IEH Institute of Environment and Health

ICMM International Council on Mining & Metals

The Setting and Use of Occupational Exposure Limits

Current practice

Contents

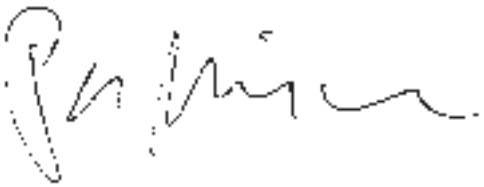
Foreword

Mining and metals companies have a duty to protect the health of their workforce and the control of exposure to harmful materials is an important part of this. Having consistent, internationally-recognized Occupational Exposure Limits (OELs) that are based on sound science is a vital element for companies to provide the best protection for their workers.

ICMM members believe that harmonization of the way OELs are set and the introduction of greater transparency in the process should be to the benefit of everyone involved. Traditionally OELs have been set by various groups using a wide variety of available information – given this background it is not surprising that there is considerable variation in the OELs in place. The result can be confusing for the companies and workforces of an industry which operates internationally.

This publication presents current perspectives on the OEL setting process from the scientific review of health data, to risk acceptance criteria and the consideration of socioeconomic factors. It is part of an ongoing ICMM project to develop an internationally harmonized approach, and an earlier draft of this publication was presented at a multi-stakeholder workshop held in London in November 2005. (The report of the workshop is available as a separate ICMM publication).

For ICMM to achieve its goal of fostering a more harmonized approach, we recognize the need for dialogue and understanding among a wide range of stakeholders, companies and territories. Accordingly we would welcome comment on this publication and on the broader initiative – details of which can be found on the ICMM website.



Paul Mitchell
President, ICMM

Executive Summary

The Institute of Environment and Health (formerly the MRC Institute for Environment and Health) was commissioned by the International Council on Mining and Metals (ICMM) to prepare a draft technical position paper as a framework for discussion on how to advance the debate on a harmonized approach to setting occupational exposure limits (OELs). The term OEL is a generic term that refers to an occupational standard for the concentration of a substance in workplace air. OELs may be defined in various ways, for example, as threshold limit values (TLVs), as developed by the US American Conference of Governmental Industrial Hygienists, or maximum exposure limits or as time related airborne chemical concentrations, such as short-term exposure limits or ceiling values, among others.

While the document focuses, in particular, on metals, metal compounds and other selected substances of importance in the metals and mining industries, the debate on harmonization of OELs is applicable to all industrial chemicals.

The document serves as a working paper to support the objective of ICMM, which is to develop, a reasoned position, based on scientific, socioeconomic and technical considerations, in order to influence and support movement towards a common, global, harmonized approach to setting OELs, in the jurisdictions in which ICMM member companies operate. Harmonizing OELs is viewed, by ICMM, as an element in the promotion of a sustainable and governance-based approach to reducing and minimizing the potential for occupational diseases internationally. Furthermore, a harmonized approach to setting OELs would represent good business practice and would enhance equality for business operations across firms and countries.

The ICMM goal is to develop a position on the harmonized approach to the review and establishment of OELs that, while taking into account the proportion of exposed workers that a given limit should be expected to protect:

- is based on a common definition of an OEL ;
- is underpinned by evidence-based, best available science;
- is consistent in the application of risk assessment;
- recognizes that any science-based value should be achievable in terms of socioeconomic impacts and technical achievability; and
- is open and transparent to all stakeholders.

OELs to limit concentrations of substances in workplace air have now been used for around a century as a means of assessing and/or controlling worker exposure to a wide range of airborne substances (e.g. dusts, particles, aerosols, gases, vapours). These have included organic and inorganic substances and pharmaceuticals, and have ranged from cotton dust, nicotine and coal dust, to specific chemicals such as chromic acid mist and vinyl chloride. OELs are not to be confused with ambient air standards, which are used to protect the general population. OELs have been set on a wide variety of available information and by various groups — some informal professional groups and some formalized regulatory expert bodies. These groups have evolved their own procedures and paradigms for recommending limits, and their outputs may or may not have been part of the national regulatory framework. The information available on which to base OELs has varied from a few informal observations on worker health to a large published toxicological and human-health database.

Given this background, it is not surprising that, worldwide, there has been a wide variation in the numerical value of many OELs for the same substance, which has led to confusion and perhaps a lack of confidence, both among the social partners (industry and worker representatives), concerning health and cost implications, and also among the regulators who have the responsibility for enforcement and assessment of industry compliance.

Nonetheless, with industrial globalization, the value of harmonizing approaches to setting OELs is becoming increasingly apparent. Harmonization does not mean standardization; that is, it is not to be expected that all jurisdictions should use identical approaches and generate identical standards; rather, differences in approaches should clearly reflect identifiable differences in scientific policy or scientific judgement, which should be communicated in a transparent manner.

Under national and international health and safety regulations and guidelines, most employers, worldwide, are required to protect workers from exposure to chemicals that may be harmful to health. Where health-based risk assessment indicates workplace airborne exposure, appropriate control measures may include consideration of worker protection, which is usually provided by the utilization of OELs. This, in turn, promotes both

best practice in exposure control (e.g. by the implementation of a hierarchy of control measures, from elimination of airborne exposure at source to safe working practices and the use of personal protective equipment) and the use of management systems to ensure compliance.

The primary objective in setting OELs is the protection of workers from occupational illness or disease, both locally, in the respiratory tract, and systemically, by setting an occupational exposure level at which no adverse health effects can be anticipated, either in the short-term or during a standardized working lifetime. To this end OELs may be set for both short-term exposures and longer term, time-weighted average exposures. In addition to worker protection, OELs may be set for the protection of the offspring of workers. Currently, the establishment of an OEL, generally, involves two phases. One phase, based on best available science, is the development of either a recommended health-based limit, which is derived from exposure–effect and exposure–response data, or, where a numerical health-based limit cannot be set (e.g. for compounds for which it is not possible to identify a threshold for effects, such as genotoxic carcinogens), a pragmatic numerical value based on a risk assessment, a health statement or, for example, a requirement to reduce levels as far as reasonably practicable. The other phase is the translation of a quantitative health-based limit into a practical, operational limit. The second phase may include several processes dealing with issues such as technical feasibility and economic factors. Thus, OELs may not always be simply health-based limits; pragmatism is often an essential element of setting an operational OEL. The different approaches to setting health-based limits, dealing with non-threshold compounds and addressing pragmatic and operational issues that are adopted by different jurisdictions are discussed in the report.

Currently, there are no formally recognized, internationally agreed, harmonized methodologies for the development of OELs, although the general procedures and processes used would be broadly agreeable to most standard-setting bodies. Recognizing that the development of OELs should be based on best available science, reflect risk acceptance criteria and take account of socioeconomic consequences, technical feasibility and the practicalities of measurement techniques and assessing compliance, this document explores:

- current perspectives on OELs across a range of national and international organizations;
- the use of data from experimental and human studies in setting health-based OELs;
- exposure measurement methodologies;
- risk assessment methodologies; and
- procedures for setting OELs in a number of jurisdictions.

Reflecting the particular focus on metals and mining, several chemicals of particular relevance for these industries are used as case studies within the report to illustrate some of the general points made and explained herein. These are — nickel metal and nickel compounds, palladium and soluble palladium salts, lead, chromium and manganese, as examples of metals important in the industry, and nitrogen dioxide, sulphur dioxide, sulphuric acid mists and crystalline silica. Metals provide a unique challenge when setting OELs as metal speciation (a variety of oxidation states and of metal compounds) may affect health impact. Similarly, other parameters become important when considering gases, mists, and particles of varying size and physical form, owing to deposition or absorption characteristics in the respiratory tract and the potential for acute or chronic effects. For each of the case studies, descriptions are given of measurement techniques, and comparisons are made of current OELs in selected countries and the procedures through which they have been established.

Finally, a number of proposals are made for harmonization of approaches to setting OELs (see below). The goals of the ICMM (above) are discussed — in particular the extent to which it is necessary to establish a common definition of an OEL and the potential for doing so and also to what extent numerical values for OELs can or should be more standardized. The framework for a harmonized approach proposed herein shares many elements with proposals put forward by ICMM member companies during the course of the

present exercise. The ICMM proposals are annexed to this report.

The benefits of a harmonized approach include increased transparency about the uses and limitations of an OEL, enhanced confidence in the process, pooling of resources across jurisdictions and a clearer definition of protections for workers, globally. Essential in the derivation of an OEL is clear documentation of acceptable health risk from a scientific viewpoint and, where appropriate, transparent justification of the technological and socioeconomic factors that may amend or refine a final recommendation for an OEL.

A proposed framework for a harmonized approach to setting OELs is as follows.

- Literature review of relevant scientific data according to standardized criteria
- Evaluation of literature review according to standardized criteria
- Selection of critical health endpoint(s)
- Determination of whether critical effects are threshold/non-threshold
- Selection of key studies for OEL
- Selection of point of departure
- Selection of factors influencing uncertainty
- Application of individual uncertainty factors to each such influencing factor
- Determination of composite uncertainty factor
- Identification of non-scientific influences on development of OEL
- OEL
- Discussion on the availability and accuracy of sampling technology
- Documentation and publication of all key steps, above

Throughout this publication, in addition to the standard references, electronic based resources are identified by red superscript numerals. Expanded descriptions including the relevant web links can be found in the web publications section on page 92.

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Current Perspectives on Occupational Exposure Limits

1. Current Perspectives on Occupational Exposure Limits

1.1 Introduction

This document has been prepared by the Institute of Environment and Health (IEH) for the International Council on Mining and Metals (ICMM) in order both to provide a framework for discussions on a harmonized approach to setting occupational exposure limits (OELs) and to facilitate activities related to the development of a common, global strategy to promote movement towards such an approach. While the document focuses on metals and their compounds and other selected substances of importance in the metals and mining industries, the debate on harmonization of OELs is applicable to all industrial chemicals.

The document supports an overall objective of the ICMM, which is to develop, a reasoned position, based on scientific, socioeconomic and technical considerations, in order to influence and support movement towards a common, global, harmonized approach to the review and establishment of OELs, in the jurisdictions in which ICMM member companies operate. This overall objective of ICMM is underpinned by the view that harmonization of OELs is an important element in the promotion of a sustainable and governance-based approach to reducing and minimizing the potential for occupational ill-health and disease. Furthermore, a harmonized approach to setting OELs would represent good business practice and would enhance equality for business operations across firms and countries.

The goal is to develop a harmonized approach that, taking into account the proportion of exposed workers that a given limit should be expected to protect:

- is based on a common definition of an OEL;
- is underpinned by evidence-based, best available science;
- is consistent in the application of risk assessment;
- recognizes that any science-based value should be achievable in terms of socioeconomic impacts and technical achievability; and
- is open and transparent to all stakeholders.

OELs to limit concentrations of substances in workplace air have now been used since around the turn of the 20th century. The first published report on a permissible exposure level was for carbon monoxide in Germany in 1883; other examples followed, including, in 1916, exposure limits for dusts with high quartz content in South African gold mines and, in 1921, the setting of exposure limits, by the US Bureau of Mines, for 33 substances encountered in the workplace (Cook, 1986). Since then, OELs have been used as a means of assessing and/or controlling worker exposure to a wide range of substances (e.g. dusts, particles, aerosols, gases, vapours). These have included organic and inorganic substances and pharmaceuticals, and have ranged from cotton dust, nicotine and coal dust, to specific chemicals such as chromic acid mist and vinyl chloride.

OELs are not to be confused with ambient air standards, which are used to protect the general population. While OELs are derived to protect relatively healthy workers during their working career, environmental ambient air standards protect the weakest individuals (youngest, oldest, and physically compromised) 24 hours a day, every day, for an average lifetime. Unlike some ambient air standards, exposure to levels at OELs will not necessarily prevent discomfort or injury to all those exposed owing to wide ranges in individual susceptibilities (Paustenbach, 2000).

OELs have been set on a wide variety of available information and by various groups — some informal professional groups and some formalized regulatory expert bodies. These groups have evolved their own procedures and paradigms for recommending limits, and their outputs may or may not have been part of the national regulatory framework. The information available on which to base OELs has varied from a few informal observations on worker health to a large published toxicological and human-health database. Furthermore, extensive national programs to update OELs across the world are not in place. The fact that some national OELs have not been re-reviewed in decades may be a factor that leads to differences in numerical values between countries.

Given this background, it is not surprising that, worldwide, there has been a wide variation in the numerical value of many OELs for the same substance, and this has led to confusion and, perhaps, a lack of confidence, both among the social partners (industry and worker representatives), concerning health and cost implications, and also among the regulators who have the responsibility for enforcement and assessment of industry compliance.

The objective in setting OELs is the protection of workers from occupational ill-health and disease, both locally, in the respiratory tract, and systemically, by setting a highest occupational exposure level at which no adverse health effects can be anticipated in workers and their offspring. Currently, the establishment of an OEL, generally, involves two phases. One, phase, based on best available science, is the development of a recommended health-based limit, which is derived from exposure–effect and exposure–response data, or, where a health-based numerical limit cannot be set (e.g. for genotoxic carcinogens), a pragmatic numerical value based on a risk assessment, a health statement or a requirement to minimize exposure levels. The other phase is often the translation of a quantitative health-based limit into a practical, operational limit. The second phase may include several processes dealing with issues such as technical feasibility and economic factors. Thus, OELs may not always be simply health-based limits; pragmatism is often an essential element of setting an operational OEL.

While many organizations around the world develop and use OELs, there are disparities in the OEL values of different organizations and the methodologies use to derive them (Haber and Maier, 2002). This review seeks to identify the differences and similarities in the development and use of OELs in different jurisdictions around the world and to identify ways to make such standard setting more harmonized and transparent.

Currently, there are no formally recognized, internationally agreed, harmonized methodologies for the development of OELs, although the general procedures and processes used would be broadly agreeable to most standard-setting bodies. Recognizing that the development of OELs should be based on best available science, reflect risk acceptance criteria and take account of socioeconomic consequences, technical feasibility and the practicalities of measurement and assessing compliance, this document reviews:

- current perspectives on OELs across a range of national and international organizations (Section 1);
- the use of data from experimental and human studies in setting health-based OELs (Section 2);
- exposure measurement methodologies (Section 3);
- risk assessment methodologies (Section 4); and
- procedures for setting OELs in a number of jurisdictions (Section 5).

