Guidance on Setting In-House Occupational Exposure Limits for Airborne Therapeutic Substances and their Intermediates

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Foreword

The Association produced the second edition of Guidelines for the Control of Occupational Exposure to Therapeutic Substances in April 1992.

In the light of the experience of the use of the Guidelines it was felt that further guidance on setting occupational exposure limits for therapeutic substances would be helpful. This guidance has been produced to assist members in developing their own schemes for setting exposure limits. More detailed information is provided on how to identify the lead effects for occupational exposure, taking into account data quality and quantity. The guidance outlines an approach to setting limits for intermediates or substances under development when available data will be very limited.

The Association wishes to acknowledge the helpful comments provided by the Tripartite Forum of the Pharmaceutical Industry and the Chemical Manufacturing National Industry Group (NIG) of the Health and Safety Executive. Thanks are also due to the ABPI working group which gave freely of its expertise and time in drafting the document. The guidelines were developed to be consistent with other industry guidelines on setting occupational exposure limits and the Association is grateful to the Chemical Industries Association for permission to use parts of their publication 'Guidance on Setting In-House Occupational Exposure Limits'.

Contents

1 Introduction

1.1 Under the Control of Substances Hazardous to Health Regulations 1994 (COSHH), the potential risks to health arising from exposure to hazardous substances at work need to be assessed. Exposure to a hazardous substance should be prevented, or if this is not reasonably practicable, adequately controlled (COSHH Regulation 7 has been reproduced in Appendix 1, Crown copyright is reproduced with the permission of the Controller of HMSO).

For many common substances Maximum Exposure Limits (MELs: COSHH Schedule 1) or Occupational Exposure Standards (OESs) have been set. Lists of MELs and OESs are reproduced in the current edition of EH40 (revised annually). The requirements for complying with an MEL or OES are set out in the Regulations and associated Approved Code of Practice.

1.2 For substances which have not been assigned an MEL or OES, the COSHH general Approved Code of Practice, paragraph 38 (Appendix 2), gives practical advice that exposure should be controlled to a level to which nearly all the population could be exposed, day after day, without adverse effects on health. If employees could be exposed to airborne concentrations of such substances, then an in-house standard should be set.

The guidance below has been produced to help companies set such standards, herein called 'in-house' Occupational Exposure Limits (OELs), specifically for therapeutic substances and their intermediates. It does not apply to radiopharmaceuticals or to other hazards associated with therapeutic substances and their intermediates (e.g. flammability).

1.3 ~~The availability of data for setting an in-house exposure limit will vary from substance to~~ substance for both existing and new therapeutic substances or their intermediates. For new substances, during the research and early development stages, data will be minimal and it may not be appropriate to set an exposure limit. In this situation existing qualitative assessment programmes and robust control strategies should be retained.

The guidance outlines a scheme for setting exposure limits which accommodates variations in data quality and quantity that may be experienced with both new and existing substances. Whilst the limit setting process can and should be initiated during the development phase for a new substance, there is no unique, optimal time for changing from a qualitative risk assessment process to one which encompasses the use of exposure limits at which stage precautionary control measures may possibly be relaxed. Companies will need to make a judgement about how to integrate limit setting procedures into their drug development and health risk assessment programmes.

2 Explanation of Terms

2.1 Occupational Exposure Limit (OEL)

While any exposure limit is intended to protect health, the term OEL is used in the guidelines to describe a 'health based limit' which is derived solely from health related data. This may include human data, animal data and certain physicochemical properties of the substance. The limit value takes no account of whether exposure can be controlled below the limit. The ability to set a health based limit is dependent on the type of effect and data quality and quantity. Ideally, human data should be available, supported by good quality animal and physicochemical data, although animal and physicochemical data may suffice in some cases.

A health based limit will be expressed as an average concentration of a substance present in the breathing zone of a person over a specified reference period, to which, according to current knowledge, the majority of employees may be exposed day after day without adverse effects.

2.2 Occupational Exposure Band

There may be insufficient data to assign an OEL, for example, under the following circumstances:

- During the development phase for new products
- For intermediates where the pharmacological and toxicological data may be limited
- For established products where available data may be limited.

In these circumstances it may be possible to assign the substance or intermediate to one of a limited number of Occupational Exposure Bands (OEBs) on the basis of the available hazard data. The term OEB indicates that the numerical figure assigned to the substance, within the band, is only a best estimate of the concentration to which the substance should be controlled. All reasonably practicable measures should be taken to control exposure below the quoted figure whilst recognising that exposure above the figure may not be a source of undue risk. However, it is still a 'health based limit' which is set taking no account of whether exposure can be controlled below a set value.

Ideally OEBs should be of a temporary nature, the objective being to set a full health-based OEL for all substances. However, for many intermediates or established products it may not be reasonable to generate sufficient health related data and an OEB may need to be retained.

