(a) *The meaning of the no-effect level*

Interpretation of what constitutes a 'no effect level' can be very difficult. ZBINDEN (1979) correctly called it an "old bone of contention". It is often referred to as a 'no observed effect level' which has been defined as "the highest dose level of a chemical that, in a given toxicity test, caused no observable adverse effects in the test animal" (HODGSON *et al.*, 1988), or as "The greatest concentration or amount of an agent, found by study or observation, that causes no detectable, usually adverse, alteration of morphology, functional capacity, growth, development or lifespan of the target" [International Programme on Chemical Safety/Joint FAO/WHO Committee on Food Additives (IPCS/JECFA, 1987)].

In practice, it is the 'no observed adverse effect level' (NOAEL) which is required (see FERON *et al.*, 1990). Although it has never been defined in terms relevant to risk evaluation, it is a hazard statement derived directly from the experimental data, and because of the statistical and biological limitations of the experimental techniques used to define it, it has an associated level of uncertainty.

Essentially, establishing a NOAEL requires a consideration of what constitutes an adverse effect. Some criteria are contained in Environmental Health Criteria 6 (WHO, 1978), when it suggests that non-adverse effects are those which do not cause "change of morphology, growth, development or life span", and which do not result in "impairment of functional capacity or impairment of the ability of the organism to maintain homeostasis and do not enhance susceptibility to the deleterious effects of other environmental influences". Adverse effects, by inference do have these effects.

SHARRATT (1976) stated that "The figure determined [for a NOAEL] in short- and

long-term experiments is influenced by the species and strain of animal used, by sex and by other factors. The exposure level at which no adverse effects are detected in animal experiments is often as little as one-tenth of the nearest higher dose level at which minimal adverse effects, or effects of doubtful toxicological significance are found". He pointed out that "the criteria of 'no-effect' also change as more sensitive methods for detecting abnormalities are introduced and as knowledge of the mechanisms involved become available".

A knowledge of the type of effect seen, and its seriousness, is important when trying to relate the 'NOAEL' to a risk criterion.

(b) *Criteria for defining the numerical value for a NOAEL*

(1) *Statistical significance and biological relevance.* In general an effect is described in terms of the frequency and/or the magnitude of the response seen in a particular parameter or parameters. It is therefore amenable to a statistical assessment of significance. However, a professional judgement on the importance of the effect is also required. If other parameters relating to a biological effect are also higher in the same animals, but not quite to statistical significance, then the effect is probably biologically important. Toxicological importance ('adverseness') depends on a further, judgmental evaluation of the effects see (FERON *et al.*, 1990). The language used in such judgements must be carefully chosen, as ambiguity must be avoided when conveying strength of meaning (see WOODWARD and DAYAN, 1990).

(2) *Effects at or near the 'no observed adverse effect level'.*

(i) Biological effect monitoring indices

The monitoring of biological effects is generally based on the concept that the index being monitored is a minor reversible, sub-clinical biological effect caused by the agent. Thus the indices used are based on the idea that an adverse health effect would occur if the person were either exposed to higher concentrations of the relevant agent, or exposed to it for a longer period of time. Effects being monitored are therefore probably those just observed near the appropriate level for a 'NOAEL'. An example might be the detection of a slightly higher level of, say, γ-gluatamyl transferase (a serum marker enzyme for liver dysfunction) in some, but not all, those exposed to a particular concentration of a chemical known to cause overt liver damage at higher levels of exposure.

(ii) Respiratory irritants

Respiratory irritants can be divided, at least conceptually, into sensory irritants and those causing inflammatory responses. Sensory irritation is often regarded as a 'nuisance' rather than as a health effect. Some particularly evil smelling substances (often containing sulphur atoms) can provoke an ill-health response for which there is no apparent physiological cause, usually headache, nausea and vomiting. This must be treated as important. Any OEL will need to be set at concentrations below those at which odour provokes this type of illness. Respiratory irritation involving inflammation is considered to be a health effect, albeit usually relatively minor and reversible. Thus, the coughing, watering of eyes, etc., caused by riot control agents would be considered adverse effects if they occurred in the workplace. In these circumstances

there is a need for a judgement concerning 'adverseness' which at present is on a case-by-case basis.