Reflecting a particular focus on the metals and mining industries, several chemicals of particular relevance for these industries are used as case studies within the report, to illustrate some of the general points made and explained herein. These are — nickel metal and nickel compounds, palladium and soluble palladium salts, lead, chromium and manganese, as examples of metals important in the industry, and nitrogen dioxide, sulphur dioxide, sulphuric acid mists and crystalline silica. For each of the case studies, descriptions are given of measurement techniques (Section 3.4), and comparisons are made of current OELs in selected countries and the procedures through which they have been established (Section 5.7). Summaries of information underpinning the case studies are given in Annex 1. The document concludes (Section 6) with a number of proposals for harmonization of approaches to setting OELs. Proposals put forward, separately, by ICMM member companies can be found in Annex 2.

Metals and metal compounds and other chemicals encountered during mining, production and downstream uses cover a wide range of substances, some of which can cause the total spectrum of health outcomes, from minor irritation through to neurological illnesses and cancer; such substances thus exemplify all the historical and regulatory issues that have been pertinent to the establishment of OELs.

Owing to the scale of the task, preparation of this document has relied strongly on review material. Recent reviews that have been cited include those by Haber and Maier (2002), which looks at some of the problems in setting air standards for metals and mining related substances, the European Union (EU) Scientific Committee on Occupational Exposure Limits (SCOEL; CEC 1999), which discusses the methodology for the derivation of OELs, and the UK Interdepartmental Group on Health Risks from Chemicals (IGHRC) and its forerunner (Risk Assessment and Toxicology Steering Committee, 1999a,b,c; IGHRC, 2003; 2004), on approaches to risk assessment. A review by Paustenbach (2000) also provides a wealth of background on the history and the biological basis for OELs.

1.2 Descriptions

1.2.1 Air limits

There have been many descriptions of OELs, which is the generic term now favoured by the International Labour Organization (ILO) and the World Health Organization (WHO) to describe a range of workplace air standards, many of which have very specific descriptions and are often related to regulatory or advisory frameworks. However, while recognizing potential pragmatic constraints, whether these are set for regulatory or guidance purposes, they all generally adhere to the same broadly accepted principle that OELs are levels of substances in workplace air that are believed to be low enough to provide protection for workers and their offspring from adverse effects arising from breathing workplace air, even when exposure is repeated on a regular basis over a working lifetime (CEC, 1999).

Although countries such as the UK and Germany developed some of the early air standards for workplace control of some substances, it is generally accepted that the first country to develop a systematic and comprehensive approach to setting OELs was the USA. The American Conference of Governmental Industrial Hygienists (ACGIH; a professional organization of occupational hygienists and other professionals from universities or governmental institutions) first published Maximum Allowable Concentrations (MACs) from 1946 (Stokinger, 1970; Stokinger, 1981). These were later renamed TLVs. Similar approaches were subsequently adopted by the Deutsche Forshungsgemeinschaft (DFG) in Germany (maximum workplace concentration, MAK, Maximale Arbeitsplatzkonzentrationen), the Netherlands and Scandinavia. The UK Health and Safety Executive (HSE) followed later with the system of maximum exposure limits (MELs) and occupational exposure standards (OESs).

Although the two-OEL system in the UK has recently been replaced by a single OEL system of workplace exposure limits (WELs; HSE, 2005b), in which many of the existing MELs and OELs have been converted to WELs, for the purpose of this review, it has been more appropriate to refer to the former MEL and OEL definitions, as it is for these that the documentation and supporting evidence for UK OEL recommendations are available.

OELs to protect against ill health as a consequence of long-term occupational exposures are usually based on the assumption that a worker can be exposed to a substance for a working life of 40 years with 200 working days per year[1], on the basis of a typical 8-hour (h) working day and a nominal 40-h working week. Such an OEL is usually set as an 8-h time-weighted average (TWA; see also Section 3.3). OELs are set not just to protect workers during their working lifetime but also to protect them for the remainder of their lifetime and to protect their offspring. Short-term exposure limits (STELs) may also be set for substances that cause acute toxicity or to prevent adverse effects that may arise owing to peak exposures that are not controlled by application of an 8-h TWA (CEC, 1999). STELs are often set for 15 minutes (min). However some US Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) have 30-min STELs; this also is the length of the TLV excursion limit.

Initially a major concern in setting OELs was the reduction of occupational exposure to chemicals that cause frank toxic effects, such as hepatotoxicity, neurotoxicity, nephrotoxicity, and carcinogenicity. However, the majority of OELs, for example the ACGIH TLVs and German MAKs, are actually set at levels intended to prevent sensory irritation (Paustenbach, 2001), which may or may not be the most sensitive endpoint.

Physicochemical and physiological characteristics, speciation and essentiality

Physicochemical properties will influence the deposition and absorption characteristics of gases, mists and particles of varying size and form and will therefore impact on the development of OELs.

A specific issue for metals is the setting of OELs for different forms of the metal, which depends on the degree to which speciation (different oxidation states and the variety of metal compounds) affects toxicological properties (Haber and Maier, 2002). Examples given in the case studies (Section 5.7 and Annex 1) include soluble nickel and palladium salts and different oxidation states of chromium.

While for many metals, toxic effects can occur at high exposures, because many metals are 'essential', insufficient intake can also lead to adverse health effects (Haber and Maier, 2002). Such considerations impact on the choice of uncertainty factors in risk assessment (see Section

4.2). This special consideration does not occur for most other substances for which OELs are set.

1.2.2 Biological limits

Biological limits have developed into a number of forms, generally used for either exposure/uptake monitoring (biological monitoring) or effect monitoring (biological effect monitoring). With biological monitoring as an exposure measure, the chemical or the metabolite of the chemical is measured in a biological matrix such as urine, blood, or expired air, to estimate the uptake of that chemical at a particular time; for example, the measurement of cadmium in urine of cadmium-exposed workers. In biological effect monitoring, an effect caused by the chemical or its metabolite on some kind of biochemical or physiological function in the body is measured; for example, reduction in cholinesterase levels in plasma caused by exposure to organophosphorus pesticides.

Biological monitoring in general is to be seen as a complementary means of assessing worker exposure rather than an alternative to air monitoring, as each provides different kinds of information.

Broadly, two approaches to the derivation of biological limits are in use. Biological exposure indices (BEIs) are exemplified by the ACGIH approach, in which the recommended BEI is based on the equivalent to the amount of that same chemical that would be taken into the body from exposure by inhalation to the current ACGIH OEL value over an 8-h period (ACGIH, 2003a). The other approach is the Biologische Arbeitsstofftoleranzwerte (biological tolerance value or BAT) used in Germany by the DFG Commission. These are said to be health-based values; they are limits set on health effects and represent levels in the body at which no harm will occur (DFG, 2004; DFG, 2005b). A similar approach is used in the UK for their Health Guidance Values, but in addition the UK HSE has also developed a pragmatic Benchmark Guidance Value (BMGV), which is not health-based but is a practical achievable level set at the 90th percentile of available biological monitoring results, collected from a representative sample of workplaces with good occupational hygiene practices (HSE, 2002).

1.2.3 Occupational exposure limits in different jurisdictions

There are relatively few bodies, worldwide, that independently set OELs; many jurisdictions substantially follow the methodology and guidelines from the EU SCOEL, German DFG, UK HSE, US ACGIH or US OSHA.

Descriptions of some national OELs are summarized in Table 1.1. The processes for developing and setting OELs in different countries are described and compared in Section 5.2. The advisory or legal status of OELs in different jurisdictions is indicated in the table. The status of such limits may impact on the numerical value and application of the limit (also discussed further in Section 5).

Within the EU, competent national authorities or other relevant national institutions set OELs as limits for concentrations of hazardous compounds in workplace air. OELs for hazardous substances represent an important tool for risk assessment and management and valuable information for occupational safety and health activities concerning hazardous substances[1].

The US ACGIH TLVs are widely used both within and outside the USA and have been adopted entirely in dozens of countries. For example, the Australian National Occupational Health and Safety Commission (NOHSC) initially adopted many of its national exposure standards (NESs) from the ACGIH list of TLVs (NOHSC, 1999), as did the UK HSE until the early 1980s. However, within the USA, ACGIH TLVs are only recommendations and do not have legal force[1]. The US OSHA sets regulatory limits for the USA; these are published PELs, which were historically based on the ACGIH TLVs. Like the TLVs, PELs may include TWAs, action levels, ceiling limits, STELs, excursion limits and in some cases BEIs[1]. The US National Institute for Occupational Safety and Health (NIOSH) recommends, to OSHA, exposure levels that are protective to workers. These recommended exposure levels (RELs) have no legal force; RELs also include TWAs, STELs, ceiling values and BEIs[1].

[1] The ACGIH policy statement on the use of TLVs is that they are developed as guidelines to assist in the control of health hazards, and that the recommendations or guidelines are intended for use in the practice of industrial hygiene, to be interpreted and applied only by a person trained in this discipline.

1.3 Other limit values

Apart from OELs to facilitate potential risk management in the occupational environment, many other standards or maximum levels of a chemical that should not be exceeded are relevant to risk management in the general population. Such standards or recommended maximum levels may be expressed, for example, as a concentration of a chemical in a medium, such as air, water or food, or may be expressed as an upper limit for human intake, such as amount ingested or inhaled. In the UK and elsewhere, some standards may have advisory status, such as soil guideline values, air or water quality standards or acceptable or tolerable daily intakes (ADIs and TDIs) for food additives and contaminants. Other standards, may, like OELs, be mandatory, for example standards for pesticides or veterinary residues in food stuffs (IGHRC, 2004).

Table 1.1: Occupational exposure limits in different jurisdictions

Country/Region	OEL	Regulatory/advisory status	Specified exposure scenarios	Workers protected (specified health endpoints)
European Union (CEC, 1999)	IOELVs (Indicative Occupational Exposure Limit Values) BLV (Binding Limit Value); risk of adverse health effect at specified levels when no-effect level cannot be identified	Recommendation to Member States for adoption into national legislation		
Germany, Ausschluss für Gafahrstoffe (AGS)	TRK (Technische Richtkonzentrationen; technical guidance concentration)	Common national legislation	Category 1, 2 or 3 carcinogens; concentration in workplace air that can be reached using best available technology	Healthy adults
Germany (DFG, 2004)[1]	MAK (Maximale Arbeitsplatzkonzentrationen, maximum concentration in workplace); 8-h TWA	Recommendations to AGS	Substance-specific acceptable peak concentrations and durations defined; skin uptake indicated; MAK-values for category 3 and 4 carcinogens for which a harmless minimum concentration can be determined Limits for substances in the human body	
	BAT (Biologische Arbeitsstofftoleranzwerte); biological tolerance value	Recommendations	In addition to OELs, special rules for individual substances or substance groups such as hydrocarbon mixtures, diesel engine emissions, or different types of fibres and dust	
The Netherlands (Dutch Expert Committee on Occupational Standards, 2000)	MAC (Maximaal Aanvaarde Concentraties, maximum air concentration in working area); 8-h TWA and 15-min TWA MAC-C (ceiling value)	Some legally binding, others administrative and not legally binding		
	Exposure–response relationship only (genotoxic carcinogens)		No OEL for genotoxic carcinogens	

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Table 1.1: Occupational exposure limits in different jurisdictions *continued*

Country/Region	OEL	Regulatory/advisory status	Specified exposure scenarios	Workers protected (specified health endpoints)
UK (HSE, 2002)*	MEL (Maximum Exposure Limit); 8-h TWA or 15 min STEL	Legally enforceable	Exposure reduced as far below level as possible; set for substances for which not possible to determine NOAEL	(e.g. Carcinogens and asthmagens)
	OES (Occupational Exposure Standard); 8-h TWA or 15 min STEL	Legally enforceable	Level to which exposure to be reduced; STEL, only, for substances, for which even brief exposure considered critical	No indication of risk to health of workers exposed by inhalation day after day
	BMGV (Biological Monitoring Guidance Value)	Non-statutory	Some OELs for multi-substance exposure prescribing process emissions like welding fumes	
USA ACGIH (ACGIH, 2003a)[1]	TLV (Threshold Limit Value)-TWA; 8-h TWA	No legal status in the USA. May have legal status in other countries		Nearly all workers, day after day, for working lifetime, without ill effect
	TLV–STEL; 15-min TWA	No legal status in the USA	Continuous exposure for short period not to be exceeded at any time	(To protect from irritation, chronic/irreversible tissue damage, narcosis)
	TLV-C (ceiling)	No legal status in the USA	Concentration not to be exceeded any part working day	
USA NIOSH[1]	REL (Recommended Exposure Level); TWA; STEL, ceiling value and BEI	No legal force, recommendations to OSHA		
USA OSHA[1]	PEL (Permissible Exposure Limit)	Regulatory; historically based on ACGIH TLVs		
Australia (NOHSC, 1999)[1]	NES (National Exposure Standard) Airborne	Advisory character, except where law, other than the NOHSC Act, or instrument made under such a law, makes them mandatory; application of any National Commission document in any particular State or Territory of Australia is prerogative of that State or Territory		Concentrations that should neither impair health nor cause undue discomfort to nearly all workers; (additionally, to guard against narcosis or irritation)[2]

*** OES and MEL recently replaced by WEL (Workplace Exposure Limit)**

2

Occupational Exposure Limits

2. Use of Experimental and Human Studies in Deriving Occupational Exposure Limits

Data from experimental and epidemiological studies are used to derive health-based limits as a first step in setting OELs (ECETOC, 1984). When available, data from human studies will generally be preferred for the development of OELs; however, in the absence of human data or where such data are few, experimental studies may be used as the basis for developing OELs. Most organizations define neither a minimal database nor a rigid hierarchy for selecting studies to be used in deriving OELs; instead a weight of evidence approach, which looks at all available data, is frequently used (Haber and Maier, 2002).

2.1 Experimental studies

For many industrial chemicals, there is very little human published data and thus a great reliance has to be placed upon the available experimental studies. For many traditional chemicals, some of the studies available are quite old, going back to the 1930s and 1940s, and they were often conducted to standards that would not be readily acceptable now; therefore they have to be interpreted with a great deal of caution.