2.3 Action Level

In some cases an 'action level' may be set locally, based on any of the above standards. This is usually designed to trigger a specific management action or procedure appropriate to a particular situation and is not in itself an exposure limit. Typical action levels may be between 25 and 50 per cent of an OEL.

3 Situations Requiring the Establishment of Exposure Limits

3.1 An in-house exposure limit may be needed for any substance which could contaminate the workplace atmosphere. The initial COSHH Assessment (produced in accordance with Regulation 6) may establish that an exposure limit is desirable as part of the process of ensuring that there is an adequate control of risk.

Exposure limits may be required for customers where the nature of their product use at work is such that exposure by inhalation could reasonably occur.

3.2 Some data relevant to the establishment of OELs are generated as part of the research and development of all new drug substances. These data may not be readily available for some well established substances and an OEB may have to be set depending upon the data quality and quantity.

3.3 At the early stages of research and development many new substances will be synthesised and very little information may be available to gauge their effect on the health of the workforce. It is not feasible to set OELs at these early stages and a company's COSHH assessment and control strategy will need to take this fact into account. However, when a potential product candidate has been identified the scale of work and amount of available pharmacological and toxicological data will increase and the use of a suitable OEB may be appropriate. The time for this will undoubtedly vary with the circumstances surrounding the development of a particular drug substance and each one needs to be considered individually.

3.4 Intermediates in the synthetic route for a drug substance may well have to be isolated during manufacture or the process may tend to emit material into the workplace atmosphere by aerosol generation or release of a volatile substance. Some intermediates may exhibit pharmacological effects as well as being toxic. It is unlikely that the testing of intermediates will provide the same quantity or quality of data as would be available for a drug substance and OEBs may be an appropriate way of defining control standards for these substances. Subsequent work with these materials during production should allow generation of workplace data leading to a revised OEB or perhaps an OEL. However, when exposure to an isolated intermediate is predictable it could be appropriate to extend the amount of toxicological testing to allow an exposure limit to be set at the earliest opportunity. Such testing is unlikely to include human data but where this is available it should be used.

4 Procedure for Setting OEL's

4.1 The derivation of an in-house OEL for a therapeutic substance or intermediate is not a precise scientific exercise. There is no simple formula or checklist for the derivation of these limits and each substance must be considered on its own merits. The process is essentially judgemental, involving a balance of scientific data, conservative assumptions and informed judgements. The establishment of OELs is best performed by a multi-disciplinary group with relevant expertise in toxicology, pharmacology, occupational medicine and occupational hygiene. The constitution, remit and accountability of the expert committee should be formally recorded.

4.2 The procedure to follow when setting any OEL or OEB is essentially the same. The procedure should be documented. The most appropriate type of limit to set will be determined by the quantity and quality of the data available.

Using the definitions given in Section 2, a possible relationship between the various types of limit during the development of new therapeutic substances is illustrated in Appendix 3. This encapsulates the continuous nature of the limit setting process.

Sections 4.3 to 4.5 below describe the limit setting process as it would apply to an OEL.

4.3 Preliminary Step

The initial step in establishing an OEL for a therapeutic substance is to assemble all the relevant data. These may include:

- Compound Identity.
  CAS Number/Approved Name/Company Number/Synonyms.
  Chemical Structure.
- Physicochemical properties.
- Names of chemically, physically or biologically analogous substances for which health based OELs already exist, plus supporting documentation.
- Pharmacological effects:
  pharmacodynamics
  pharmacokinetics
  biological half life
  side-effects and drug interactions.
- Any epidemiological data, information concerning accidental over-exposure or poisoning in humans, health surveillance data or occupational hygiene data.
- Toxicity:
  acute
  chronic
  carcinogenicity/mutagenicity/reproductive toxicity.
- Irritancy:
  skin, eyes, mucous membranes.
- Allergenicity:
  skin, respiratory tract.

A literature search should be carried out to ensure that all relevant information has been retrieved. The toxicological and pharmacological data generated during drug development may not be sufficient for setting an OEL. For example, in some cases data such as inhalation toxicity or inhalation kinetics may be appropriate. The need for additional data should be evaluated on a case by case basis.

All references should be listed, numbered and annotated in an appropriate fashion and against each it should be noted whether the information comes from an abstract, summary or full report or publication. Where possible, original publications should be reviewed.

4.4 The Qualitative Hazard Assessment

This step is to establish a list of biological effects in animals or man to be considered in the quantitative hazard assessment together with any relevant physicochemical properties, eg pH or partition coefficient. All effects noted in humans should be considered. Each effect seen in animals should be considered individually and a decision is taken as to whether it is likely to be expressed in humans. Effects to be considered might include:

- a pharmacological/toxicological effect
- respiratory/mucous membrane irritation
- respiratory sensitisation.