(iii) Behavioural effects

Behavioural effects, such as changes in reaction times, alertness or mood, often noted in volunteer studies investigating the acute effects of organic solvent exposure, represent changes in functional capacity which are normally readily and rapidly reversible on cessation of exposure. Other changes in behavioural parameters, such as those of pre-senile dementia, may be irreversible. Thus, if the subjects have been properly examined and the effects found to be sufficiently prevalent they indicate that the NOAEL has been exceeded. Often both subjective and objective assessments are used. Statistically significant changes in subjective measures of behaviour need to be considered on a case-by-case basis. Because studies usually involve few subjects, any statistically significant relevant objectively measured prevalence of an effect is likely to exceed the 'negligible' risk level, and therefore any OES would need to be set below the levels of exposure at which it was observed.

(c) *Safety factors*

(1) *Safety factors for 'negligible' 'involuntary' risk.* Theoretically, when setting OELs, one should check that likely frequencies for all effects are at or below those set as criteria for judging the acceptability of the limit. In practice, this cannot be carried out directly as the criteria refer to the population at risk, not the populations (of animals or of workers) studied. Extrapolation from studies involving animals requires a consideration of inter-species and inter-individual variation. Also animal studies are usually conducted under controlled exposure conditions and involve small numbers of relatively homogeneous, healthy individuals. The human population is likely to be exposed to variable concentrations of the chemical, to be variable in size and to be heterogeneous: it will contain groups or individuals likely to be more susceptible because of genetic predisposition (FESTING, 1987) or ill health. Workers are normally healthier than the general population, as exemplified by the 'healthy worker effect' in mortality studies, but they still include people of widely differing health and genetic make-up. People are rarely exposed solely to a single substance, and substances may interact synergistically (as for example, methyl ethyl ketone and *n*-hexane) or additively, or they may not interact at all; nevertheless it is assumed that mixed exposure is not normally the principle cause of variation in response in man. Safety factors therefore allow for uncertainty in the data and in the extrapolation, as well as for differences in risk criteria.

Use of particular numbers in safety factors must be considered specific to a particular set of circumstances, but it is possible to set some broad guidelines for different categories of circumstances.

(2) *Numerical values considered appropriate for 'negligible' 'involuntary' risk.* In the food or pesticides areas a factor of 100 is usually used for a (reversible) toxic effect identified in good animal toxicity studies (see e.g. RUBERY *et al.*, 1990; FERON *et al.*, 1990, LU, 1988). Irreversible effects, such as those related to non-genotoxic carcinogenesis and teratogenicity, may call for larger safety factors (IPCS/JECFA, 1987): a factor of 1000 has been suggested for teratogens (see JOHNSON, 1988). These

factors represent uncertainties in inter-individual and inter-species variation as well as differences in what is regarded as a 'negligible' risk level for when it relates to an 'involuntary' risk (see Appendix 3 for definitions of these terms). They can be examined in individual cases in the light of expert judgement on the quality of the evidence available concerning the dose–response relationship and the uncertainty of the extrapolation. Of these overall safety factors one factor of 10 is intended to represent inter-individual variation and a further factor of 10 (or 100) to represent inter-species variation: the consequences of this assumption are shown in Table 1.

TABLE 1. SAFETY FACTORS USED IN EXTRAPOLATING FROM ANIMAL TOXICITY STUDIES TO HUMAN EXPOSURE

	Safety factor			
Toxic effect seen	Overall *value**†	Value if stripped of inter species *variation*†	Possible value for an occupational ('voluntary' but 'negligible') risk exposure (animal data *only*)	*(human data)*
Genotoxic carcinogenic effects	N/A	N/A	N/A	N/A
Non-genotoxic carcinogenic effects Teratogenic effects	around 1000	around 100	around 100	around 10
Other (minor) effects seen in toxicity studies‡	around 100	around 10	around 10	minimal

N/A = not applicable.
*Based on RUBERY *et al.* (1990) and JOHNSON (1988).
†These factors are for 'neglible' 'involuntary' risks to the general public such as those arising from ingestion of a food chemical.
‡These may include some effects suitable for use as biological effect monitoring indices.
In all cases these are guidelines and each substance must be considered indvidually.