The main source of widely accepted methodologies for *in vitro* and experimental animal toxicity testing is the Organization for Economic Co-operation and Development (OECD) manual entitled *'OECD Guidelines for the Testing of Chemicals'* (OECD, 2000). The aim of the OECD guidelines is to make available methodology, for each toxicity test, which is sufficiently well defined to enable the tests to be conducted in a similar manner in different laboratories across the world, and to produce results that will be acceptable to various regulatory bodies. By taking a harmonized approach it is hoped that wasteful duplication or repetition will be avoided. The OECD test guideline manual warns that when assessing the results of toxicological testing on any chemical, the limitations of the test must be borne in mind. Consideration must also be given to the fact that extrapolations from animals or *in vitro* test systems might not be accurate, and judgement must be exercised as to whether a particular method is suitable for testing the chemical in question, as the experimental designs are not designed to be appropriate to all chemicals under all exposure scenarios (OECD, 2000). Similar criteria are described in the European Council Directive 67/548/EEC, with numerous updates[3].

2.1.1 Assessing study quality

In the course of a toxicological review, many data from different sources and of different ages will need to be considered. The OECD test guidelines provide a useful reference with which the methodology used to generate experimental data can be compared, to judge their quality and validity. Although the guidelines do not provide a rigid study protocol, they can be used to make sure that experimental methodologies have included important considerations, such as selection of animals, housing conditions, preparation of animals and doses, the number and sex of the animals used, the dosage, administration, observations and pathological examinations (OECD, 2000). The guidelines also give an indication of the findings that the experimental report or publication should include. Deviations from the current OECD test guideline do not render a study invalid, but they should be scientifically justified. In addition, a lack of information does not mean that the study is invalid, but rather that the validity cannot be judged, so the results should be interpreted with caution.

Another indication of the quality of a study is whether it has been conducted to the OECD principles of Good Laboratory Practice (GLP), which were introduced in 1981. GLP embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived, and the implementation of GLP compliance is verified by laboratory inspections and study audits. More information on GLP can be found on the OECD website[4].

Where studies have been conducted prior to OECD test guideline adoption or GLP implementation, expert judgement is required to judge whether the studies meet current standards and to what degree their outcome can contribute to the overall database.

2.1.2 General toxicity

The most relevant information to set OELs derives from 28- and 90-day inhalation studies. There are several OECD test guidelines to investigate the general toxicity of a substance following short- or long-term exposure. Table 2.1 summarizes the guidelines available and highlights those that relate to inhalation toxicity. The hazards of inhaled substances are influenced by inherent toxicity and

by physical factors such as volatility and particle size. These studies and considerations are particularly important for setting OELs. It is also important to consider the explosive potential of test substances, and care should be taken to avoid generating explosive concentrations, therefore the test concentration might be limited for some substances. Other important information that the study report should include is the concentration of the test substance, which should be kept as constant as possible, and where particles are generated, what the particle size distribution and consistency of this distribution was. The pathological examination following inhalation exposure should thoroughly investigate the tissues of the respiratory tract. It is also important to note whether the animals were exposed nose-only, head-only or whether their whole bodies were exposed to the test substance, as this might influence the pattern of effects observed (OECD, 2000).

Tests for general toxicity can be used to assess the potential of a substance to cause a large number of effects. The OECD test guidelines generally recommend that pathological examinations of all the major tissues and organs be conducted, as well as haematological examinations and clinical biochemistry determinations. Body weights, food consumption and visual assessment of general condition should all be recorded (OECD, 2000). Yanagida et al. (2005) have shown a relationship between OELs and the lethal dose 50 (LD_{50}) values of rats or mice for metals and metallic compounds.

In addition to the test guidelines for general toxicity described above, there are several test guidelines that relate to neurotoxicity. Most of these have been specifically designed to investigate the properties of organophosphate compounds, but OECD test guideline 424 can be used for other compounds to test for neurotoxic properties in rodents. This test can be combined with the repeated dose toxicity tests, or conducted alone. This guideline specifically addresses administration via the oral route, but it is acknowledged that the guideline could be adapted to other routes, including inhalation (OECD, 2000).

Table 2.1: Summary of studies used to investigate the general toxicity of a substance

OECD test guideline number	Title of guideline
401	Acute oral toxicity
402	Acute dermal toxicity
403	Acute inhalation toxicity (recently updated)
407	Repeated Dose 28-Day Oral Toxicity Study in Rodents
408	Repeated Dose 90-Day Oral Toxicity Study in Rodents
409	Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents
410	Repeated Dose Dermal Toxicity: 21/28-day Study
411	Sub-chronic Dermal Toxicity: 90-day Study
412	Repeated Dose Inhalation Toxicity: 28-day or 14-day Study
413	Sub-chronic Inhalation Toxicity: 90-day Study
420	Acute Oral Toxicity - Fixed Dose Method
423	Acute Oral toxicity - Acute Toxic Class Method
425	Acute Oral Toxicity: Up-and-Down Procedure
433	Acute inhalation toxicity – fixed dose procedure
434	Acute dermal toxicity – fixed dose procedure
452	Chronic Toxicity Studies
453	Combined Chronic Toxicity/Carcinogenicity Studies

Source: OECD (2000)

2.1.3 Irritancy

There are several OECD test guidelines to determine the irritating potential of substances (see Table 2.2). There are no guidelines to assess the potential for respiratory irritation, but such an effect is likely to be detected in the tests for general toxicity (OECD, 2000).

In the interest of animal welfare, OECD recommends that studies into irritation/corrosive properties should not be conducted if the substance has predictable corrosive activity (e.g. strong acid or alkaline) or is highly toxic via the dermal route or if the substance did not produce irritation in an acute dermal toxicity test up to a dose of 2000 mg/kg bw. The duration of the test should also be sufficient to evaluate the reversibility of any effects (OECD, 2000).

The OECD test guideline for dermal irritation does not specifically discuss how to deal with gaseous or particulate materials, because it is generally accepted that dermal irritation is not of concern for these substances. OECD test guideline 405 does provide guidance on how to administer substances to the eye and how to estimate the dose.

A comprehensive review of nearly 300 chemicals tested using the American Society for Testing and Materials (ASTM) mouse bioassay or some variation of the assay found that the concentrations capable of producing a 50% decrease in respiratory rate (RD_{50}) for SW, CF1 and OF1 strains of male mice all predict TLVs, on the same basis, that is $0.03xRD_{50}$. The strongest correlation between TLV and RD_{50} was found in male SW mice. The use of different strains provides a range of sensitivities (Schaper, 1993).

2.1.4 Odour

There is no OECD test guideline for odour.

2.1.5 Sensitization

There are two OECD test guidelines to investigate the potential for substances to cause skin sensitization: OECD test guideline 406 (skin sensitization) and OECD test guideline 429 (skin sensitization — the local lymph node assay; OECD, 2000). Neither of these tests is suitable for testing gaseous or particulate materials. There is no OECD guideline on how to test for respiratory sensitizing potential, which for gaseous/particulate substances is of more concern than skin sensitization.

Methodologies, which are based on the results of skin and eye irritation tests conducted in experimental animals, are available for setting preliminary OELs for sensory irritants, until human data become available (Paustenbach, 2001).

2.1.6 Genotoxicity and cancer

There are many OECD test guidelines that relate to the potential of a test substance to cause genetic damage and two guidelines for cancer (see Table 2.3). In general, the two guidelines for cancer can be adapted to any route of exposure, including inhalation. Of paramount importance to these studies is the identity of the test substance. It is essential that composition, including major impurities, and the stability of the test substance be known before the study is initiated. OECD test guidelines 451 and 453 provide some detail on inhalation studies, as the technical problems involved are complex. Long-term exposures are usually based on projected industrial experiences

Table 2.2: Summary of OECD test guidelines for irritancy and corrosion

OECD test guideline number	Title of guideline
404	Acute Dermal Irritation/Corrosion
405	Acute Eye Irritation/Corrosion
435	*In Vitro* Membrane Barrier Test Method for Skin Corrosion (adopted 2004)
430	*In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test (TER)
431	*In Vitro* Skin Corrosion: Human Skin Model Test

Source: OECD (2000)

Table 2.3: Summary of OECD test guidelines for genotoxicity and carcinogenicity

OECD test guideline number	Title of guideline
Cancer	
402	Carcinogenicity Studies
403	Combined Chronic Toxicity/Carcinogenicity Studies
471	Bacterial Reverse Mutation Test
Genotoxicity	
473	*In vitro* Mammalian Chromosomal Aberration Test
474	Mammalian Erythrocyte Micronucleus Test
475	Mammalian Bone Marrow Chromosomal Aberration Test
476	*In vitro* Mammalian Cell Gene Mutation Test
477	Genetic Toxicology: Sex-Linked Recessive Lethal Test in Drosophila melanogaster
478	Genetic Toxicology: Rodent Dominant Lethal Test
479	Genetic Toxicology: *In vitro* Sister Chromatid Exchange Assay in Mammalian Cells
480	Genetic Toxicology: Saccharomyces cerevisiae, Gene Mutation Assay
481	Genetic Toxicology: Saacharomyces cerevisiae, Miotic Recombination Assay
482	Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells *in vitro*
483	Mammalian Spermatogonial Chromosome Aberration Test
484	Genetic Toxicology: Mouse Spot Test
485	Genetic Toxicology: Mouse Heritable Translocation Assay
486	Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo*

Source: OECD (2000)

(animals dosed for 6 h/day, 5 days/week), or possible environmental exposures (animals dosed 22–24 h/day, 7 days/week). Therefore it is important that the exposure period and frequency of dosing are taken into account when extrapolating the results to humans. As previously mentioned, it is important that the exposure concentration is constant and that the particle size distribution of the solid or liquid aerosol is maintained throughout treatment (OECD, 2000).

Since no single assay has proved capable of detecting mammalian mutagens and carcinogens, it is usual practice to apply the assays in 'batteries'. There are various approaches, and batteries generally comprise two to five tests, which include tests on prokaryotic and eukaryotic cells and cover the major genetic changes possible. Selection of the tests is dependent upon the known characteristic of the test material. As a general rule though, *in vitro* tests for gene mutation and chromosomal aberrations are conducted, and where the results from either of these tests are positive further *in vivo* testing is conducted.

For gaseous or particulate materials, for which the most likely route of exposure is inhalation, the *in vitro* tests can be adapted by testing in sealed culture vessels (OECD, 2000). The OECD test guideline manual gives references for accepted methods for testing gaseous or volatile materials for each test. The test guidelines relating to *in vivo* genotoxicity tests generally note that, where appropriate, the inhalation route may be used, but they do not discuss any special considerations. However, it would be reasonable to assume that the points of discussion for general toxicity testing and carcinogenicity testing for inhaled materials also apply to *in vivo* genotoxicity testing.

Table 2.4: Summary of OECD test guidelines for reproductive and developmental toxicity

OECD test guideline number	Title of guideline
414	Prenatal Developmental Toxicity Study
415	One-Generation Reproduction Toxicity Study
416	Two-Generation Reproduction Toxicity Study
421	Reproduction/Developmental Toxicity Screening Test
422	Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

Source: OECD (2000)

2.1.7 Reproductive toxicity

There are several OECD test guidelines to investigate the potential for a substance to cause reproductive or developmental effects (see Table 2.4). The guidelines largely describe testing via the oral route of exposure, but also acknowledge that for some substances inhalation is more appropriate and that the test can be modified accordingly. Whatever the route of exposure, dosing should occur at the same time each day (OECD, 2000). Although the OECD test guidelines do not discuss issues specific to dosing via inhalation, it would be reasonable to assume that the points of discussion for general toxicity testing also apply to reproductive and developmental toxicity testing.

2.2 Epidemiological studies and other studies in humans

2.2.1 Principles for using human studies in setting occupational exposure limits

Good quality epidemiology studies coupled with good exposure assessments can yield the best information for setting OELs for potential chronic health effects, and for this reason good quality human data, in particular, are preferred to animal data for human health risk assessments. With the exception of volunteer studies, which mainly address acute effects, exposure characterization in human studies is often limited and dose-response relationships are rarely demonstrated. Such considerations may limit the weight given to human studies in establishing OELs. While case-reports cannot, alone, provide a basis for establishing an OEL, they can be useful in indicating a relationship between exposure and effect that merits further investigation, as can cross-sectional studies. Well-conducted volunteer studies can be useful when a key adverse effect has already been identified. Case-control, historical cohort or longitudinal prospective studies are the only satisfactory way to investigate long-term effects in humans and provide sufficient evidence for risk assessment and development of OELs, as long as exposure is well characterized and potential biases and confounders are well controlled (CEC, 1999; see also below).

Guidelines on the use of epidemiological evidence in environmental health risk assessment have been produced by WHO (2000). The guidelines focus on the use of epidemiological data for two distinct activities — health hazard characterization, that is the identification of environmental hazards by the collection, evaluation and interpretation of epidemiological and other evidence on an association between an environmental factor and human health; and health impact assessment, taken to mean the quantification of an expected health burden related to an exposure in a particular population. Some of the key guidance is summarized in Table 2.5.

A further initiative to develop reporting guidelines for observational epidemiological studies, including case–control, cohort, and cross-sectional studies — STandards of Reporting of OBservational studies in Epidemiology (STROBE)[5] — has recently been established.

In interpreting epidemiological studies, account must be taken of bias, confounding and chance. Bias is caused by factors in the study that lead erroneously to a stronger or weaker association between exposure and effect than actually exists; confounding occurs when there is an association between the supposed causal factor that is under investigation and another factor that is also associated with the endpoint under investigation.