The seriousness of each effect should be judged and the following scale, may be used:

Severe: This category includes risk of premature death, deformity or irreversible change.

Moderate: Changes which are easily detectable and which resolve on cessation of exposure.

Minor: Changes of little or no clinical significance which do not progress and resolve promptly on cessation of exposure.

The relevance and the quality of the data (e.g. study protocols) should be assessed for the data package and in particular for that data which may play a leading role in the establishment of the OEL. Clear reasons should be recorded for disregarding any specific piece of evidence.

4.5 Quantitative Risk Assessment

~~Each effect listed should be considered to see whether a clear dose-effect relationship has been~~ established. If not, the reason for any inference as to the dose-effect relationship should be clearly stated. In animal studies, appropriate allowance should be made for species difference and account taken of the extent of agreement between species in cases where several have been tested. In the absence of inhalation studies the most appropriate alternative dosing studies will need to be identified. Appropriate allowance should be made for the seriousness of effects especially where dose-effect relationships do not allow definition of an exposure level which is without adverse effect (no observed adverse effect level). This process should make obvious the lead effect or effects (effects which will determine the level of an OEL).

The lead effect is therefore not necessarily the most severe effect or alternatively that which has the lowest no observed adverse effect level. All factors relating to the data need to be considered including uncertainties in the data. Where exposure to a substance may cause effects from acute or prolonged exposure there may be two lead effects, one the basis of a 'short term' exposure limit, the other a 'long term' exposure limit.

Aspirin provides one example for the establishment of a lead effect (ACGIH, 1991). Interference with platelet aggregation (moderate effect) was identified as the lead effect in preference to teratogenicity (severe effect) and several other severe and moderate effects. Having made allowances for the severity of the various effects etc, it was considered that an OEL set to prevent interference with platelet aggregation was adequate to prevent the other potential adverse effects. A further example is provided in Appendix 6.

An OEL should not be set which would allow employees to be exposed to airborne concentrations which can give rise to cumulative inhaled doses equivalent to or greater than the minimum therapeutic dose for the substance in most cases.

The time base for the OEL should be established. For substances which produce effects following long term exposure, an eight hour time weighted average OEL is normally appropriate. For substances which have concentration related effects or other acute effects, a short term exposure limit would be required. These are normally set as fifteen minute time weighted average OELs. Some substances exhibiting both long and short term effects may require two limits to be set. Alternative time bases for limits could be chosen if indicated by the mode of action and biological half life.

In deriving an OEL, the weight of an average worker is normally taken as 70kg. The volume of air breathed in an 8 hour shift is usually assumed to be 10 cubic metres.

Particular difficulties may arise where the lead effect is respiratory sensitisation or carcinogenesis with a genotoxic mechanism of action. In such cases, it may not be possible to establish a clear no observed adverse effect level with any certainty. Given this situation, requirements for any additional data need to be identified and a precautionary approach to control should be adopted by minimising exposure even when an OEL is set.

Finally, the data should be re-examined and classified into that which are critical to the setting of an OEL and that which are supportive in nature. A check should be made that critical data are fully documented and have been reviewed by appropriate specialists. Where this has not been done the OEL should be designated 'provisional' until a specialist review has been made.

During consideration of the pharmacological and toxicological properties of substances, the likelihood that unduly susceptible individuals or groups may be present in the exposed population should be considered. In the latter case, it may be necessary to develop a system for identifying (screening) hypersensitive individuals as an adjunct to the development of an OEL. Where the prevalence of hypersensitivity may be significant, the OEL may have to be lowered.

The effects of the route of absorption which differ from the clinical situation should be considered. They may significantly affect absorption or the distribution to target organs. In the absence of direct effects on the respiratory system, when an effect is the result of systemic absorption, it should normally be assumed that one hundred percent of the inhaled substance will be absorbed unless evidence to the contrary is available.

The level at which the OEL is established in relation to the no observed adverse effect level should be based on the presence or absence of a threshold, the nature of the lead effect and the quality, relevance and extent of the data available to the expert committee.

~~The derivation of the 8 hour time weighted average limit value, taking the various factors into account~~, can be summarised by the following formula:

$$OEL = \frac{NOAEL \times BW}{10K} mg/m^3$$

Where:

10 is the volume of air in cubic metres breathed in an 8 hour shift.

NOAEL is the estimated or established no observed adverse effect level in animals or humans (mg/kg) (this should not exceed the minimum therapeutic dose).

BW is the representative human body weight (kg).

K represents the uncertainty in the data and is a modifying factor based on:

- The quantity and type of information.
- The requirement to extrapolate from animal studies in the absence of appropriate human data.
- The severity or irreversible nature of the effects eg. carcinogenicity, mutagenicity, sensitisation or reproductive effects.
- Areas of uncertainty or special concern. For example, dependence liability, or to allow for differences in uptake in target organs from routes of administration other than inhalation.

