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THE UNCERTAINTY FACTOR IN THE SETTING OF OCCUPATIONAL EXPOSURE STANDARDS

Steven Fairhurst

Toxicology Unit, Technology and Health Sciences Division, Health and Safety Executive, Magdalen House, Stanley Precinct, Bootle, Merseyside L20 3QZ, U.K.

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Abstract—In recent years new programmes have appeared within the EC and OECD involving risk assessment of chemicals in relation to their potential health effects on various sections of the human population, including workers. As an element of such programmes judgements are required to be made about the acceptability of occupational exposure to chemicals at particular levels, taking into account the toxicological data available. Some of these programmes seek to establish 'health-based' occupational exposure limits. Uncertainty Factors have a significant influence in such considerations. There is a notable absence of published information in relation to the quantitative aspects of decision-making in this area.

This paper discusses the current situation regarding Uncertainty Factors involved in deriving a 'health-based' occupational exposure limit, the Occupational Exposure Standard (OES) in the U.K. The Uncertainty Factors involved in the proposals of the WATCH (Working Group on the Assessment of Toxic Chemicals) panel of the Health and Safety Commission's Advisory Committee on Toxic Substances, for OES values for substances considered in the period 1990–1993 have been analysed.

INTRODUCTION

In establishing standards for the control of exposure to chemical substances the intention is usually to signify a level of exposure at which some assurance of freedom from health effects is provided (although this is not always possible for some substances). In relation to human health, such standards are set for a number of different exposure scenarios, such as occupational exposure limits, environmental air quality standards, or Acceptable Daily Intakes for food additives and contaminants. These standards are often described as 'health-based'.

Ideally a 'health-based' standard would be established on the basis of:

(a) reliable data from relevant human populations exposed to known levels of the substance, with at least one exposure level being a clear no-effect level for those health aspects that can be monitored; and

(b) confidence from the general physicochemical and toxicological picture available that other possible health effects that are difficult to monitor directly in humans (e.g. mutagenicity, reproductive toxicity) give no cause for concern for the substance in question.

Unfortunately, almost invariably the toxicological information available on substances of interest is not sufficient, in extent or quality, to allow the direct and confident extraction of such a standard from the data set. One is often faced with one or more of the three general extrapolation questions in toxicology—interspecies variation (e.g. how do data from rats relate to humans?), intraspecies variation (e.g. how do data obtained from young, healthy individuals relate to elderly, infirm individuals?) and

high dose to low dose extrapolation. These problems are frequently exacerbated by concerns about the quality and reliability of the available toxicological data itself. In most cases such difficulties confound the construction of a detailed and reliable dose–response curve for the effects of a particular substance in humans, or the quantification of the risk of ill health in humans in the low dose–low incidence region of a dose–response relationship.

Therefore, in seeking to establish a 'health-based' standard, a regulatory body is often faced with a position which is far from ideal. For most substances there is a paucity of documented information on direct human experience during or following exposure. Experimental animal data may be all that is available and even this may be of limited quality and quantity.

The conventional approach adopted in standard setting in dealing with this situation is to seek to identify from the available information a reference point, usually a 'no observed adverse effect level' (NOAEL) in experimental animal studies. From this point, a standard is set at a lower level of exposure, which is considered to meet the stipulated health protection criteria attached to that standard.

Within the range of exposure levels stretching from the NOAEL back to zero exposure there are many potential points at which it could be postulated that exposure at that level would meet the minimum health protection criteria for the type of standard in question. The further down the exposure scale one moves, the more confident one becomes that there will be no health consequences, i.e. that exposure is below the threshold for any adverse health effects in the human population. However, the further down the exposure scale one seeks to move, the more onerous, difficult and perhaps ultimately unrealistic may become the control requirements. Whilst zero exposure offers absolute protection, this is not a practical option in most cases.

Clearly there is a balance to be struck. The issues to be considered in striking this balance are discussed below. The margin between the reference point referred to above (e.g. a NOAEL) and the standard established has been termed the Uncertainty Factor; the term is appropriate, since the factor is introduced to allow for the uncertainty in the risk assessment process caused by limitations in the data. Alternative terms are also in the literature, such as safety factor, safety margin, extrapolation factor or assessment factor.