Table 2.5: Recommendations for use of epidemiological studies in health risk assessment

General
Precise description of exposure characteristics, exposure–response function
Distinguish acute from chronic effects of exposure
Health hazard characterization
Systematic review of evidence according to predefined protocol
• specification of questions to be addressed • justification for expertise of expert group assessing data • specification of methods for identifying relevant studies
Identification of relevant studies
• criteria for bibliographic searches • other search methods • use of publicly available / unpublished data
Assessment of validity of epidemiological studies
• evidence for strength of association (temporality, biological plausibility, coherence, consistency, specificity) • characterization of exposure–response • alternative explanations (chance, bias, confounding) • sensitivity analysis
Use of meta-analysis
• inclusive rather than exclusive • use of quality scores not recommended • account for publication bias • quantitative summary estimates (aggregative meta-analysis)
Drawing conclusions
• expert judgement • weighting of studies • contribution of non-epidemiological evidence to overall judgement • move to standardization of scales for weight of evidence
Health impact assessment
Protocol
• purpose of assessment • quantification of uncertainty • exposure metric (temporal and compositional, as required) • separate impact assessment for each of multiple health outcomes • well-defined process to derive exposure–response function, quality of exposure measurement, consistency of exposure metrics across studies • baseline frequency of health outcomes • estimate population attributable cases
Interpretation
• assumptions and limitations • impact of uncertainty of findings

Source: WHO (2000)

Such factors can be minimized or accounted for in study design and analysis.

However, Pocock et al. (2004), in their review of a sample of 73 epidemiological studies in general populations, published since 2001 (37 cohort, 25 case–control, 10 cross-sectional, 1 case–cohort), report some limitations in conduct and analysis of epidemiological studies. For example, while 67 articles included statistical adjustments for potential confounders, few explained the choice of confounding variables. Furthermore, while 43 studies performed subgroup analyses, interaction tests were rare (reported in 8 articles) and some studies investigated multiple associations between exposure and outcome, increasing the likelihood of false positive results. The authors also reported evidence of publication bias. Some of the key conclusions from the study are summarized in Table 2.6.

Epidemiology in the occupational setting has its own peculiarities, which can both strengthen and weaken the possibility for drawing conclusions about causal relationships. These can include contaminant exposure to a range of hazardous substances other than the one for which an answer is being sought and the potential loss of ill employees (caused by the substance of interest) in cross-sectional studies. In the first case, the results may be complicated by confounders and in the latter by an under-reporting bias.

Epidemiological data need to be evaluated carefully to determine whether they are sufficient to establish causality; criteria for judging causality are well recognized (e.g. WHO, 2000). Sometimes, while few data for epidemiological or monitoring studies are available in the published literature, 'grey' literature, such as company records, may provide useful information. However, developing OELs on the basis of such data has the disadvantage of lack of transparency. If such data are to be used, it would be helpful if they could be made openly available in some form, for example in a supporting criteria document, as was the case in a recent Criteria Document on manganese (IEH, 2004).

2.2.2 Exposure data in epidemiological studies

The goals of exposure assessment in occupational epidemiology are to determine estimates of mean exposures for an occupational group and to determine the homogeneity of exposure within and between the group (Rappaport, 1991b). Guidelines for good exposure assessment practice have been put forward by IGHRC (2004).

Estimation of exposure is often made using categorical descriptors, based on job title and

Table 2.6: Recommendations for design and reporting of epidemiological studies

Information on exclusion/refusals
Assessment of quality of data collected
Adequate size of study and power calculations
Rationale for categorizing quantitative exposure variables
Statistical cut off points not to be over interpreted
Rationale for selection and adjustment of potential confounders
Appropriate methods and interaction tests for subgroup analyzes — not to be over interpreted
Risk of false positives from multiple associations

Source: Pocock et al. (2004)

duration of exposure; such procedures are particularly used in retrospective exposure assessment. However, such estimates may have limited value (Rappaport, 1991b). An analysis by Rappaport et al. (1993) of 183 homogenous exposure groups (HEG; i.e. groups defined by job title, location and other features of work environment, also described as similar exposure groups (SEGs) or job exposure groups (JEGs)) showed that only 20% of the HEGs were uniformly exposed, while a similar proportion showed high variation between workers.

An example of exposure reconstruction is that conducted for several chromium (VI)-exposed occupational cohorts in Ohio, USA. Historical exposure information was often incomplete, qualitative or could not be defined on a worker-specific basis. Although exposure data were more robust for later cohorts, such cohorts lacked sufficient latency for observations of any possible increased cancer risk. Exposure reconstruction involved exhaustive review of historical hygiene records, reconstruction of worker histories, reconstruction of job titles over time and identification of JEG areas, which were used to relate air-monitoring locations to job titles. TWA airborne exposures were calculated on the basis of variability of airborne concentrations in JEG areas during an 8-h shift and expected movement of workers, by job title, through the plant (Proctor et al., 2004).

In their review of recently published epidemiological studies, Pocock and colleagues (2004) noted that, while in most studies (50/73), exposures were quantitative, they were usually grouped in ordered categories (42 articles) rather than analyzed as a continual variable. Yet few articles (22) gave the rationale for the choice of categories.

2.2.3 Data on sensory irritation

Many, if not most, airborne substances are able to produce irritation to the nose and eyes and upper respiratory tract at some concentration. Sensory irritation (including perception of unpleasant odours) is a single exposure, threshold phenomenon, which is mediated by damage or nervous stimulation via the vagus or trigeminal nerves. In some cases, it is hard to distinguish between irritation and unpleasant odour. Human data on such effects are normally derived from volunteer or workplace studies. In many cases OELs have been based on such irritant effects and often there is a debate about whether these are truly harmful or simply objectionable effects. (Paustenbach, 2001; Dalton, 2001; Meldrum, 2001).

2.3 Mechanisms of toxicity

Consideration of how mechanisms of carcinogenesis can be used in risk assessment (e.g. from IARC, 1992a) can give some insights into how toxic mechanistic data might impact on risk assessment more generally.

Increased understanding of the critical biological effects of carcinogenesis (or other toxicities) allows the possibility of using data from studies on putative intermediate effects or correlated endpoints in the assessment of the risk of exposure to some specified substances.

Advances in technology and in understanding of biological and chemical processes have led to increasing development and acceptance of test methods based on mechanistic understanding (Blaauboer, 2003), such as molecular biology, cell-culture techniques, neurophysiological measurements, and proteomics, genomics and metabolomics.

Molecular biological techniques can be increasingly used in human biological monitoring studies to measure internal dose and help elucidate intermediate steps leading to toxicity and may have an increasing part to play in molecular epidemiology studies. For example, if it were possible to measure, in humans, the occurrence of some intermediate effect, such as the occurrence of a specific genetic mutation that is known to be a prerequisite for cancer occurrence, then epidemiological studies with this effect as an outcome could rapidly provide data for carcinogenic risk assessment. As well as improving exposure measurement and detecting early biological effects believed to form part of the toxicological process, molecular epidemiology studies can help in the elucidation of sources of interindividual variability, for example metabolic polymorphisms in humans. However, as noted by the International Agency for Research on Cancer (IARC, 1992a), caution is needed in interpreting studies on early biological effects, as the use of biomarkers for early effects depends on knowledge about the significance of the effect as a predictor of subsequent risk of cancer in humans; this limits the use of such studies for cancer risk assessment.

Where, especially in the absence of good quality data from human studies, data from studies in experimental animals are key to risk assessment and subsequent development of OELs, evidence about whether an identified mechanism of toxicity in animals does or does not operate in humans is particularly important.

As an example of the increasingly important role of mechanistic considerations, IARC may now, exceptionally, classify agents as *carcinogenic to humans*, even if the evidence for carcinogenicity in humans is less than *sufficient*, if there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts on a relevant mechanism of carcinogenesis. Conversely an agent may, exceptionally, be considered as *not classifiable as to its carcinogenicity to humans* despite *sufficient evidence* of carcinogenicity in experimental animals if there is strong evidence that the mechanism of carcinogenicity in animals does not operate in humans (IARC, 1992a).

3

Measurement of Exposure

3. Measurement of Exposure

3.1 Estimating exposure

Good exposure assessment practice is necessary for effective assessment and management of health risks from chemicals and for effective monitoring, control and enforcement of regulatory standards. Aspects to be considered in exposure assessment include the sources and pathways of exposure, the magnitude, duration and frequency of exposure and population variability. Since the degree of exposure may vary with time, the period over which an exposure estimate is based can greatly influence the result (IGHRC, 2004). With a focus on the concept of SEGs, Mulhausen and Damiano (1998) provide detail on basic exposure characterization, qualitative and quantitative risk assessment and priority setting, monitoring, interpretation and decision making, recommendations and reporting.

While traditional exposure assessment practices have assumed that exposure is uniform within a particular job, exposure assessment should, ideally, take into account both within- and between-individual variability in exposure (Rappaport, 1991b; Symanski and Rappaport, 1994). Statistical approaches can be used to deal with variation in exposure within and between workers in a given occupational group (Rappaport et al., 1995). It has been suggested that a statistical sampling strategy, designed to minimize variability in exposure assessment, should ideally begin with a random sampling design, using a sufficient number of workers over a sufficient period of time to account for job rotation and the full range of possible exposure and should allow for changes made to the production process or to the workforce, by conducting analyzes before and after any period of change; furthermore a sampling program should not be restricted to particular times or phases of the production process (Symanski and Rappaport, 1994). Weaver et al. (2001) have developed a statistical method to extend assessment of workplace exposures on a group-by-group basis to allow for simultaneous assessment of exposures, relative to some prescribed OEL, for multiple groups within the same industry.

Assessing a worst-case scenario is a useful device when a combination of low probability events may have a serious adverse impact. The worst-case scenario usually refers to a hypothetical situation in which everything that can plausibly happen to maximize exposure does happen. Such an approach usually overestimates exposure in a specific situation. Reasonable worst-case scenarios may be applicable in occupational settings in order to define high-end exposures that do not exceed the maximum exposure that might realistically be likely to occur (IGHRC, 2004).

3.2 Quality of exposure measures

Those who provide exposure data are often remote from those who are responsible for its interpretation in an epidemiological study or exposure or risk characterization. Communication is important, as approaches used for making exposure measurements or estimates, assumptions made and errors introduced can have a substantial impact on the interpretation of the results (IGHRC, 2004). As an example, exposure-monitoring data may have been collected for compliance purposes, in which case, the worst-case rather than typical exposure might have been sampled.

It is rare for 'raw' exposure data to appear in the published literature, and for the most part summarized data are reported. Statistical analysis of exposure measurement data can produce summary measures, such as means, medians, percentiles and estimates of variability. Statistical analysis may highlight data gaps and unusual values or outliers (Mulhausen and Damiano, 1998; IGHRC, 2004).

It is now generally accepted that most exposure measurement data tend to fit a log normal distribution, characterized by the geometric mean and geometric standard deviation. However, the arithmetic mean, as estimated by the sample mean, has been shown to be appropriate for an estimate of long-term exposure (Smith, 1987; Rappaport, 1991a,b). Any exposure assessment will be subject to some degree of uncertainty, owing to lack of knowledge about factors that affect exposure, leading, potentially, to inaccurate or biased estimates. Uncertainty analysis can be undertaken to help the end-user reach a reasonable judgement about the validity of the exposure estimate (IGHRC, 2004).

It is generally recognized that better exposure data need to be reported. It might be generally acceptable to present raw data on a web site, to which a primary published article could make reference and which researchers and regulators could consult. A number of national occupational exposure databases do exist that attempt to make such data available.

3.3 Short-term and long-term measures of exposure

In many situations, exposures may be continuous but fluctuate in level, as may be the case, for example, at various stages during an industrial process. Many acute harmful effects, such as irritancy or pre-narcosis, are related to short-term peaks in exposure. It is therefore important to measure short-term peaks, which might be missed in longer-term sampling undertaken to estimate average exposure. In the occupational setting, direct reading instruments can measure peaks for periods as short as 15 seconds (IGHRC, 2004) or less (e.g. carbon monoxide can be measured in 1–3 second intervals).

Where onset of ill health is a consequence of long-term exposures to chemicals or mixtures of chemicals, the more relevant and accessible measure for exposure assessment is an exposure averaged over a prolonged period of time. In an occupational setting an 8-h TWA limit is a surrogate for a working lifetime, up to 40 years at 8 h/day, 5days/week, 52 weeks/year (IGHRC, 2004). However, there are many occupational scenarios, including many in mining and mineral processing, where such a week is rarely, if ever worked; instead shifts may last up to 12 h. In such circumstances OELs may need to be adjusted, if the working week is different to a standard 40-h week (Brief and Scala, 1975; Hickey and Reist, 1977; Paustenbach, 1985).

While it is usually the case that the frequency of peak exposures is correlated with the long-term mean exposure, the frequency of peak exposures over time may, in itself, be important for chronic health effects. It has been suggested, for example, that a series of high intermittent peaks may cause greater damage than the same total dose received on a steady-sate basis over the same period of time (IGHRC, 2004). ACGIH TLVs address this with the application of excursion limit values. In the absence of established STELs or ceiling values, an 8-h TWA is multiplied by 3 for an excursion limit value of 30 minutes and multiplied by 5 as a surrogate ceiling value (ACGIH, 2003a).

In contrast, in the case of exposure to organic compounds that require metabolism to cause toxicity, it could be argued that peak exposures might reduce long-term risk, owing to saturation of metabolism. Indeed, physiologically based toxicokinetic modelling has demonstrated that long-term doses of metabolites of benzene, perchoroethylene and acrylonitrile resulting from highly variable exposures are marginally lower than those arising from constant exposure (Rappaport et al., 2005).

Nonetheless, notwithstanding potential impacts of peak exposures, Rappaport (1991b) has proposed that cumulative exposure should be a valid predictor of damage, as long as rates of elimination and repair are first order; even where this is not the case, he proposes that damage is unlikely to be affected by peak exposures as long as the mean exposure in less than 1/4–1/8 of that which gives rise to the threshold burden of damage. However, it should be noted that the above arguments, which really relate to dose-delivery of active metabolite to target tissue, may not apply so well to respiratory sensitizers, where there is some anecdotal evidence that induction of sensitivity is more related to effects from a number of high peak exposures than to lower steady state exposure.

Ulfvarson (1987) proposed three approaches to setting better standards for the assessment of concentration peaks, as follows. For fast-acting substances (effect in less than 1 h) only ceiling limits should be set. When structure analogy is justified for narcotic and irritating gases, limits should be set at the same thermodynamic activity (relative saturation) rather than at the same concentration. TWA limits are appropriate for slowly absorbed and eliminated substances (hours or more) but the possibility of total body burden, as an outcome of bioaccumulation, should be considered.