Factor K will require expert evaluation and an appropriate loading for each substance (see, for example ILLING, 1991; McHATTIE, 1988; SARGENT, 1988).

It is recommended that, as a matter of good practice, any 8 hour time weighted average OEL derived using the above process should be subject to an upper limit of 5 mg/m^3 for total inhalable dust or 500 ppm for vapours.

4.6 Determination of OEBs

At an early stage of testing a new chemical entity, whole animal pharmacology studies, acute and sub acute toxicity tests and in-vitro studies may be available.

These data can be used to place a substance in a particular OEB. It is suggested that four discrete bands would be appropriate as set out in Table 1.

Table 1

OEB	OEB VAPOURS (ppm)	OEB DUSTS mg/m^3
A	10 - 500	1 - 5
B	1 - 10	0.1 - 1
C	0.1 - 1	0.01 - 0.1
D	<0.1	<0.01

A different number of bands may be appropriate, for example: fewer bands could be used to facilitate transfer from a qualitative hazard categorisation scheme to an OEB scheme during product development or more bands, EF etc could be added to accommodate more potent or toxic materials.

Assignment of a substance to a band need not be at the upper limit and a substance could be given a limit value anywhere within the band where this was considered appropriate. The application of a banding scheme is very flexible and the scheme can be developed to meet an individual company's requirements.

Subsequent data, including reproductive and sub acute or chronic toxicity data, are generated in the early clinical phase of drug development. This accumulating data, together with any exposure data, reports of adverse health effects etc, may be used to refine the banding until sufficient data are available to allow an OEL to be set. OEBs are of a transitory nature and limit values could go up or down during the ongoing review process until good human data become available. A precautionary approach to setting OEBs should be established such that OEBs should rise rather than fall, for the majority of substances, as data quality and quantity improve. Such a precaution is necessary as an absence of information does not necessarily equate to an absence of hazard. A possible set of criteria for the assignment of substances to a particular band is attached (Appendix 4) with some examples (Appendix 5).

5 Notations

Where an OEL or OEB is being set and there is evidence that the substance can be taken up across the skin and contribute to systemic toxicity, leading to adverse effects with little or no warning, this must be made clear (eg. by accompanying the OEL with the word skin (or SK). Adequate precautions would be required to prevent dermal absorption of such substances.

Other notations may be appropriate where, for example, specific management actions are required. This could include teratogens and respiratory or skin sensitisers, for example.

6 Measurement Methods

The group responsible for setting the OEL should consult relevant experts to ensure that appropriate sampling and analytical methods are available for measurement of the substance. Methods should be validated to appropriate standards (ABPI, 1992). If validated methods are not available, the OEL should be established and steps taken to develop such methods.

7 Documentation and Information Recording

7.1 For individual substances, records should be made of the information used at each stage of the process, including the reasons for disregarding any specific piece of data or the decisions reached from contradictory evidence. All documentation used should be listed such that primary source documents can be retrieved when required.

Sufficient information should be available for the rationale of establishing the OEL or OEB to be evident.

7.2 Milestone Dates – The date at which the OEL or OEB was set should be clearly recorded. Particularly for OEBs or provisional OELs, these should be kept under frequent review and it may be appropriate to set specific review dates.

An established OEL should be reviewed after an appropriate interval. For a new chemical entity this could be 2 years after first entering full scale production. For well established products a longer time scale may be appropriate. This will allow any new evidence to be considered and the limits to be revised if necessary. A record of the review should be kept and the OEL documentation updated to take account of any new data. One example of suitable documentation is given in Appendix 6. Alternative styles may be adopted, e.g., that used by HSE in EH64 'Occupational Exposure Limits: Criteria Document Summaries'.

References

ACGIH (1991) Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th Edition, American Conference of Governmental Industrial Hygienists Inc, Cincinnati, USA.

ABPI (1992) Guidelines for the Control of Occupational Exposure to Therapeutic Substances, 2nd Ed, Association of the British Pharmaceutical Industry, London, UK.

ILLING H. P. A. (1991) Extrapolating from Toxicity Data to Occupational Exposure Limits: some considerations. Ann. Occup. Hyg. 35 (6). 569-580.

McHATTIE G. V., RACKHAM M. and TEASDALE E. L. (1988). The Derivation of Occupational Exposure Limits in the Pharmaceutical Industry, J. Soc. Occup. Med. 38, 105-108.

SARGENT E. V. and KIRK G. D. (1988) Establishing Airborne Exposure Control Limits in the Pharmaceutical Industry, Am. Ind. Hyg. Ass. J. 49 (6), 309-313.

Appendix 1 COSHH Regulation 7

Prevention or control of exposure to substances hazardous to health.