This paper addresses the Uncertainty Factors involved in setting the 'health-based' standard applied in the U.K. in the occupational context, namely the Occupational Exposure Standard (OES). The paper is timely, in that in recent years there has been the appearance within the EU and OECD of new programmes and associated documents dealing with risk assessment which involve judgements of satisfactory levels of exposure for various sections of the human population, including workers. These include the EC "7th Amendment" Directive and Existing Substances Regulation, the OECD High Production Volume existing chemicals programme, and the attempt of DGV in the EC, working with its Scientific Experts Group, to develop a list of European occupational exposure limits (EEC, 1992, 1993). In all such programmes, judgements will have to be made concerning the acceptability of occupational exposure at particular levels, set against the toxicological data available. Uncertainty Factor consideration will significantly influence such judgements and yet there is a notable absence of published guidance to inform the quantitative aspects of decision-making in this area.

ISSUES INFLUENCING THE SIZE OF THE UNCERTAINTY FACTOR

The principal issues influencing the size of the Uncertainty Factor are listed below. It is important to acknowledge that the values of such factors do not arise via a strictly 'numerical' exercise—the size of the factor is influenced by a host of variables, many of which cannot be formally quantified. This means that it is difficult to set, from fundamental principles, a simple and workable numerical framework, or set of rules for Uncertainty Factors which is free from the influence of 'expert judgement'.

(1) *Availability of toxicological information*

Amount of data. In general, the greater the scope of the data and the larger the number of studies, the lower will be the uncertainty. However this is by no means always the case—a lot of information can produce a confused overall picture of the toxicity of a substance, particularly where the data are not of high quality.

Species studied. Direct observations on humans will reduce uncertainty, but if no firm data on human responsiveness are available, then there will always be some degree of uncertainty about the relative sensitivity of humans compared to the animal species on which data are available.

Route of exposure. It is desirable that in setting an exposure limit for a particular exposure route (i.e. inhalation for occupational exposure limits) the toxicological data relate to that route of exposure. If the only data available are for other routes of exposure, the uncertainty is increased (e.g. evaluation of systemic effects of inhalation exposure from oral data) or route-to-route extrapolation may be impossible (e.g. evaluation of local effects of inhalation, such as pulmonary irritation or dust-induced lung fibrosis from oral or dermal data).

Quality of data. Better quality data give more confidence–less uncertainty than poorer quality data. The term 'quality' embraces the scope, rigorousness and conformity with accepted standards of the studies conducted, and the thoroughness of reporting of the findings.

Availability of an identified 'no effect level'. A preferred starting point for the derivation of a standard is a 'no observed adverse effect level' (NOAEL). However, for some substances the data may offer only a 'lowest observed adverse effect level' (LOAEL) [i.e. often some minor, (possibly) adverse effects at the lowest exposure level investigated]. A larger uncertainty factor is likely to be employed in the latter case.

Note. Toxicological information is not limited to actual experimental–observational data on the substance under investigation, but includes data on chemically and physically similar substances. Prediction from structure–activity relationships has an important role, although great care should be taken in its use.

(2) *Nature and severity of principal adverse effects*

In general, the more severe the threat to life and well-being presented by a substance, the greater is the need to be certain about the safety of exposure in humans and hence usually the larger will be the Uncertainty Factor involved in deriving acceptable exposure levels. Other considerations also have an influence, such as the

slope of the dose–response curve and the degree of, or lack of, information on interspecies variation. The following two extremes exemplify this.

(a) Only a small uncertainty factor (perhaps a factor of 1) seems necessary where:
—the principal effect of an airborne substance is sensory irritation (perception of eye–mucous membrane irritation without pathological damage) which is rapidly and clearly apparent, and readily and completely reversible on removal from exposure; and
—there are reliable data for this endpoint from animals, with perhaps some comparable human observations (relatively little interspecies variation would be expected for this local, surface effect).

(b) A relatively large uncertainty factor seems appropriate where:
—the principal effect of an airborne substance is serious and irreversible (e.g. teratogenicity); and
—data for this endpoint are limited, e.g. from one rodent species (a complex, systemic effect with considerable scope for interspecies variability in toxicokinetics and toxicodynamics).