3.4 Dose metrics

Depending on the nature of the chemical, certain kinds of dose (e.g. short-term, long-term, inhalable, respirable, soluble, insoluble, etc.) dictate the likelihood of disease.

In the case of beryllium, for example, prevention of sensitization appears to be critical (see Section 4.2.5); it is plausible that even stringent OELs may have little effect on disease, yet particle size and solubility also appear to have a substantial impact. Thus a complex set of OELs, varying with particle count, dust fraction and solubility, might be the way forward (Paustenbach et al., 2001). Such thinking has been more recently reinforced with arguments that, for poorly soluble inert particles of low toxicity, most of the early increases in inflammatory markers in the lungs of experimental animals are more closely related to particle size than to particle mass.

For dioxin, for example, an OEL that protects against the putative chronic toxic effects should also provide an ample margin of safety to prevent chloracne following repeated, acute exposure (Leung et al., 1988). As another example, the UK guideline for asbestos is based on a cumulative action level in combination with short-term control limits (HSE, 2001).

Generally, for irritants, it is the short-term limits that are needed; for systemic toxicants the 8-h TWA is more appropriate.

However, in the end, a balance will have to be struck between setting and measuring exposures that are most closely related to the health effect of concern and having overly complex monitoring and measurement techniques that become prohibitive and too difficult to use in the workplace.

3.5 Measurement techniques

Where and how exposure measurements are made can have a major bearing on the results obtained. Direct methods of measurement monitor the exposure at the environment/person interface at the moment it occurs. Such methods may be used for checking compliance. In occupational monitoring, where the source is already known, personal monitoring (within the breathing zone) is the generally accepted method. While static monitoring can be carried out anywhere in the workplace and can be useful to identify emission sources and check effectiveness of controls, OELs relate directly to personal exposure and so compliance testing should continue to rely on personal monitoring (IGHRC, 2004).

In the occupational environment, many exposures may be to industrial dusts. As most industrial dusts contain particles of a wide range of sizes, the concentrations of dusts in different size fractions are important. When particle size selective personal monitoring methods are utilized, the size fractions most commonly measured are the inhalable (<100 μm) and the respirable (<10 μm) fractions (IGHRC, 2004). Particle size selection is very much dependent on the sample lead and flow rate used. A number of national and international documents give guidance on the measurement of concentrations of inhalable and respirable dusts in air, for the purpose of monitoring workplace exposure (e.g. ISO, 1995; HSE, 2000). ISO 7708 (ISO, 1995) defines sampling conventions for the inhalable, thoracic and respirable fractions and methods for estimating extrathoracic and tracheobronchial conventions. Aerosols should be collected using equipment that complies with such standards, while recognizing, as in ISO 7708, that it is only possible to make a statement of probability that an instrument's characteristic falls within a certain range.

The ACGIH recommends particle size-selective TLVs (PSS-TLVs; ACGIH, 2003a). Three PSS–TLVs are defined as:

- inhalable particle mass TLVs (IPM–TLVs) for materials that are hazardous when deposited anywhere in the respiratory tract
- thoracic particulate mass TLVs (TPM–TLVs) for materials that are hazardous when deposited anywhere within the lung airways and the gas-exchange regions
- respirable particulate mass TLVs (RPM–TLVs) for materials that are hazardous when deposited in the gas-exchange region.

Analytical methods should follow well validated measurement methodologies, such as those that have been published by the HSE (2000) and NIOSH (e.g. see Table 3.1 and endnotes) among others. This will help ensure that collected exposure data will be readily repeatable by other researchers and by those attempting to assess compliance (see Section 5.3).

Biomonitoring can be an important method of monitoring exposure, uptake and early biological or physiological changes. However, the application of biomonitoring is frequently limited by the availability of biomarkers. It has been successfully applied in some occupational health scenarios, where the concentration of certain chemicals in biological tissues, such as lead in blood, can be directly related to known health endpoints (IGHRC, 2004).

Examples of measurement techniques used for some chemicals particularly relevant to metal and mining industries (see Case Studies, Section 5.7 and Annex 1) are summarized in Table 3.1 on page 28.

Table 3.1: Exposure measurement methods for case studies

Substance	Method
Nickel and nickel sulphate ($NiSO_4$)	Sampling using cellulose ester (0.8 µm) or PVC (5 µm) membrane filter; measurement using inductively coupled argon plasma, atomic emission spectroscopy; detection limit 0.2 µg/l and the working range is 0.005–2.0 mg/m³ for a 500 l air sample[6]
Palladium and soluble palladium salt (e.g. palladium chloride)	Sampling using a Teflon membrane filter (flow rate unspecified) and measurement by X-ray fluorescence analysis. Lowest reported limit of detection 0.001–0.0005 µg/m³ (working range unspecified; WHO, 2002)
Lead	Sampling using cellulose ester (0.8 µm) or PVC (5 µm) membrane filter; measurement using inductively coupled argon plasma, atomic emission spectroscopy; detection limit 0.2 µg/l and the working range is 0.005–2.0 mg/m³ for a 500 l air sample[6]
Cr metal and CrIII	Sampling (Cr metal, Cr III) using cellulose ester membrane (0.8 µm) filter; measurement using atomic absorption flame detection; detection limit 0.6 µg/l and the working range is 0.05–2.5 mg/m³ for a 100 l air sample[7]
Cr VI	Sampling (Cr VI) using polyvinyl chloride membrane filter (5 µm); measurement using atomic absorption flame detection; detection limit 0.2–7.0 µg/l and the working range is 0.001–5 mg/m³ for a 200 l air sample[8]
Manganese	Sampling using cellulose ester membrane (0.8 µm) or polyvinyl chloride membrane (5 µm); measurement using inductively coupled argon plasma, atomic emission spectroscopy; detection limit 0.2 µg/l and the working range is 0.005–2.0 mg/m³ for a 500 l air sample[6]
Nitrogen oxide and dioxide	Sampling (NO and NO_2) using sorbent tubes with an oxidizer and triethanolamine-treated molecular sieve; measurement using visible absorption spectroscopy; detection limit 1 µg NO_2 per sample and the working range for NO is 1.3–61 mg/m³ for a 1.5 l air sample and for NO_2 is 1–47 mg/m³ for a 5 l air sample[9]
Sulphur dioxide	Sampling using cellulose ester membrane (0.8 µm) filter and then collected on Na_2CO_3 treated filter; measurement using ion chromatography; detection limit 3 µg SO_2 per sample and the working range is 0.5–20 mg/m³ for a 100 l air sample[10]
Sulphuric acid mists	Sampling using solid sorbent tubes; measurement using ion chromatography; detection limit 0.9 µg per sample and the working range is 0.01–5 mg/m³ for a 50 l air sample[11]
Silica (crystalline)	Sampling (respirable) at flow rate 2.2 l/min with pump fitted with nylon or Higgins-Dewell cyclone onto a 5mm polyvinyl chloride filter (flow rate is variable — and accuracy essential — based on cyclone used); measurement by visible spectrophotometry, detection limit 10 µg SiO_2 per sample, working range of 0.04–5 µg/m³ for 500 l air sample, by X-ray powder diffraction, detection limit 5 µg SiO_2 per sample, working range of 0.025–2.5 mg/m³ for 800 l air sample or by infra-red absorption spectroscopy, detection limit 5 µg SiO_2 per sample, working range 0.025–0.4 mg/m³ for 400 l air sample[12]

4

Risk Assessment

4. Risk Assessment

4.1 Interpreting risk: acceptable and tolerable risk

Varying descriptions of acceptability of risk are adopted by different organizations. In the case of OELs, the description and purpose of OELs promulgated by various organizations usually contain some expression of risk in terms of the intended level of protection.

In a broader sense HSE, for example, has developed a framework for the tolerability of risk that describes risks ranging from the negligible to the unacceptable (Hester and Harrison, 1998). At one level there is what is described as broadly acceptable risk; that is, risks that are considered to be acceptable, as they are typical of small risks that do not cause people concern or cause them to alter their behaviour, and as they result only in a small addition to background levels of risk. At the other extreme is unacceptable risk, which is considered intolerable, whatever the benefit. Between these two extremes lies the region of tolerable risk, where a balance has to be found between risk and benefit. Tolerance of risk is strengthened by control of risks, such that they are as low as reasonably practical (ALARP).

The dividing lines between unacceptable/tolerable and tolerable/broadly acceptable may vary according to societal values and who is exposed to the risk. The HSE has proposed that, for workers, a risk of death of 1 in 1,000 per year should be the dividing line between tolerable and unacceptable risk. For the general public, the proposed dividing line between tolerable and unacceptable risk would be 1 in 10,000 per year and a proposed broadly acceptable individual risk of death would be 1 in 1,000,000 (Hester and Harrison, 1998).

As another example, the US Environmental Protection Agency (EPA) assess risk tolerances for pesticides under the 1996 Food Quality protection Act according to a standard of reasonable certainty of no harm[13].

4.2 Risk assessment methodology

A basic framework for the process of risk assessment — hazard identification, hazard characterization, exposure assessment and risk characterization — is well accepted (WHO, 1994). The aim of toxicological risk assessment is not, generally, to estimate the magnitude of any risk but to determine what assurance there may be for negligible risk, in a specific exposure situation (IGHRC, 2003).

Hazard identification describes a qualitative evaluation of available data (toxicological, epidemiological, biological, structural, etc; e.g. as described in Section 2) to identify the types of adverse effect that might result in humans as a consequence of exposure to an agent (Paustenbach, 2003).

Hazard characterization describes the quantitative relationship between exposure and the incidence of toxicity or adverse effect (Paustenbach, 2003). As such dose-response data are often limited for humans, it is frequently necessary to extrapolate from data obtained from experimental animals to the human situation. Such extrapolation requires both inter species adjustments and extrapolation from dose-response relationships at doses used in experimental animals to doses to which the human population is likely to be exposed. For non-carcinogenic effects, which are not thought to occur until a threshold level of exposure has been reached, identification of a suitable level relative to potential harm may include several approaches, such as use of a no-observed-effect level (NOEL) with uncertainty factors, mathematical models with thresholds, the benchmark dose and physiologically based pharmacokinetic (PBPK) modelling (see below).

Exposure assessment describes the nature and size of the exposed population and the magnitude and duration of the exposure (Paustenbach, 2003; see also Section 3). Increasingly probabilistic rather than deterministic methods are applied to exposure assessment (see below).

Finally risk characterization describes the likelihood that a human population of interest will experience any adverse effects associated with the agent of concern, under known conditions of exposure (Paustenbach, 2003).

4.2.1 Adverse effect levels: point of departure

For the majority of toxicities a threshold or level below which no adverse effect is likely to occur is assumed. Thus experimental studies are evaluated to determine a dose without effect, that is, a No Observed Adverse Effect Level (NOAEL)[2] in the most sensitive species, using the most sensitive indicator of toxicity (e.g. Risk Assessment and Toxicology Steering Committee, 1999c). There are some differences in the definition of a NOAEL; for example, the US Environmental Protection Agency defines a NOAEL as 'the highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of an adverse effect between the exposed population and its appropriate control'; and the WHO International Program on Chemical Safety defines a NOAEL based on there being 'no detectable adverse alteration of morphology, functional capacity, growth, development or lifespan of the target'. In the occupational environment, SCOEL has developed a severity scale for systemic and irritant effects, defining adversity as beginning at concentrations that induce effects at a particular level on the scale; it has been suggested that such an approach promotes transparency and consistency (Haber and Maier, 2002).

In some cases, the available data do not allow a NOAEL to be established, instead a Lowest Observed Adverse Effect Level (LOAEL) may be estimated, based, for example, on some minor (possibly) adverse effects at the lowest exposure level investigated (Fairhurst, 1995).

The point of departure (POD) is defined as the concentration that, with the use of appropriate uncertainty factors (see 4.2.2, below), is used to derive the OEL. Usually this will be a NOAEL or a LOAEL, although the benchmark dose approach (see 4.2.3, below) may also be used.

[2] Or No Observed Acute Effect Concentration (NOAEC).

4.2.2 Uncertainty factors

Approaches for dealing with uncertainties and the use of uncertainty factors in risk assessment for chemicals used by UK Government departments and agencies have been reviewed (IGHRC, 2003). One key factor demonstrated in the IGHRC review was that the uncertainty factors used in setting OELs were far smaller than those applied in other areas of standard setting for human exposure to chemicals, such as exposure to pesticides, food contaminant residues and environmental contaminants.

Fairhurst (1995) describes how, ideally, a health-based exposure standard would be based on:

- reliable data from human populations with exposure to known levels of the chemical in question, with at least one level being a clear no-effect level for the health impact of concern; and
- confidence, based on physicochemical and toxicological parameters, that other possible health effects give no cause for concern in relation to the chemical in question.

However, generally, sufficient, quality data are not available to provide such a basis. Instead, using available data normally requires extrapolation between species (i.e. interspecies variation between e.g. rats and humans), across species (i.e. intraspecies variation between, e.g. young healthy and elderly infirm individuals) and from high to low dose (Fairhurst, 1995). If human data are not available, committees establishing OELs tend to apply extra uncertainty factors to an animal NOAEL when setting OELs (Paustenbach, 2001). Thus the conventional approach is to identify a reference point, such as the NOAEL in experimental studies, and set a standard at a lower level of exposure that is considered to meet whatever health protection criteria are to be met by the standard. The margin between the reference point and the established standard is the 'uncertainty factor' (Fairhurst, 1995).

Several variables, which are often formally unquantifiable, influence the size of the uncertainty factor; it has been suggested that this means that it is not realistic to expect to establish a simple numerical framework or set of rules for uncertainty factors that is free from 'expert judgement' (Fairhurst, 1995). Indeed, ECETOC (1984) has noted that the use of generalized mathematical schemes for deriving uncertainty factors has limitations and should not replace expert judgement.