(Reproduced from Statutory Instrument 1994 No 3246, The Control of Substances Hazardous to Health Regulations 1994, Crown copyright is reproduced with the permission of the Controller of HMSO).

(1) Every employer shall ensure that the exposure of his employees to substances hazardous to health is either prevented or, where this is not reasonably practicable, adequately controlled.

(2) So far as is reasonably practicable, the prevention or adequate control of exposure of employees to a substance hazardous to health, except to a carcinogen or biological agent shall be secured by measures other than the provision of personal protective equipment.

(3) Without prejudice to the generality of paragraph (1), where the assessment made under regulation 6 shows that it is not reasonably practicable to prevent exposure to a carcinogen by using an alternative substance or process, the employer shall employ all the following measures, namely:

(a) the total enclosure of the process and handling systems unless this is not reasonably practicable;

(b) the use of plant, processes and systems of work which minimise the generation of, or suppress and contain, spills, leaks, dust, fumes and vapours of carcinogens;

(c) ~~limitation of the quantities of a carcinogen at the place of work~~;

(d) the keeping of the number of persons who might be exposed to a carcinogen to a minimum;

(e) the prohibition of eating, drinking and smoking in areas that may be contaminated by carcinogens;

(f) the provision of hygiene measures including adequate washing facilities and regular cleaning of walls and surfaces;

(g) the designation of those areas and installations which may be contaminated by carcinogens, and the use of suitable and sufficient warning signs; and

(h) the safe storage, handling and disposal of carcinogens and use of closed and clearly labelled containers.

(4) Where the measures taken in accordance with paragraph (2) or (3), as the case may be, do not prevent, or provide adequate control of, exposure to substances hazardous to health to which these paragraphs apply, then, in addition to taking those measures, the employer shall provide those employees with such suitable personal protective equipment as will adequately control their exposure to those substances.

(5) Any personal protective equipment provided by an employer in pursuance of this regulation shall comply with any enactment (whether in an Act or instrument) which implements in Great Britain any provision on design or manufacture with respect to health or safety in any relevant Community directive listed in Schedule 1 to the Personal Protective Equipment at Work Regulations 1992(a) which is applicable to that item of personal protective equipment.

(6) Where there is exposure to a substance for which a maximum exposure limit is specified in Schedule 1, the control of exposure shall, so far as the inhalation of that substance is concerned, only be treated as being adequate if the level of exposure is reduced so far as is reasonably practicable and in any case below the maximum exposure limit.

(7) Without prejudice to the generality of paragraph (1), where there is exposure to a substance for which an occupational exposure standard has been approved, the control of exposure shall, so far as the inhalation of that substance is concerned, be treated as being adequate if:

(a) that occupational exposure standard is not exceeded; or;

(b) where that occupational exposure standard is exceeded, the employer identifies the reasons for the standard being exceeded and takes appropriate action to remedy the situation as soon as is reasonably practicable.

(8) Where respiratory protective equipment is provided in pursuance of this regulation, then it shall:

(a) be suitable for the purpose; and

(b) comply with paragraph (5) or, where no requirement is imposed by virtue of that paragraph, be of a type approved or shall conform to a standard approved, in either case, by the Executive.

(9) In the event of the failure of a control measure which might result in the escape of carcinogens into the workplace, the employer shall ensure that:

(a) only those persons who are responsible for the carrying out of repairs and other necessary work are permitted in the affected area and they are provided with suitable respiratory protective equipment and protective clothing; and

(b) employees and other persons who may be affected are informed of the failure forthwith.

(10) Schedule 9 of these Regulations shall have effect in relation to biological agents.

(11) In this regulation, 'adequate' means adequate having regard only to the nature of the substance and the nature and degree of exposure to substances hazardous to health and 'adequately' shall be construed accordingly.