(3) *Extrapolation from human information.* Although an 'acceptable daily intake' for a chemical in food would be set below the NOAEL obtained from human studies (LU, 1988), by a factor of perhaps 10, such NOAELs are usually not available. A similar safety factor is not normally applied in the workplace when setting OELs. Perhaps this is because:

(a) it is easier to monitor exposure levels;
(b) generally speaking, workers are relatively healthy when occupationally exposed;
(c) it is possible to monitor exposed workers medically, and to remove them from exposure should symptoms of ill-health occur; and
(d) occupational exposure to a substance is at least in part, a 'voluntary' activity, entered into by a limited portion of the population; environmental exposure is considered an 'involuntary' activity imposed on the general population.

(a), (b) and (c) above reduce the uncertainty attached to the hazard evaluation, whereas (d) means that a higher risk level is perceived as 'negligible' (see ILLING, 1991).

If the OEL set is based on a 'tolerable' rather than a 'negligible' level of risk, then

it involves a risk/benefit analysis for the increased risk of minor ill health that is tolerated. This option is rarely needed when dealing with acceptable daily intakes (see ILLING, 1991).

If the data being examined refer to severe effects such as death or organ failure, it will still be necessary to use a safety factor. The magnitude of the safety factor will depend on the quality of the reports and of the data presented, the effects measured, and their prevalence in the populations studied.

Case reports are of limited value when setting OELs, as they lack information on prevalence, and often also lack exposure level data. Morbidity studies are useful, provided they are accompanied by good exposure data. They can give information on the effect measured and on the dose–response for that effect. Mortality studies tend to be less important, as death is an outcome too extreme to use when handling non-stochastic effects.

(4) *Extrapolation from animal studies.* Where data in man is not available, or of poor quality or of doubtful relevance, extrapolation from animal studies is normally necessary. Ideally, this should be based on toxicokinetic and toxicodynamic considerations, such as those used in physiologically based pharmacokinetic models (e.g. ANDERSEN *et al.*, 1991). As, usually, insufficient data are available, more pragmatic approaches are employed. These depend on the *a priori* assumption that, until otherwise proven, the test species and man handle the chemical similarly and the chemical has similar effects in both species.

When extrapolating between species, scaling factors (allometric scaling) are often employed as a means of allowing for the different sizes of the species studied. Any of several bases can be used, two of the most common being body weight and body surface area (CALABRESE, 1983; VOISIN *et al.*, 1990). Surface area is claimed to be more relevant, but, when a substance is administered orally or parenterally, the doses used in animal studies are normally quoted in mg kg^{-1}. Thus, for simplicity, the correction is usually for body weight.

For inhalation studies there are two parallel extrapolations—one for body weight or surface area and the other for the surface area of the lung (the absorbing tissue). For practical purposes these can be regarded as cancelling each other out (FERON *et al.*, 1990), so exposures are usually quoted as a concentration and duration of exposure, without further correction.

The actual magnitude of the safety factor will depend on the quality of the studies and the type of toxicity in terms both of its severity and of its reversibility. A NOAEL for a well conducted study might be translated to an OEL if the only effect seen at the next highest dose level (probably 5–10-fold higher than the NOAEL) were statistically significant, but merely consisted of minor changes in biochemical or behavioural parameters which were investigated specifically as early indicators for a potential toxicity. More severe changes (including conventional clinical chemical and histopathological effects) are required before an effect is to be considered as serious damage. Serious damage is defined in the Approved Code of Practice 'Classification and Labelling of Substances Dangerous for Supply' [Health and Safety Commission (HSC, 1988)] as clear functional disturbance or morphological change which has toxicological significance. In practice the safety factor between the level below the minimum at which 'serious damage' was seen in conventional animal toxicity tests and an OEL will

generally be 5–100 with 10 as the most common value. Exact values chosen will depend on the particular circumstances surrounding a given substance.