(3) *Nature of exposed population–exposure situation*

Age and sex. In general the greater the variation in age of the exposed population, the greater will be the uncertainty about individual sensitivity to the toxicity of a substance. Similarly, exposure of both, rather than one sex may increase this uncertainty.

Health status. In general, the greater the variability in the underlying health status of those exposed, the greater will be the possible variability in sensitivity to certain toxic effects and hence the greater is the factor required to accommodate this feature.

Presence of checks. Reducing the uncertainty factor is justifiable where there is assurance that exposure to the substance is being monitored and controlled to particular levels, where the health of the exposed population can be and is being monitored, and where the ability to attribute any emerging health effect to a particular substance and to take effective remedial action is available.

These features provide justification for accepting smaller uncertainty factors in setting workplace 'health-based' exposure limits than in setting environmental controls for the general population as a whole.

(4) *Degree of control achievable*

The size of any Uncertainty Factor is influenced by the number and type of control options available and the extent of control achievable in the particular population exposed (e.g. workplace population or the general public). The sociological and economic impact of the controls are also important influences on the Uncertainty Factors empoyed in standard setting. Where a large Uncertainty Factor can be applied to give a guarantee of absolute safety, or where a demand for a large Uncertainty Factor would effectively result in a ban on the substance, with relatively minor repercussions, then large Uncertainty Factors can be applied liberally (e.g. with a new fragrance or a colourant for foodstuffs). For the vast majority of industrial situations

such freedom does not exist, and for technical and socio-economic reasons the size of Uncertainty Factors must be lower, while still seeking to introduce standards which will eliminate or minimize the risk to health.

UNCERTAINTY FACTORS USED IN SETTING 'HEALTH-BASED' OCCUPATIONAL EXPOSURE LIMITS

Many issues must be taken into account in relation to an Uncertainty Factor. Some, but not all, are scientific or technical issues and even for these there is often insufficient data to provide a clear solution. This means that the size of the Uncertainty Factor is inherently arbitrary, debatable and potentially variable, depending on particular circumstances.

Within the literature there have been several schemes put forward for deriving 'appropriate' Uncertainty Factors for use in standard setting, based on specified contributions from individual elements, for example a factor '*x*' to allow for the unknown extent of interspecies variation, a factor '*y*' to allow for the unknown extent of intraspecies variation. These approaches, using values of 10 (or fractions of 10) for each element have a strong tradition in regulatory toxicology. Such schemes have been proposed mainly for non-occupational exposure (Lu, 1988; Rubery *et al.*, 1990; Renwick, 1993), although a similar scheme for dealing with occupational exposure has been offered (Zielhuis and van der Kreek, 1979). However, there are considerable problems with these schemes, created by the number of elements to be taken into account and the difficulty in justifying specific numerical values for each individual element considered.

A particular problem is that the limited toxicological data available on many substances, the size of the values proposed to account for each 'unknown' element and the multiplication of individual elements which is a feature of these schemes would produce, in many cases, an Uncertainty Factor so large that a standard so derived would be in an unrealistically low exposure region. Enforceable occupational standards at such low levels would not be viable.

Hence schemes such as these, with fixed values for specified elements, have not been used in setting OES values in the U.K., nor indeed for establishing realistic, enforceable 'health-based' occupational exposure limits anywhere else in the world. This paper looks retrospectively at the actual Uncertainty Factors involved in the proposals for occupational standards emanating from an expert committee faced with all the issues discussed above.

WATCH RECOMMENDATIONS FOR OES VALUES 1990–1993; ANALYSIS OF UNCERTAINTY FACTORS INVOLVED

The U.K. Control of Substances Hazardous to Health (COSHH) Regulations came into force on 1 October 1989 and brought in a new two-category system of U.K. occupational exposure limit—the Occupational Exposure Standard (OES) and the Maximum Exposure Limit (MEL). The OES is a 'health-based' standard, being:

> The concentration of an airborne substance, averaged over a 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.