Appendix 2

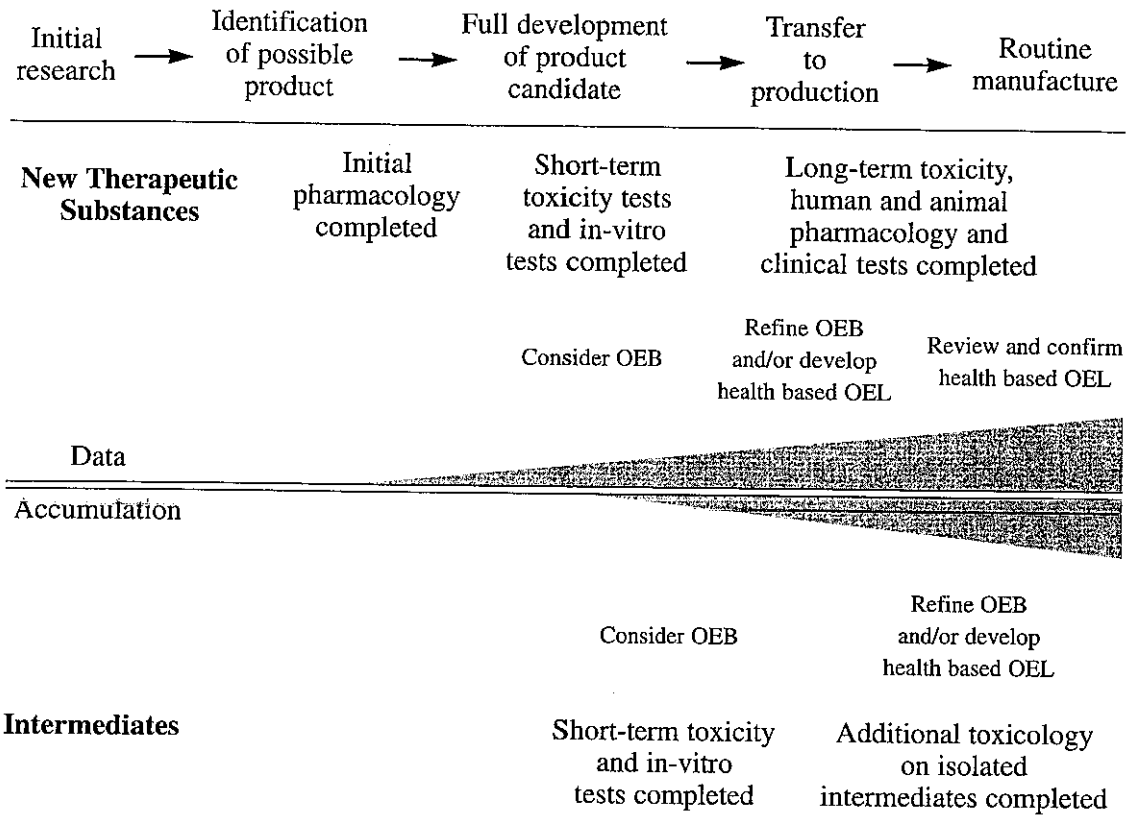
Paragraph 38 of the General Approved Code of Practice to the COSHH Regulations.

Inhaled substances not assigned MELs or OESs.

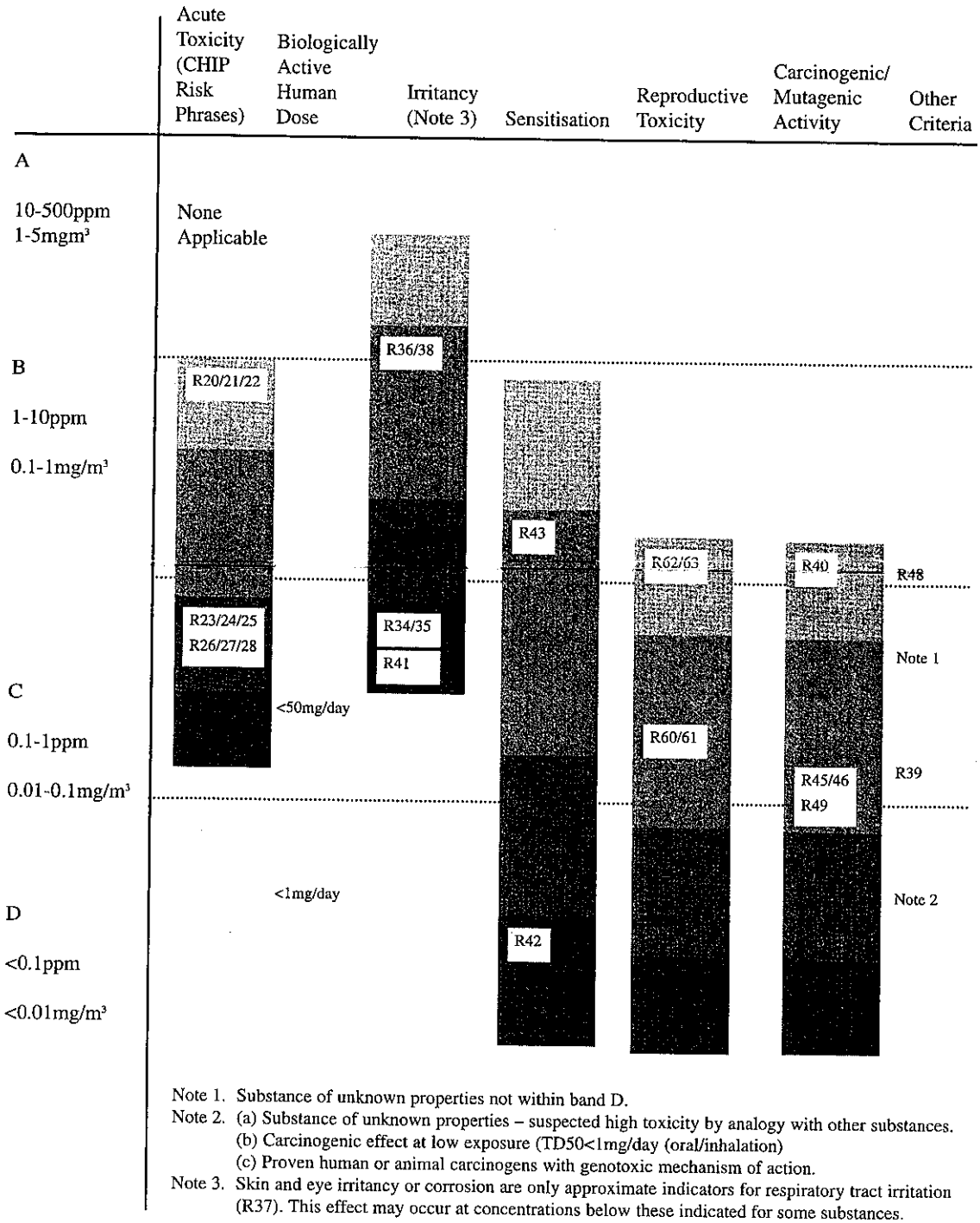
38 The absence of a substance from the lists of MELs and OESs does not indicate that it is safe. In these cases, exposure should be controlled to a level to which nearly all the population could be exposed, day after day, without adverse effects on health. As part of the assessment required to be carried out under regulation 6, the employer should determine his own working practices and standards for control. In some cases there may be sufficient information to set a self-imposed working standard, eg from manufacturers and suppliers of the substance, from publications of industry associations, occupational medicine and hygiene journals.