Because of the definition of an OES in Guidance Note EH 40 (HSE, 1990), some evidence from human studies, often very slight, will be used to supplement these animal data. For 'in house' OELs, confirmation that the proposed OEL is adequate (health surveys or biological monitoring information) could be obtained after the setting of the OEL.

(5) *Extrapolation between routes of exposure.* Extrapolation from one route of exposure to another poses difficulties associated with several factors. Most notable are possible differences in absorption and metabolism between routes. Any calculation of the amount of a substance or toxic metabolite absorbed which is based on information associated with one route of exposure may be irrelevant for another route (PEPELKO and WITHEY, 1985; WITHEY, 1987; PEPELKO, 1987). The effects of complete absorption (as occurs following appropriate parenteral administration) may be used as a 'worst case' approximate prediction of what might occur following inhalation.

Use of oral data to predict inhalation effects (the 'Stockinger–Woodward' approach) has severe limitations owing to the ways in which the dose is presented and to the metabolic capacities associated with the 'portals' of entry. This extrapolation assumes that a dose (in mg kg^{-1} for an 80 kg man) causing a toxic effect is completely absorbed and is contained in a volume of air approximating to that breathed during a working day. This volume is often assumed as 10 m^3, based on the idea that physical effort is expended in doing work. If sufficient metabolic and pharmacokinetic information is available, then the extrapolation may be valid (PEPELKO and WITHEY, 1985; WITHEY, 1987: PEPELKO, 1987). However, sufficient information on inhalation toxicity *per se* is usually available before adequate toxicokinetic studies are undertaken and the inherent assumptions validated. As SHARRATT (1988) suggests, this approach to route extrapolation is probably best avoided; at most it can be used only with caution.

STOCHASTIC (AND PSEUDO-STOCHASTIC) EFFECTS

Some adverse health effects such as cancers caused as a result of mutations are essentially stochastic. In general it is the frequency that is important and in the absence of a sufficient knowledge of biochemical mechanisms it is difficult to claim that there is a 'no effect' level. Control regimes for substances which cause these effects have to be based on reducing risk 'as low as is reasonably practicable'. Should an incidence rate be sufficiently low, then in theory it would be possible to base conclusions on a consideration of the severity of the effect, the risk levels for 'negligible' risk and the incidences of the effect. In practice, this would require very low incidence rates/risk levels (e.g. 1×10^{-6} $year^{-1}$) for excess deaths due to exposure: it is unlikely that epidemiological studies of sufficient power to detect this incidence would be undertaken except in very unusual circumstances.

Generally, carcinogens are categorized in accordance with the relevance of the evidence, both in terms of source (human, animal or genotoxic evidence) and in terms of quality of study. Most classifications use groupings such as those developed by

IARC (1990), viz 'the agent is carcinogenic to humans', 'the agent is probably carcinogenic to humans' (usually based principally on good animal evidence), 'the agent is possibly carcinogenic to humans' (based on less good evidence). No formal attempt is made to establish potency, although the better data usually come from studies on more potent materials.

At present, in the absence of data on potency at the necessarily very low exposure levels relevant to setting OELs, the general approaches advocated fall into two categories. In the U.K., unless the biological mechanisms are known, the tendency is to avoid mathematical extrapolation. In the United States, mathematical extrapolation is frequently undertaken and often yields results that appear unrealistic, especially when the data feeding the model is limited. A recent example of this is the evaluation of the risk of benzene-induced leukaemias. A key paper (RINSKY *et al.*, 1987) on this employs mathematical extrapolation techniques. U.S. proposals for standards are based on this work, but the calculations are less readily accepted elsewhere (see e.g. YARDLEY-JONES *et al.*, 1991) because of limitations in the exposure data and the model. The ideal would be a mathematical model based on the biology, and such toxicokinetic models are being developed.

If mathematical modelling is not considered appropriate, and a 'NOAEL' is conceptually impossible, then it is unlikely that any exposure level which corresponds to 'negligible' risk for a serious or irreversible health effect can be defined. Any OEL for such a risk is therefore likely to be a MEL, based on a judgement of what constitutes a 'tolerable' risk.