In contrast, the MEL is not a 'health-based' standard and therefore will not be considered further in this paper.

Within the current procedure for establishing occupational exposure limits in the U.K., the WATCH (Working Group on the Assessment of Toxic Chemicals) panel of the Health and Safety Commission's Advisory Committee on Toxic Substances is the first and highly influential discussion forum in which individual substances are considered. WATCH is composed of representatives from industry and trades unions, together with independent advisers, all having expertise in occupational health and hygiene. It receives for consideration detailed, critical documentation produced by the Health and Safety Executive, covering the toxicology, occupational hygiene, analysis and exposure monitoring issues appertaining to particular substances. WATCH makes recommendations based on the scientific and technical evidence, on whether or not an OES can be established and if so, at what numerical value. Such recommendations then progress to further stages of consideration and consultation within the U.K. system before a final regulatory position is established.

Since the implementation of COSHH and the introduction of the OES, detailed, critical documentation has been produced and published for all substances presented to WATCH for consideration. In this paper, substances for which OES values have been proposed by WATCH from the beginning of 1990 to the end of 1993 have been examined. The number of substances was restricted by elimination of those cases where general constraints had a heavy influence on the numerical value(s) of the OES, for example the 5 and 10 mg m^{-3} general dust limits or the 1000 ppm (8-h TWA) ceiling on U.K. occupational exposure limits. A total of 24 substances met the criteria for inclusion in this analysis.

Table 1 summarizes the collective results of the WATCH assessment of these 24 substances, and the major issues surrounding each substance. It does not indicate every factor that was involved in each OES recommendation, or every comparison that could be made between the OES values recommended and the available toxicological data on a substance. Such a comprehensive presentation of information would be unwieldy and too detailed for this analysis. However, detailed critical documentation for each of these substances is available in HSE's publications series. Further details are given below for two substances, as examples of the type of information available and the arguments developed from such data in deriving OES values.

Ammonia

25 ppm 8-h TWA and 35 ppm STEL OESs.

There is a substantial body of toxicological data available from both animal and human studies.

In relation to sensitization and mutagenicity–carcinogenicity, where positive findings give rise to most difficulties in establishing health-based limits, no experimental sensitization data are available but extensive human experience has not indicated ammonia to be a sensitizer. A single Ames test, which was negative, consitutes the only useful genotoxicity data for ammonia, although structure–activity relationships suggest it would not be genotoxic. No carcinogenicity studies are available for ammonia.

A number of repeated or continuous exposure studies in animals indicated that at concentrations of 100 ppm and above the upper respiratory tract is damaged. Several

studies involving continuous exposure of rats, rabbits, guinea pigs, dogs, monkeys and pigs to between 4 and 72 ppm of ammonia for up to 114 days have shown little or no effect. Against this background the results of a poorly reported Russian study, in which rats exposed to 30 ppm for 4 h per day, 5 days per week for 1 month apparently demonstrated an impairment of olfactory function and inflammation of the upper respiratory tract, were considered unreliable. In mice and guinea pigs exposed continuously (24 h per day) to 20 ppm ammonia for 42 days there were some indications of congestion, oedema and haemorrhage in the lungs. Pigs continuously exposed to 50 ppm for up to 5 weeks showed reduced body weight gain and signs of upper respiratory tract irritation. It is anticipated that for any particular atmospheric concentration, the effects arising from continuous exposure would be more severe than those following exposures for 8 h per day.

In humans, the only clearly established effect arising from exposure to concentrations of less than 200 ppm ammonia is irritation of the skin, eyes and upper respiratory tract. In unacclimatized subjects, sensory irritation was reported with exposure to 50–55 ppm for periods of a few minutes or 6 h. At higher concentrations more severe irritation was apparent: in two studies eye or nasal irritation were reported with exposure to 100–110 ppm for only 15–30 s. Some individuals have exihibited signs of slight irritation when exposed to 25–30 ppm for periods of between 10 min and 2 h. In one anecdotal report, 20 ppm was claimed as irritating to mucous membranes. There is some evidence that repeated exposure to ammonia may result in some degree of acclimatization. A number of Russian reports are available of studies in which humans were exposed to concentrations of less than 20 ppm of ammonia for varying lengths of time. Only slight effects were observed and these are of very doubtful toxicological significance.