Table 4.1: Influences on the size of the uncertainty factor

Availability of toxicological information
• amount of data • species — direct observation in humans reduces uncertainty • route of exposure — preferably route of relevance to route in humans • data quality • availability of NOAEL — in some cases only a LOAEL may be identifiable, usually requiring larger uncertainty factor
Nature and severity of principal adverse effects
• more severe the threat the greater the need to be certain of safety and the larger the uncertainty factor • small uncertainty factor if principal effect is clearly apparent and rapidly reversible (e.g. sensory irritation) and reliable data from animals, with some human observations and little interspecies variation • large uncertainty factor if principal effect serious and irreversible (e.g. teratogenicity) and data for end-point limited (e.g. from 1 rodent species only)
Nature of exposed population
• age and sex — greater variation, greater uncertainty about individual sensitivity • health status — greater variation, greater uncertainty about individual sensitivity • presence of checks — if exposure monitored and controlled, may be justification for reducing uncertainty factor (e.g. applicable to occupational scenarios providing justification for smaller uncertainty factors than are applied to environmental standards for general population)
Degree of control achievable
• socioeconomic impact — large uncertainty factor where guarantee of safety very important, smaller e.g. in industrial setting where technical feasibility and economics become relevant

Source: Fairhurst (1995)

Some factors that influence the size of the uncertainty factor are summarized in Table 4.1.

Despite some concerns about schemes for assigning numerical weightings for individual elements that affect uncertainty factors, for example a factor '*x*' to allow for interspecies variation and a factor of '*y*' to allow for intraspecies extrapolation, several such schemes have been widely adopted, notably for the determination of ADI values for contaminants or residues in food. Traditionally values of 10 (or fractions of 10) have been used for each element (Fairhurst, 1995), leading, for example, to the 100-fold margin of safety to account for uncertainties in intra- and interspecies extrapolation (IGHRC, 2003). More recently, proposals to divide each of the 10-fold factors for intra- and interspecies differences into sub-factors to allow for toxicokinetic and toxicodynamic difference (3.2 for each) have also achieved wide acceptance (IGHRC, 2003). It should be noted that, traditionally, the factor to account for human variability has been lower in setting occupational limits than in setting limits for the general public (for example an uncertainty factor of 3, rather than 10, may be applied). This has been because the working population is generally considered to exclude some potentially sensitive groups, such as children, the elderly and 'unhealthy' adults (Haber and Maier, 2002).

Other uncertainties may arise owing to the inability of available studies to detect adverse health impacts; this may lead to the introduction of uncertainty factors for the adequacy of the database (Haber and Maier, 2002).

The rationale for the use of uncertainty factors, the areas of uncertainty covered and any numerical default values vary between organizations that set OELs. Furthermore, it is generally recognized that values for uncertainty factors are established on a case-by-case basis. Recently, proposals for working towards a more chemical-specific basis for the derivation of uncertainty factors have been put forward (Haber and Maier, 2002).

As an example of a numerical scheme, default values used in the Netherlands for OELs are as follows: 3 for interspecies difference; 3 for intraspecies difference; 1–10 for differences between experimental conditions and the exposure pattern of workers; and 1 for each of — type of critical effect; dose-response curve; confidence in data base (Dutch Expert Committee on Occupational Standards, 2000).

4.2.3 Dose-response relationships and the benchmark dose

Recent approaches to setting OELs have included establishing dose-response curves, based on high quality studies, which represent a weight-of-evidence approach to identifying 'safe' levels of exposure (Paustenbach, 2001).

The benchmark dose approach uses experimental dose-response curves to determine a dose corresponding to a predetermined response level, which can then be used as a POD for developing OELs. The advantages of the method are that it uses all dose-response data, a benchmark dose can be determined even if an experimental study did not identify a NOAEL and the POD is not restricted to tested dose levels. The benchmark dose approach could be applied to make better use of epidemiological data, by conducting dose-response modelling of exposure data on individuals, rather than grouping individuals with similar exposure (see Section 2.2.2), as is often the case (Haber and Maier, 2002).

4.2.4 Default factors in extrapolating from animals to humans

When the POD for developing an OEL is derived from animal data it is necessary to extrapolate exposure levels to humans; this may even include route-to-route extrapolation. Such extrapolation should take account of differences in breathing rate, respiratory structure, bodyweight, deposition in the lung (for inhaled particles) and so on (Haber and Maier, 2002). Standard default factors may be used for some such extrapolations and PBPK modelling and probabilistic modelling can also be helpful (see below).

4.2.5 Non-threshold agents

In some circumstances it is not possible to identify reliably a threshold for the level at which an adverse effect does not occur; this is the case, most notably, for genotoxic carcinogens but may also apply to respiratory sensitizers.

Carcinogens

Different approaches to the risk assessment of carcinogens are adopted by different organizations. Carcinogen classification schemes vary and while some organizations (e.g. ACGIH) set quantitative health-based OELs for carcinogens with a separate categorization of carcinogenic potential, others derive them only for carcinogens with thresholds (e.g. DFG, DECOS) or make only qualitative evaluations of risk (e.g. most UK regulatory authorities; Risk Assessment and Toxicology Steering Committee, 1999c; Haber and Maier, 2002).

SCOEL recognizes that although it may not be possible to identify exposure levels below which there is no risk of carcinogenic effect, it can be assumed that the lower the exposure, the lower the risk of cancer (CEC, 1999). In the case of genotoxic carcinogens, standard-setting bodies, such as SCOEL, will, if possible, provide a risk assessment for excess cancer cases estimated to occur at a range of exposure concentrations. This risk assessment is then carried forward for consideration by the social partners who may take into account this risk, practicability and socioeconomic consequences in aiming to establish an OEL. In the case of non-genotoxic carcinogens, it may be possible to identify, with reasonable certainty, a threshold for the carcinogenic effect. This can then be the basis for setting an indicative occupational exposure limit value (IOELV).

While metals with positive results in genotoxicity assays are typically considered to be carcinogens for which it is not possible to identify a threshold reliably, metals can induce genotoxicity through diverse mechanisms, such as direct DNA reactivity, inhibition of DNA repair or formation of reactive oxygen species. The identification of a particular pathway will affect whether or not the metal can be considered as a threshold or non-threshold carcinogen, for the purposes of setting an OEL (Haber and Maier, 2002). Such considerations are becoming increasingly important, and Section 2.3

gives examples where understanding the toxicological mechanism can assist greatly in both hazard and risk assessment.

Respiratory sensitizers

Sensitization may be defined as a condition of acquired specific (usually immunological) alteration in the responsiveness of a biological system, initiated to a sensitizing substance and, after an incubation period, characterized by evocation of enhanced reactivity upon re-exposure to the same or closely related substance. In the workplace, sensitizers may affect the respiratory system, the conjunctivae and the skin, but in the context of OELs the former two are most relevant.
Such substances present a great problem for the setting of OELs because once the airways have become hyper-responsive, further exposure to the substance, perhaps even to lesser, minute quantities, may cause respiratory symptoms that may range from a runny nose to severe asthma. Furthermore, not all workers who are exposed to a sensitizer become hyper-responsive and it is not possible to identify in advance all those who are likely to become hyper-responsive. It is important to distinguish substances that may trigger the symptoms of asthma in people who may already have pre-existing hyper-responsiveness in the airways from those substances that do not induce the disease themselves. The latter may be irritants, but are not respiratory sensitizers.

Most OELs for respiratory sensitizers are based on the assumption that the OEL will limit the risk of the induction of the underlying immunological asthmatic condition as, once the condition is induced, the limit is unlikely to produce any protection. Thus, following initial sensitization, subsequent exposure to even extremely low levels of allergens can trigger severe, adverse health impacts, meaning that such sensitizers can be considered as non-threshold or very low threshold chemicals. Many standards setting bodies, including ACGIH, use a sensitizer notation to highlight these risks.

The problem in setting OELs for respiratory sensitizers is that the database is generally quite poor and difficult to interpret and thus, for many respiratory sensitizers, the limits are somewhat pragmatic.

The potential complexities associated with setting OELs for sensitizers are exemplified by the case of beryllium. The focus has been to determine whether an OEL could be set that would be protective for chronic beryllium disease (CBD). CBD results from an immunological response to beryllium particles, and subclinical CBD can be diagnosed by the blood lymphocyte proliferation test. Sensitization to beryllium and then subsequent exposure appear to be necessary for CBD to develop. Particle size, chemical form, concentration and genetic susceptibility are all factors that appear to complicate the relationship between airborne beryllium levels and CBD.
Based on current understanding of the aetiology of CBD, it has been suggested that a series of OELs for different forms of beryllium rather a single OEL for all forms of beryllium might be appropriate (Paustenbach et al., 2001).

Although most allergens generally only cause adverse reactions in a small subset of the population, the approach adopted in the UK, for example, has been to set a MEL for occupational exposure to such a material (Risk Assessment and Toxicology Steering Committee, 1999c); although this approach has since been reconsidered (HSC, 2003).

4.2.6 Advances in methodology

PBPK modelling

It has been suggested that the ultimate approach to the replacement of default uncertainty factors (see above) has been the development of physiologically-based toxicokinetc/toxicodynamic modelling, which predicts how a chemical is handled in the body (Risk Assessment and Toxicology Steering Committee, 1999b). Such PBPK models can be used to help improve extrapolations between species, between dose levels and between different exposure scenarios (Blaauboer, 2003).

For example, in one study, PBPK modelling with Monte Carlo simulations (see below) was applied to the theoretical derivation of OELs for selected ethylene glycol ethers. In the absence of adequate human exposure data to assess developmental and reproductive outcomes for glycol ethers, PBPK models for rats and humans were used to convert an animal NOEL to an exposure concentration that would result in an equivalent internal human dose (inter species variation). Monte Carlo simulation

was used, in addition, to refine inputs on pharmacokinetic variability between humans (intraspecies variability). Proposed OELs determined by the study were lower than the OSHA and ACGIH limits at the time. (Sweeney et al., 2001).

Quantitative structure-activity relationships

Increasing knowledge about molecular processes and chemical reactivity, leading to the identification of molecular fragments with certain chemical functionalities, may lead to an estimation of a chemical's reactivity in a biological system (Blaauboer, 2003).

For example, an association has been demonstrated between equilibrium dissociation constants for organic acids and bases that produce irritation as their primary adverse effect and their OELs. A physicochemical parameter may reasonably be considered to be a predictor of biological response when the parameters are mechanistically associated. Use of such parameters, in quantitative structure activity relationships, might provide another way to establish preliminary OELs, for example for organic acids and bases and other compounds with no existing limit (Leung and Paustenbach, 1998).

Identified relationships between the structure and biological properties of chemicals can be programed into knowledge-based expert systems that can be used to assess the relationship between certain structures in the molecule and a variety of toxicological endpoints (such as genotoxicity, skin sensitization etc). Other physicochemical properties, such as lipophilicity, hydrophilicity, molecular weight etc) may also impact on the relationship between structure and toxicity; knowledge of physicochemical properties is also important to the understanding of biokinetic behaviour and biotransformation pathways. As quantitative structure-activity relationship models become more predictive of biological activity, they might be used for developing hypotheses about mechanisms of toxicity and might be integrated into risk assessment strategies (Blaauboer, 2003).

Probabilistic methods

Historically, methods used to compare exposure and toxicity, in chemical risk assessment, have been deterministic in approach. Yet any health-based risk assessment should take account of variability (e.g. the natural variation between individuals in sensitivity or between chemical exposure levels) and uncertainty (e.g. lack of knowledge in risk specification). Deterministic methods for risk characterization deal with variability and uncertainty by adopting a conservative approach, which has been considered appropriate for regulatory purposes. However, such an approach only works effectively for exposure to a single substance from a single source and route; a conservative, deterministic approach may not be appropriate for multiple chemical exposures via multiple pathways. In contrast, a probabilistic approach, in which outputs are expressed in the form of probabilities for each outcome, takes account of variability by replacing point estimates with distributions (COT, 2002).

For example, Finley et al. (1994) proposed standard distributions for common exposure factors, such as bodyweight, inhalation rate and time spent at one job, for use in Monte Carlo models for screening assessments to characterize health risks of exposures; and in the study described above (Sweeney et al., 2001), Monte Carlo simulations were used in conjunction with PBPK models to examine OELs for ethylene glycol ethers.

Monte Carlo techniques were applied in a re-evaluation of exposure assessments in a benzene-exposed occupational cohort in the USA (Pliofilm Cohort) that has provided key input into cancer risk estimates for benzene and the setting of TLVs. Many discrepancies and criticisms of earlier exposure estimates for the cohort had been reported, so probabilistic techniques were used to improve exposure assessment. Distributions of benzene exposures for various job categories in the cohort were estimated, based on input parameters covering the likely range of exposure values, taking into account likely decreases in workplace concentrations over time; probability distributions were also estimated for other parameters, including dermal exposure, respirator use and efficiency, and weekly working hours (Williams and Paustenbach, 2003).

A probabilistic approach can also provide a framework for incorporating uncertainty and expert judgment into risk assessment (COT, 2002).

4.2.7 Estimating the size of the affected population

In some cases it may be possible to estimate the proportion of an exposed population that would be affected at different levels of exposure and thus to estimate the proportion that could be protected by setting an OEL at different limits. This has been done for formaldehyde, for example, where evaluation of experimental studies, volunteer studies, surveys and epidemiological data identified that asthmatics were not especially sensitive to the airways effects of formaldehyde and permitted estimations of the percentages of workers that could be expected to exhibit various signs of irritation at different levels of exposure. For example, 5–25% of workers might report eye irritation associated with 15 min to 6 h exposure to 0.5–1 ppm formaldehyde, although responses rates around 20% are near background response levels; an OEL of 0.3 ppm would protect nearly all workers; and a ceiling value of 1 ppm for up to 15 min would protect at least 75% of workers. (Paustenbach et al., 1997).

4.2.8 Expert judgement

Expert judgement is a term used to describe the process by which knowledgeable persons on a subject arrive at a decision based on both the available information and their expert or considered opinions, underpinned by their experience, usually taking into account some kind of paradigm. When it comes to setting OELs, the gaps in knowledge can be quite vast and thus it is necessary to use information from related chemicals as a 'read across' to help predict effects. It is also common for expert committees to apply uncertainty factors in an *ad hoc* fashion, again based on expert judgements. This will take into account the severity of the most serious effect, the quality of the dataset, including gaps in knowledge, and the number of workers that might be exposed in the population. In the past, it was quite common for expert judgement not to be apparent in the deliberations of such committees, but nowadays, owing to better transparency in decision-making, it is usual to be able to see where science ends and expert judgement begins.