Appendix 3

Possible relationships between exposure limits and product development



Appendix 4



Note 1. Substance of unknown properties not within band D.

Note 2. (a) Substance of unknown properties – suspected high toxicity by analogy with other substances.
(b) Carcinogenic effect at low exposure (TD50<1mg/day (oral/inhalation)
(c) Proven human or animal carcinogens with genotoxic mechanism of action.

Note 3. Skin and eye irritancy or corrosion are only approximate indicators for respiratory tract irritation (R37). This effect may occur at concentrations below these indicated for some substances.

Risk Phrases:

R20	Harmful by inhalation
R21	Harmful in contact with skin
R22	Harmful if swallowed
R23	Toxic by inhalation
R24	Toxic in contact with skin
R25	Toxic if swallowed
R26	Very toxic by inhalation
R27	Very toxic in contact with skin
R28	Very toxic if swallowed
R34	Causes burns
R35	Causes severe burns
R36	Irritating to eyes
R37	Irritating to respiratory system
R38	Irritating to skin
R39	Danger of very serious irreversible effects
R40	Possible risk of irreversible effects
R41	Risk of serious damage to eyes
R42	May cause sensation by inhalation
R43	May cause sensation by skin contact
R45	May cause cancer
R46	May cause heritable genetic damage
R48	Danger of serious damage to health by prolonged exposure
R49	May cause cancer by inhalation
R60	May impair fertility
R61	May cause harm to the unborn child
R62	Possible risk of impaired fertility
R63	Possible risk of harm to the unborn child

Appendix 5 Examples: Setting OEBs

1. Substance A

A solid with anticoagulant properties.

Oral LD_{50} (rat) 160 mg/kg

IV LD_{50} (rat) 186 mg/kg

The substance would be classified as toxic (CHIP) and assigned to OEB-Band C (0.01-0.1 mg/m^3)

2. Substance B

A solid with analgesic activity

Oral LD_{50} (rat) 400-800 mg/kg

The substance would be classified as harmful (CHIP) and assigned to OEB-Band B (0.1-1mg/m^3)

3. Substance C

A solid with antiemetic properties

Oral LD_{50} (rat) >160 mg/kg

No activity as a skin irritant or mutagen but is a severe irritant to mucous membranes.

On the basis of its irritancy the substance would be placed in band B (0.1-1.0 mg/m^3). However, the substance would be classified as toxic (CHIP) on available evidence although the actual LD_{50} could be above 200 mg/kg. The substance would therefore be assigned to band C (0.01-0.1 mg/m^3).

4. Substance D

A solid with no activity as a skin or eye irritant and no activity in mutagenicity tests.

Single oral lethal dose (rat) >2000 mg/kg

The substance is a weak skin sensitiser in animal tests. A related substance is an established skin sensitiser in humans and suspected respiratory sensitiser with an OEL of 0.05 mg/m^3.

On the basis of the acute toxicity data OEB Band A would be appropriate but on the basis of the sensitisation potential of the substance and its structural relationship to an established sensitiser with potential respiratory effects Band C would be selected (0.01-0.1 mg/m^3) and a specific figure of 0.05 mg/mg^3, may be appropriate by analogy with the existing substance.