The critical effect for determining the OES for ammonia was the eye and respiratory tract irritation seen in humans. Slight sensory irritation has been observed in individuals exposed to 25–30 ppm of ammonia. Since there is no evidence that such levels of exposure would result in any long-term effects and since acclimatization to the slight sensory irritation may occur it was decided to set the 8-h TWA OES at 25 ppm. However, at higher levels (e.g. 50 ppm) even short-term exposures have given rise to significant sensory irritation and consequently a short-term OES was set at 35 ppm to restrict short peak exposures.

Carbon tetrachloride

2 ppm (8-h TWA) OES.

There is a substantial amount of animal toxicological data available but human data are limited.

In relation to sensitization and mutagenicity–carcinogenicity, where positive findings give rise to most difficulties in establishing health based limits, no sensitization data are available but generally this class of chlorinated hydrocarbons is not associated with cutaneous or pulmonary sensitizing potential. Ames tests were adequate and negative. While other genotoxicity tests are inadequate there is no good evidence for genotoxic activity. Carbon tetrachloride was not teratogenic in one adequate inhalation study; other reproductive toxicity studies are inadequate.

Repeated exposure effects in animals have been studied extensively, although the investigations were not conducted to present day standards. Inhalation exposure for

Table 1. Uncertainty Factors used by WATCH in recommending OES values

Point from which Uncertainty Factor applied	Size of Uncertainty Factor (UF)	Representative substance (UF given in brackets)	
Human data			
Eye–respiratory tract sensory irritation in humans	In establishing 8-h TWA OES		
NOAEL	1	Chlorine	(1)
Level producing occasional slight irritation, with acclimatization	1	Butan-2-one Acetone	(1) (1)
LOAEL for reliable evidence of significant irritation	2	Chlorine Ammonia	(2) (2)
Level producing occasional slight irritation, with acclimatization	In establishing STEL OES 1–2	Ammonia Chlorine 1,4-DCB Phosphorus pentoxide Phosphoric acid (by SAR* analogy)	(1) (1) (1) (2) (2)
Neurobehavioural effects–symptoms of mild CNS disturbance in humans	In establishing 8-h TWA		
NOAEL for single or repeated exposure in humans (h)	1–1.5	4-Methylpentan-2-one 1,1,1-Trichloroethane Xylene	(1) (1) (1.5)
LOAEL for single or repeated exposure in humans (h)	2	4-Methylpentan-2-one Heptan-2-one* Heptan-3-one* 5-Methylhexan-2-one* 1,1,1-Trichloroethane Xylene	(2) (2) (2) (2) (2) (2)
LOAEL for single exposure in humans (min)	In establishing STEL OES 2	1,1,1-Trichloroethane	(2)
Organ–organ function effects	In establishing 8-h TWA		
'Low-effect' level (slight change of doubtful health significance) for repeated exposure in humans	1 (dose extrapolation)	Kaolin	(1)

Animal data			
NOAEL for repeated exposure in animals (no corresponding human data)	In establishing 8-h TWA OES	Carbon tetrachloride	(2.5)
		Cumene	(4)
		Cyclohexane	(4)
		1,4-DCB	(4)
	2.5–10	Trimethylbenzenes	(4)
		Chloroform	(5)
		Halothane	(10)
		Sulfotep	(10)
NOAEL for repeated exposure in animals (with supporting human data)	1	Chlorine	(1)
LOAEL for repeated exposure in animals (no corresponding human data)	In establishing 8-h TWA OES	Dimethylacetamide	(4–6)
		Carbon tetrachloride	(5)
		1,4-DCB	(6–7)
		Trimethylbenzenes	(6)
	4–12	Cyclohexane	(8)
		Chloroform	(12)
Reproductive toxicity in animals (no corresponding human data), where this is an issue	In establishing 8-h TWA OES		
NOAEL: any reproductive effect	4–12	Trimethylbenzenes	(4)
		Nitrous oxide	(5)
		Butan-2-one	(5)
		Dimethylacetamide	(10)
		Isoflurane	(12)
LOAEL: some questionable feto toxicity	8–30	Trimethylbenzenes	(8)
		Nitrous oxide	(10)
		Chloroform	(15)
		Dimethylacetamide	(30)
: teratogenicity	40–60	Dimethylacetamide	(40–60)

*Structure–activity relationship.