4.3 Multiple exposures and multiple health endpoints

4.3.1 Occupational exposure limits for mixtures

The majority of OELs are set for single compounds or substances, although some have been set for substances that may contain a common element or radical, for example 'tungsten compounds' and 'isocycanates' (HSE, 2005b). A few OELs may be set for complex mixtures of variable composition such as 'rubber fume' or 'welding fume'. In the case of hydrocarbons, which are normally supplied as complex mixtures, some jurisdictions have recommended the use of a reciprocal calculation, so that producers and suppliers of mixed hydrocarbon blends can derive an appropriate 'in-house' OEL (HSE, 2005b). In this specific case, the procedure covers aliphatic hydrocarbons in the range C_5 to C_{15}, cycloalkanes in the range C_5 to C_{16} and aromatic hydrocarbons. It excludes halogenated or oxygenated hydrocarbons and only applies to vapours, not mists. The calculation to reach the mixture OEL is as follows:

$$1/OEL_{SOL} = \frac{FR_a}{OEL_a} + \frac{FR_b}{OEL_b} + \frac{FR_n}{OEL_n}$$

where OEL_{sol} = OEL of the hydrocarbon solvent mixture (mg/m^3); OEL_a = OEL of component 'a' (mg/m^3); and FR_a = fraction (w/w) of component 'a' in the solvent mixture.

When it comes to assessing the potential health effects from exposure to more than one substance in the workplace, a number of strategies can be applied, but that of the ACGIH is one that seems the most widely practiced in one form or another.

ACGIH adopts the approach that the combined effect of a mixture of two or more hazardous substances, which act on the same target organ, should be given primary consideration, rather than the effects of each substance individually. Thus, in the absence of information to the contrary, the effects of the different hazards should be considered as additive. However, if the chief effects of a series of different substances are not additive but act independently (e.g. on different target organs), then the OEL for the mixture is considered to be exceeded only when at least one member of the series exceeds its OEL (ACGIH, 2003a).

Interactive processes are divided into potentiation (combined effect greater than additive) and antagonism (combined effect less than additive; COT, 2002). Combinations where synergistic action or potentiation occur are currently dealt with on a case-by-case basis (ACGIH, 2003a).

4.3.2 Cumulative and aggregate exposure and risk assessment

In recent years, much attention has been given to developing newer risk assessment methodologies to deal with human exposure to mixtures of chemicals. One major area of concern has been that of a variety of low-level exposure to pesticides through foodstuffs. Much work has been done in this area by the US EPA and their definitions of the terms cumulative and aggregate have permeated through other areas of human exposure to mixtures of chemicals.

Aggregate exposure refers to exposure to one chemical from all sources. Cumulative exposure refers to exposure to multiple chemicals that have a common mechanism of action (COT, 2002). Both need to be taken into account in risk assessment, as exposure to multiple substances may result in several different types of combined action.

4.3.3 Determining critical health endpoint

It is often common to think that OELs are based on only one serious, harmful effect of a substance. However, many chemical substances are able to produce a constellation of toxic or harmful effects — some acute effects, which are produced under high exposure conditions and some chronic effects, which are produced over extended periods of exposure and in the absence of acute effects. When setting OELs, most committees will expect to review a complete dossier of human and animal data, which represents the complete spectrum of potential health endpoints and takes into account all the exposure scenarios under which workers might be exposed, even under poor practices or accidental situations.

With all this available data, it should be possible to draw up a toxicological and ill health profile for all likely acute and chronic effects and, ideally, dose-response relationships for these. From such data, both short-term and long-term OELs can be derived, in order to prevent most of these conditions, but at the same time taking into account all other conditions. If a substance is a genotoxic carcinogen, this would be the 'lead effect'; normally, no OEL based on a NOEL would be derived and the level would be set so low that it would be unlikely that other effects would be expected. It is often common to have acute effects prevented by a short-term limit, such as a 15-min STEL, set on one health endpoint, such as irritation, and chronic effects prevented by an 8-h TWA, based on a systemic effect at an organ such as the kidney.

4.4 Biological exposure limits

As noted in Section 1.2.2, biological exposure limits, such as BEIs or BATs, may be used for either biological monitoring, in which case the worker is simply being used as a way of collecting the chemical or metabolite of the chemical within a biological matrix, or biological effect monitoring, where the same matrix may be used to examine early and reversible non-clinical changes. Either may be used as part of a regulatory or advisory framework, as part of risk assessment and risk management, and monitoring tools have been developed with variable applications. As an example, the monitoring of lead workers for blood lead (biological monitoring) is virtually mandatory and, in terms of risk assessment and management, is used both as a way of monitoring build-up of lead and as a means of indicating the need to remove people from further exposure if a certain level is reached. Concurrent zinc protoporphyrin analysis (biological effect monitoring) can also help pinpoint how long ago lead exposure occurred.

In setting biological exposure limits, a lot of information has to be obtained and guidance given as to when to collect samples, how to interpret them and the ethical implications of their use. For example, many metals have long half-lives, which means their excretion might become quite stable; therefore, unless there is a need to monitor any weekly build up in levels, the timing of sampling at the end of a working week is not especially critical.

The importance of biological monitoring and biological effect monitoring is that they provide information for risk assessment that may be otherwise unattainable from air monitoring alone. Biological monitoring and biological effect monitoring both take into account, for example, factors such as skin uptake, individual working habits (including hand-to-mouth contact) and uptake from other sources of exposure to the same substance that might be experienced outside the working environment, from past-times, hobbies or secondary occupations.

5

Setting and Using OELs

5. Setting and Using OELs

5.1 Factors that influence setting of occupational exposure limits

Health-based OELs can be established when it is possible, based on scientific evidence, to identify a clear threshold dose below which exposure is not expected to lead to an adverse response (see also Section 4.2.1). For adverse effects for which it is not possible to identify such a threshold reliably (Section 4.2.5), where it may be assumed that any level of exposure carries some finite risk, OELs must be established pragmatically, at levels considered to carry a sufficiently low level of risk (CEC, 1999).

As noted by Haber and Maier (2002) some of the diversity apparent in the development of OELs across different organizations arises from different risk management approaches, such as determining appropriate levels of residual risk to an exposed population or weighing health-based limits with technical feasibility or economic impact. Paustenbach (2000) notes other factors that might account for diversity in OELs, as follows: differences in philosophical objectives of the limits and the untoward effects they are meant to eliminate or minimize; differences in the predominant age and sex of workers; length of the working week; economic considerations in different countries; and differences in enforcement. It is also worth noting that many OEL-setting groups must work within a prescribed regulatory framework with specific definitions of certain terms.

Differing views as to the proportion of people that it is thought should be protected from adverse health effects (see Section 4.2.7, above) or, indeed, the adverse impacts against which it is deemed necessary to protect workers (Paustenbach, 2000) might affect approaches to setting OELs and numerical values for OELs. For example, while in some countries irritation is accepted as a critical effect (Remaeus, 2001), in the USA it is accepted that some workers exposed at the OEL might experience some degree of transient irritation or even more substantial impacts (ACGIH, 2003a).

Nonetheless, it should be recognized that the ACGIH TLVs, which are the world's most recognized and adopted OELs, are purportedly entirely health-based and do not take factors such as risk management, technical feasibility or economic impact into account in their development.

5.2 Comparison of the process between countries/jurisdictions

Summaries of information on procedures for setting OELs in some EU member states and in non-member states are provided by the European Agency for Safety and Health at Work (EU-OSHA Network, 1998–2005)[1] and in the review by Walters et al. (2003). Useful summaries of the OEL setting processes of the US ACGIH, German DFG, UK HSE and other organizations are also given in NOHSC (1999). However, it should be recognized that extensive national programs to update OELs across the world are not in place. The fact that some national OELs have not been re-reviewed in decades may be another factor leading to differences in numerical values between countries. Furthermore, although groups such as the ACGIH, HSE and DFG produce annual updates, these should not be mistaken for annual reviews of all substances listed therein. While recognizing the importance of national OEL guidelines, it should be acknowledged that there are no OELs for the vast majority of the thousands of chemicals that are used routinely in industry. As a result, many businesses have established their own in-house limits (Paustenbach and Langner, 1986). This particularly applies to the pharmaceutical industry, which has to deal with a large number of biologically active substances with pharmacological as well as toxic properties.

General procedures in different regions are compared and contrasted in Table 5.1. Some general principles are outlined below, region-by-region.

5.2.1 European Union

Walters et al. (2003) note strong similarities between national systems for setting and using OELs in a number of countries in the EU. The ACGIH lists of TLVs and practices in Nordic countries and in Germany have been influential. However, there are national differences in setting OELs and in their status and use.

Based on scientific evaluations, SCOEL recommends OELs to the Directorate-General (DG) for Employment, Social Affairs and Equal Opportunities. While adopting a case-by-case approach to recommending health-based OELs, general procedures followed by SCOEL include the following (CEC, 1999):

- collection of data on hazards of the substance and determination of adequacy of database;

- identification of critical adverse effect(s);
- identification of relevant studies on critical effects;
- establishment of threshold or non-threshold mechanism (if latter OEL will be pragmatically based);
- assessment of dose-response data and establish NOAEL (or LOAEL);
- decision on whether STEL required in addition to 8-h TWA;
- establishment of numerical value for 8-h TWA at or below NOAEL (or LOAEL), incorporating appropriate uncertainty factor(s);
- establishment of numerical value for STEL; and
- documentation of entire process.

5.2.2 Germany

Germany has two types of OEL — the MAK values and classifications proposed and published by the DFG (2005b) and the values published in the Technische Regeln für Gefahrstoffe (TRGS 900 for OELs; TRGS 903 for BAT values; DFG, 2004).

Derivation of a MAK value is based on identification of the most sensitive health parameter, taking into account both local and systemic effects. The minimum database for derivation of a MAK value is, normally, a NOAEL from a valid 90-day inhalation study in experimental animals. Known effects of structural analogues may be taken into account (DFG, 2005b). The values published in the TRGS 900 comprise MAK values, binding values of SCOEL and values proposed by other institutions, which have been evaluated and accepted by the Ausschuss für Gefahrstoffe (AGS), a committee of the Federal Ministry of Labour and Social Affairs. In general these are based on the current status of knowledge about the health hazards, typical industrial use and safety and hygiene requirements (DFG, 2004). The influence of the MAK, TRK (Technische Richtkonzentrationen; technical guidance concentration) and BAT values are greatly enhanced worldwide, as the values and documentation are available in English.

5.2.3 The Netherlands

The Netherlands has two types of health-based OELs (legally binding and administrative) with differing bases and status. OELs were initially based, extensively on the ACGIH TLVs.

Unlike many other organizations, the Committee on Updating of Occupational Exposure Limits of the Health Council of the Netherlands outlines minimum data requirements for the development of OELs; data on acute toxicity and repeated-dose toxicity are required, and a multi-dose study in a relevant species, using a relevant route of administration and evaluating a range of endpoints is required, as a minimum (Haber and Maier, 2002).

Legally binding OELs are based upon the health-based recommended occupational exposure level (HBR-OEL) provided by the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council but socioeconomic feasibility is also taken into account. The legal status is based on the Dutch Occupational Law, and the Labour Inspectorate controls the implementation. In a yearly working program, the Ministry of Social Affairs and Employment sets limit values in a 'three-steps' program. First a scientific evaluation of data is made by DECOS leading to an HBR-OEL; a key study is identified as the basis for deriving the recommended level. In step 2, the Social and Economic Council advises the State Secretary on the feasibility of using the health-based value derived by DECOS or recommends a different value. In step 3 the State Secretary sets a regulatory OEL (Dutch Expert Committee on Occupational Standards, 2000).

Administrative OELs are not legally binding. However, to protect workers, such levels should not be exceeded. They are derived mostly from other member states of the EU or from ACGIH TLVs[1]. The values and documentation are published in English as well as Dutch and thus are widely available and used worldwide.