Appendix 6

Example: Occupational Exposure Limit Documentation

SUBSTANCE NAME No : 01/90
Date : 10/90
Supersedes : Previous documentation

I Compound Identity

= Chemical Name

= Cas No: XX-YY-Z

II Physicochemical Properties

White crystalline odourless powder, practically insoluble in water, soluble in ethanol and acetone and freely soluble in alkaline hydroxides.

III Intended Use

Thiazide diuretic/antihypertensive

IV Clinical

= Used for a variety of indications including congestive heart failure, hypertension and renal hepatic or pulmonary failure.

\# The human dose is between 50 and 100mg/day.

\# Rapidly, but variably, absorbed (up to 61 per cent) from the GI tract, with a plasma half-life of ca.5 hours. Diuresis can persist up to 15 hours. Excreted unchanged via the urine with no evidence of bioaccumulation. Dose proportionality has been demonstrated up to 100 mg orally.

\# The only side effects that are occupationally relevant are those resulting from the diuretic effect.

\# Epidemiological data on worker exposure is not available. No adverse effects are evident in workers handling the drug in compliance with the Provisional OEL of 0.5 mg/m^3.

V Toxicology

\# Essentially non-toxic when administered as a single dose (up to 10,000 mg/kg) to a range of species by the oral route. Is non-irritant to the skin and a slight ocular irritant to rabbits. No inhalational data available.

\# Some evidence of weak mutagenicity – small increase in revertants with TA98 (no S9); positive result in mouse lymphoma assay L5178Y/TK+/– in the absence of metabolic activation; induced SCE but not chromosomal aberrations in the CHO test.

\# The kidney was the major target organ in 13 week studies in rats and mice, characterised by mineralisation (>250 ppm) and severe nephropathy (50 000ppm in rats and 12 500ppm in mice). Similar findings were reported in a one year study in rats.

\# No evidence of reproductive toxicity was seen in rats or mice when dosed orally by gavage at up to 100mg/kg and 3000 mg/kg respectively on days 6 to 15 of gestation.

\# No information on disposition and kinetic studies in rodents is available.

VI Pharmacology

The substance acts on the distal tubule resulting in an increase in sodium chloride excretion together with an accompanying volume of water. Potassium excretion may also be increased. There are no drug/drug interactions that are occupationally relevant.

VII Other Relevant Data

ABC Pharmaceuticals Ltd recommend an Exposure Control Limit of 5mg/m^3 (8 hour TWA), calculated according to recommendations by Sargent and Kirk.

The existing Provisional OEL is 0.5 mg/m^3 (8 hour TWA).

VIII Lead Effect

The major toxicological effect in animals in nephropathy which occurs in rats at high doses (in excess of 25 mg/kg/day). The lead effect is, therefore, the clinical effect which occurs at lower doses (ca 1mg/kg in man), namely diuresis.

IX OEL Rationale

The minimally effective clinical dose is 50 mg, which by introducing a safety factor of 5x as recommended by McHattie ***et al***, assuming that 10m^3 of air is breathed in an 8 hour shift, yields an OEL of 1mg/m^3. It is therefore, recommended that the existing limit value be maintained. An analytical method is available.

The recommended OEL for the substance is 0.5 mg/m^3 (8 hour TWA)

X Biological Effect Monitoring/Health Surveillance

Monitoring/Surveillance is not indicated in workers handling the substance.

XI Reference

Approved at meeting of OEL Panel – October 1990.

XXI Documentation

1. ABPI Data Sheet Compendium 1990-91.
2. Goodman and Gillman's: The Pharmacological Basis of Therapeutics. Edited by Gilman A G, Goodwin L S, Rall T W and Murad F, 7th Edition, McMillan, New York 1985.
3. Martindale, The Extra Pharmacopoeia. Edited by Reynolds J E F, 30th Edition. The Pharmaceutical Press, 1989.
4. Toxicology and Carcinogenesis Studies of x in F344/N rats and B6C3F1 mice, NTP TR 357. National Toxicology Programme, Research Triangle Park, 1989.
5. E V Sargent and G D Kirk. Establishing Airborne Exposure Control Limits in the Pharmaceutical Industry. Am. Ind. Hyg. Assoc. J 49 309-313, 1988.
6. McHattie G V, Rackham M and Teasdale E L. The Derivation of Occupational Exposure Limits in the Pharmaceutical Industry, J. Soc. Occup. Med. 38, 105-108, 1988.
7. Correspondence, Smith J to Jones G, 2.9.90.
8. Analytical Method for Environmental Monitoring: to be advised.

XIII Milestone Dates

This review: October 1990

New Review: Third Quarter 1995