7 h per day for 3 months or more showed no adverse effect levels of 5 ppm (rat, guinea pig), 10 ppm (rabbit) and 50 ppm (monkey). At twice or higher exposure concentrations, hepatic fatty degeneration, necrosis and cirrhosis were observed. The same histopathological findings in the liver in long-term animal studies were associated with liver tumour formation. One adequate carcinogenicity study in rodents is available which was conducted to a recent protocol and confirms hepatocarcinogenicity.

Carbon tetrachloride is therefore considered to be a non-genotoxic carcinogen and no adverse effect levels (NOAELs) from repeated exposure studies were used to set exposure limits designed to avoid liver damage and any consequential risk of liver tumour formation. An OES was established on this basis. The OES of 2 ppm is 2.5 times lower than the NOAEL (across all species) of 5 ppm, and 5 times lower than the LOAEL of 10 ppm in the most sensitive species. Evidence suggests that the monkey is a better model species than rodents for humans, in which case these margins would be appreciably wider.

EMERGING PATTERN AND CONCLUSIONS

As discussed above, there are many specific points (toxicological and otherwise) to be taken into consideration in selecting an appropriate Uncertainty Factor and establishing an OES value. This range of issues and the infinite variability in the nature and standard of information available on substances means that the precise situation appertaining to each substance is unique.

Some variability in the Uncertainty Factors used for what might appear (from Table 1) to be similar situations has arisen because of differences in the extent and quality of the available toxicological information surrounding the reference point to which the Uncertainty Factor was applied. For example, in relation to the NOAEL for repeated exposure in animals, the larger Uncertainty Factor used for sulfotep compared to carbon tetrachloride reflects less information and consequently greater uncertainty in the former case.

Although it is very much a case-by-case approach that is employed, one would expect to see an overall pattern of consistency in the decision-making process. Inspection of Table 1 reveals logical general trends: smaller Uncertainty Factors where the OES has been derived partly or mainly from human data rather than exclusively from animal data; and increasing Uncertainty Factors according to whether the reference point is an exposure level producing no effects, or some effects of questionable significance, or effects of definite significance. Though it is acknowledged that the total number of substances available for analysis and the number of examples in some of the situation categories used in the table are small, a consistency of approach is apparent.

The crucial question is whether or not the Uncertainty Factors applied are correct, such that the OES values confer the desired degree of health protection. It is worth reiterating that for many substances of relevance occupationally, including a number of those considered in this analysis, the toxicological database is rather weak, in both quality and quantity. Critical assessment of each individual original data source has proved essential to ensure accurate portrayal of the study findings. It has also been necessary to exercise considerable predictive and judgemental skills in attempting to construct a coherent and substantial toxicological profile of a substance from the often

rather patchy information available. Data relating to inhalation exposure may be sparse, some endpoints (e.g. reproductive toxicity) may not have been investigated and information may be lacking on the relative sensitivity of humans compared to experimental animals towards the toxicity of particular substances. Such deficiencies can introduce considerable uncertainty into the toxicological evaluation.

In seeking to assess the appropriateness of the Uncertainty Factors applied, it is an unfortunate fact that for most substances there is a paucity of well-documented health experience of the use of occupational exposure limits within the workplace. Until such information becomes available, it is difficult to assess the 'correctness', from a health protection standpoint, of the Uncertainty Factors used, in respect of their absolute numerical values.

In conclusion the Uncertainty Factors reviewed in this paper represent the judgements of an expert committee on the appropriate magnitude of such factors in deriving one particular type of 'health-based' occupational exposure limit, the OES. It would be interesting to obtain the views and discuss the practices of occupational exposure limit-setting committees–organizations in other countries and to examine the prospects for wider agreement on Uncertainty Factors and their influence in performing risk assessments and establishing 'health-based' control standards for the workplace.

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