If it is necessary to use members of a group of substances which are carcinogenic then it may also be necessary to organize pragmatic risk management procedures based on their potency. The TD_{50} is one such generalized procedure (PETO *et al.*, 1984; GOLD *et al.*, 1984). However, great care is needed when this purely mathematical approach is combined with extrapolation from animal data to man, as inter-species variation in the biochemical toxicology of carcinogens can easily invalidate the *a priori* assumption of species similarity behind the extrapolations (see GIBSON and STARR, 1988 for examples). It can be justified only as a pragmatic approach to a problem when there is likely to be a single underlying mechanism for the group of substances being investigated.

The 'negligible risk' level might actually be measurable as an incidence when a mild adverse effect is being considered, and the exposure level associated with this incidence can then be determined. In consequence, an OES might be set as the OEL.

CONCLUSIONS

This paper discusses some of the problems associated with extrapolating from hazard information when setting occupational exposure limits. It attempts to relate the conventional approaches of assessing hazard using NOAELs and safety factors to appropriate risk levels for workplace exposure to chemicals. A companion paper (ILLING, 1991) sets out the corresponding risk considerations. Theoretically, this approach could lead to quantitative risk assessment procedures. However the uncertainties currently inherent in the data gathering and extrapolation techniques mean that, in practice, the approach used will continue to be judgemental, based on the type and quality of the available data.

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APPENDIX 1

DEFINITIONS OF EXPOSURE LIMITS

Maximum Exposure Limit (MEL)

A MEL is the maximum concentration of an airborne substance, averaged over a reference period, to which employees may be exposed by inhalation under any circumstance.

[Guidance Note EH 40/90 (HSE, 1990)]

Occupational Exposure Standard (OES)

An OES is the concentration of an airborne substance, averaged over reference period, at which, according to current knowledge, there is no evidence that it is likely to be injurious to employees, if they are exposed by inhalation, day after day to that concentration.

[Guidance Note EH 40/90 (HSE, 1990)]

Acceptable daily intake (ADI)

An estimated (by JECFA) of the amount of food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg).

(IPCS/JECFA, 1987)

APPENDIX 2

INDICATIVE CRITERIA FOR OCCUPATIONAL EXPOSURE LIMITS

For a substance to be assigned an OES it must meet *all* the following three criteria.

Criterion 1. The available scientific evidence allows for the identification, with reasonable certainty, of a concentration averaged over a reference period, at which there is no indication that the substance is likely to be injurious to employees if they are exposed by inhalation day after day to that concentration.

Criterion 2. Exposures to concentrations higher than that derived under criterion 1 and which could reasonably occur in practice, are unlikely to produce serious short- or long-term effects on health over the period of time it might reasonably be expected to take to identify and remedy the cause of excessive exposure.

Criterion 3. The available evidence indicates that compliance with the OES, as derived under criterion 1, is reasonably practicable.

For a substance to be assigned a MEL it must meet *either* of the following criteria.

Criterion 4. The available evidence on the substance does not satisfy criterion 1 and/or 2 for an OES and exposure to the substance has or is liable to have serious health implications for workers.

Or

Criterion 5. Socio-economic factors indicate that although the substance meets criteria 1 and 2 for an OES, a numerically higher value is necessary if the controls associated with certain uses are to be regarded as reasonably practicable.

(HSC, 1991)

APPENDIX 3

DEFINITIONS OF TYPES OF RISK

A 'negligible' risk—events of so low a frequency that the manager or regulator of risk can reasonably regard them as negligible in their overall impact on society.

A 'tolerable' risk—a risk which can be lived with so as to secure certain benefits and in the confidence that it is being properly controlled.

'Voluntary' and 'involuntary' risk—an example of this is that an individual may willingly take part in a relatively dangerous activity such as driving a car or motor cycle or motor cycle racing, but the same individual may be unwilling to accept much lower risks from hazards that he or she is unable to avoid such as exposure to pesticide residues in food.

(ROYAL SOCIETY STUDY GROUP, 1983; HSE, 1988)