5.2.4 Nordic countries

Although, as described in Table 5.1, the scientific basis for OELs is common to all Nordic countries, based on an evaluation by the Nordic Expert Group (NEG) of scientific criteria documents, OELs are established at a national level and the actual numerical value may differ between countries. The criteria for setting OELs can only be partially

Table 5.1: Setting OELs in different jurisdictions

Region	Process		Publication	Risk assessment
	Expert committee	Review of data		Quantitive
EU (CEC, 1999)	SCOEL scrutinizes criteria documents and advises EC	Criteria documents from national limit setting systems or documents commissioned directly by EC	Detailed scientific document (with OEL) on EU website (up to 2002)[14]	8-h TWA, 15-min STEL
Germany (DFG, 2004; DFG, 2005b)	DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area	Detailed literature review made available to Commission	MAK: detailed scientific documentation in English in *Occupational Toxicants* BAT: in English in *Biological Exposure Values for Occupational Toxicants* Annual *List of MAK and BAT Values*	8-h TWA, (MAK and BAT),15-min excursion value (MAK)
Netherlands (DECOS, 2000)	DECOS a committee of the Health Council of the Netherlands Social and Economic Council advises State Secretary	Review by a Netherlands research institute	Detailed scientific document with OEL also available on website	8-h and 15-min TWA, ceiling value, exposure–response for genotoxic carcinogens
Nordic countries (Lundberg, 1991)	NEG finalizes criteria document	Criteria document produced by scientist in one of Nordic countries	Final scientific document from NEG published in Arbete och Hälsa and sent to national regulatory authorities	Numerical OEL not proposed in NEG criteria document
	National regulatory authorities set OELs	Criteria document used to produce national consensus report	Swedish reports published in *Arbete och Hälsa* others not published but publicly available	
		OEL set at national level, based on scientific and other factors	Underlying [non-scientific] data for OEL not published but publicly available	

* As a general rule OELs will use, as preferred values, multiples of given integers in ppm or mg/m^3

	Regulatory status	Transparency		
Qualitative		Key studies	Uncertainty factors	Preferred value system*
Notation: skin Risk phrases	Recommendation by SCOEL to EC DG for Employment, Social Affairs and Equal Opportunities OEL published by DG in Official Journal has regulatory status	Identified in background documentation	Identified in background documentation	1, 2, 5 ppm or mg/m^3 x 10^n
Carcinogens: no MAK or BAT values; categorical descriptors used Notations: skin absorption, cancer, sensitization, prenatal toxicity, germ cell mutagenicity	MAK values incorporated in common national legislation	Identifiable in background documentation	MAK generally at level of NOAEL in humans or 1/2 NOAEL in animals	1, 2, 5 ml/m^3 or mg/m^3 x 10^n
	State Secretary sets regulatory OEL; some limits administrative only	Identified in published documentation	Overall assessment factor, consideration given to using default values, details given in published documentation	1, 2, 5 mg/m^3 x 10^n
		Critical effect defined		
		Not clearly identified in published documentation		
	OEL has legal status in Denmark and Sweden; recommended values in Finland, Norway and Iceland			

Continued over page

Table 5.1: Setting OELs in different jurisdictions *continued*

Region	Process		Publication	Risk assessment
	Expert committee	Review of data		Quantitive
UK (HSE, 2002)	OELs set by HSC, following proposals of ACTS subsequent to evaluation of scientific data by WATCH	*Risk Assessment Documents* scrutinized and endorsed by WATCH	Summaries of risk assessment and OELs published in *EH64*	8-h TWA,15-min STEL (OES and MEL)
USA ACGIH (ACGIH, 2003 a;b)	Relevant ACGIH committee recommends documentation and OELs to ACGIH Board of Directors for ratification	Initial draft review of health science data prepared by ACGIH committee member	Initial draft documentation for substance 'under study' not publicly available On ratification proposed OELs and documentation made public as NIC OELs and documentation usually adopted 1 year after NIC and published in annual supplements	8-h TLV-TWA, 15-min TLV-STEL, TLV-C, excursion limit
Australia (NOHSC, 1999) [1,15]	HSSC proposes OELS, which are set by NOHSC	Mostly relies on OELs and accompanying documentation from ACGIH and UK HSE	Background documentation for most NES is from ACGIH, other documentation available through HSIS NES available through HSIS	8-h TWA, 15-min STEL, peak limitation

*** As a general rule OELs will use, as preferred values, multiples of given integers in ppm or mg/m^3**

	Regulatory status	Transparency		
Qualitative		Key studies	Uncertainty factors	Preferred value system*
Risk phrases	MEL and OES legally binding	Identifiable in background documentation	Not clearly identified in background documentation	
Notations: skin absorption, sensitization, carcinogen, BEI	No regulatory status	Identified in background documentation	Application of uncertainty factors not clearly described in background documentation	
Carcinogen	Some advisory, some mandatory			

Abbreviations

ACGIH
American Conference of Governmental Industrial Hygienists
ACTS
Advisory Committee on Toxic Substances
BAT
Biological Tolerance Value
BEI
Biological Exposure Indices
DECOS
Dutch Expert Committee on Occupational Standards
DFG
Deutsche Forshungsgemeinschaft
DG
Directorate General
EC
European Commission
EU
European Union
HSC
Health and Safety Commission
HSE
Health and Safety Executive
HSIS
Hazardous Substances Information System
MAK
Maximale Arbeitsplatzkonzentrationen
MEL
Maximum Exposure Limit
NEG
Nordic Expert Group
NES
National Exposure Standard
NIC
Notice of Intended Change
NOAEL
No Observed Adverse Effect Level
NOHSC
National Occupational Health and Safety Commission
OES
Occupational Exposure Standard
SCOEL
Scientific Committee on Occupational Exposure Limits
STEL
Short Term Exposure Limit
WATCH
Working Group on Assessment of Toxic Chemical
TLV
Threshold Limit Value
TLV-C
Threshold Limit Value Ceiling
TWA
Time Weighted Average
WGATC
Working Group on Assessment of Toxic Chemicals

identified, as published criteria documents are only available for some substances; for many others OELs have been set based on documentation from ACGIH, for example (Lundberg, 1991).

5.2.5 UK

OELs in the UK function under the Control of Substances Hazardous to Health Regulations (COSHH) and its mirror legislation in Northern Ireland. The Working Group on the Assessment and Control of Chemical Hazards (formerly the Working Group on Assessment of Toxic Chemicals; WATCH) evaluates toxicological, occupational hygiene and analytical data, which are reviewed in *'Risk Assessment Documents'* and other sources, and acts as a technical subcommittee of the Advisory Committee on Toxic Substances (ACTS). ACTS recommends new OELs or revisions to existing OELs, and the Health and Safety Commission (HSC) approves the OELs (HSE, 2002).

Carcinogenicity, reproductive toxicity, and irritation and sensitization potential are considered when preparing a proposal for an OEL. Some hazardous substances may not be assigned OELs and/or have their own specific legislation, including air standards, most notably asbestos and lead (HSE, 2002).

Under the former two-OEL system, for a substance to be assigned an OES it had to meet three indicative criteria concerning expectations of lack of injury, from both long-term and short-term higher exposures, and practicability of compliance. If these three criteria could not be met, the substance became a candidate for a MEL. MELs were usually reserved for carcinogens, respiratory sensitizers and other substances that present a serious hazard for which no threshold can be established (HSE, 2002).

As noted in Section 1.2.1, the HSC has recently replaced OESs and MELs by a single OEL, the WEL; the new OEL framework came into force in the first half of 2005 (HSC, 2003; HSE, 2005b).

5.2.6 USA

ACGIH is a not-for-profit professional organization, developed in the mid 1940s, which represents a wide range of industrial hygiene expertise and opinion. Its committees propose TLV and BEI guidelines for use in making decisions about safe levels of exposures to chemical and physical agents in the workplace; however, it is not a standards setting body in the USA (ACGIH, 2003a). Nonetheless, while ACGIH guidelines do not have regulatory status in the USA, they are very widely used in other national OEL processes.

The ACGIH TLVs and BEIs are solely health-based, with no consideration given to economic or technical feasibility; however the ACGIH recommends that its guidelines should not be adopted as standards without analysis of other factors necessary to appropriate risk management decisions (ACGIH, 2003a).

Substances are nominated and selected for evaluation, based on selection criteria that take into account scientific evidence and workplace experience (NOHSC, 1999). Lists of substances 'under study' are published annually, as a notification and invitation for interested parties to submit data and comments to the relevant committee. For each nominated substance, members of the appropriate committee prepare a review of the scientific literature relevant to the establishment of a guideline value. The committee may modify the review prior to its adoption as the 'Documentation' to support a recommended TLV or BEI. The documentation and proposed guidelines are recommended to the ACGIH Board of Directors for ratification and, once ratified, the proposals are published as a notification of intended change (NIC) and the draft documentation is made publicly available (ACGIH, 2003a).

The documentation supporting TLVs and BEIs transparently indicates the scientific bases that lead to the committees' recommended guideline values. The documentation considers only heath-based criteria. The impacts of the guideline on industry, socioeconomic factors or the method or processes for measurement of the value(s) are not considered.

The guidelines published as NICs are considered to be trial limits for one year, during which time interested parties may submit comments (ACGIH, 2003a). Thus, while it does not consult with

employer or employee representatives in formulating proposed standards, the ACGIH process incorporates consultation though the annual publication of the NIC (NOHSC, 1999), and within the NIC process external considerations may come into play. However, such considerations would not necessarily result in the raising of a guideline value. Instead a given chemical's value might remain on the NIC for an extended period of time (e.g. beryllium or wood dust) or eventually be removed from the NIC, which would indicate that it was not planned for adoption.

It has been suggested that the ACGIH process for setting TLVs changed during the 1990s to facilitate the adoption of sufficiently protective standards (Smith and Mendeloff, 1999).

OSHA PELs are enforceable regulatory limits in the USA. Initially, from 1971, limits were based on the ACGIH TLVs. Currently OSHA has around 500 PELs for some 300 chemical substances used in industrial settings. In establishing standards, recommendations are made by one of the OSHA Advisory Committees, all of which include representation from management, labour and state agencies; thus OSHA standards have both input from and impact on industry[1]. OSHA deliberations on OELs take into account the feasibility of achieving levels and incorporate a formalized process for the estimation of risk magnitude (Rappaport, 1993).

NIOSH has statutory responsibility to recommend exposure limits that are protective to workers and has identified RELs for some 700 hazardous substances. Recommendations for OSHA and other OEL setting institutions are made through NIOSH criteria documents[1].

The American Industrial Hygiene Association (AIHA) has published 107 workplace environmental exposure level guidelines (WEELs), which represent workplace environmental exposures levels to which it is thought nearly all individuals could be repeatedly exposed without experiencing adverse health impacts. Background information and the rationale for the WEEL are published with the WEEL values[16]. WEELs are considered for chemicals for which no alternative guideline has been established, often because they are produced in low quantities or have low toxicity (Paustenbach and Langner, 1986).

5.2.7 Australia

Initially an Exposure Standards Expert Working Group (ESEWG) recommended NESs for individual substances; NESs are set by the NOHSC, which consists of employee and employer organizations, trade unions, and industry and government representatives. The ESEWG is no longer in existence. In 1997, following an organizational re-focus, NOHSC established the Hazardous Substances Sub Committee (HSSC) to maintain the scientific integrity of the national hazardous substances regulatory package. The NOHSC had relied extensively on published standards and background documentation from the ACGIH TLVs and has adopted those found to be acceptable. A smaller number of substances (e.g. respirable crystalline silica) are reviewed in detail by the HSSC, and appropriate values are assigned[1].

The NOHSC has a program to review and update NESs, in particular to address the time lag between NESs and comparable systems overseas. The UK HSE OELs are currently used as a basis for a fast track system in the overall process (NOHSC, 1999).

5.3 Assessing compliance

Compliance checking usually involves the collection and analysis of samples in a prescribed fashion and comparison of the measured concentration, often taking into account statistical significance, with the appropriate OEL. Compliance testing comprises, typically, one-to-one comparisons of measured air levels and OELs (IGHRC, 2004). However, it should be recognized that the measurement and comparison of airborne levels and compliance testing are limited by the availability of appropriate reference standards and analytical capabilities. For compliance purposes, substances that can cause known harmful effects from peak exposures are usually subject to a 15-min STEL and/or ceiling value (IGHRC, 2004). The AIHA Exposure Assessment Strategies Committee recommends that the exposure distribution profile of a SEG should be controlled such that the 95th percentile exposure is less than the OEL (specifically, for AIHA, the OSHA PEL) for both short-term and TWA exposure limits and that, in principle, long-term exposure to chemicals associated with chronic disease should be evaluated against a long-term average exposure level or mean of the exposure profile[17].

Biological monitoring can complement air monitoring and can be especially useful where there is likely to be significant absorption from routes other than inhalation or where control of exposure depends on respiratory protective devices (HSE, 2002).

However, the effectiveness of compliance testing in assessing risk has been questioned. Although OELs tend to be set assuming long-term exposure, enforcement, generally, involves short-term comparisons of measured air levels based on very small numbers of measurements (Rappaport et al., 1998). Whereas, in compliance testing, the probability of compliance is, generally, related to the exceedance (the likelihood that any measurement would exceed the OEL), using, instead, the probability of over exposure (defined as the likelihood that individual risk — a function of cumulative exposure — exceeds the risk inherent in an OEL) as a measure of individual risk, Tornero-Velez et al. (1997) demonstrated that compliance testing can significantly underestimate health risk when sample sizes are small. Thus while, with typical sample sizes, the probability of compliance may be high, large proportions of the exposed population may have individual risks greater than the risk inherent in the OEL.

According to Mulhausen and Damiano (1998) the current approach has moved from compliance monitoring, which focuses on the high risk workers, to comprehensive exposure assessment, which addresses the situation for all workers at all exposures on all days. An exposure assessment strategy is proposed for an industrial hygiene program that encompasses:

- basic characterization of the workplace work force and exposures;
- exposure assessment to identify acceptable, uncertain and unacceptable exposure profiles for SEGs;
- updating and reassessment of acceptable exposure profiles;
- further information gathering for uncertain exposure profiles; and
- health hazard controls for unacceptable exposures.

5.4 Assessment of socioeconomic impacts

Economic analysis compares the costs and benefits of options, one of which, usually, is to continue with the current choice; that is to do nothing. To analyze fully the options available, both the costs and outcomes (benefits) of the proposal should be considered. The main types of economic analysis used are cost-effectiveness, cost-utility and cost-benefit analysis/cost benefit assessment (CBA; e.g. Schmid, 1995; Jefferson et al., 1996).

5.4.1 Cost–benefit assessment

CBA is a tool used to quantify, in monetary terms, as many of the costs and benefits of a proposal as possible, including factors, such as health status, that have no market in which choices and trade-offs can be determined (DH, 1995). Since 1982, the UK HSC has required CBAs for all major health and safety proposals, unless the costs are negligible. Costs and benefits are included in the consultation process for OELs and, since October 1998, they have been discussed within the regulatory impact assessment (RIA) framework (see section 5.4.2 below; HSC, 2002a).

Uncertainties in estimations of the costs of controls and in validation of exposure compliance data, both of which may vary with each substance, will impact on CBAs/RIAs. Quantification of the benefits of an OEL may also be difficult; it is usually based on how far the OEL reduces the risk to workers, using dose–effect information. However, when dose–effect information is unavailable, for example in the case of non-threshold carcinogens, other methods have been developed to estimate the benefits of an OEL (HSC, 2005a). Improved employee recruitment and retention, improved productivity and a reduction in product loss may result from other, more general and less quantifiable, potential benefits of an OEL, as identified by the UK HSC and listed below (HSC, 2005a).

- Definition of a level playing field for all workers
- Definition of adequate control
- Provision of clearer guidance on the level considered to be reasonably practicable
- Provision of a standard for new users
- Reduction/limitation of scope for 'discretion' by enforcing authority
- Provision of consistency with international developments
- Reinforcement/improvement of good practice
- Encouragement of proper reporting of ill-health

- Promotion of more effective health surveillance
- General reduction in ambient air contamination

The UK ACTS uses CBA and RIA as tools for decision-making for OELs and recognizes the benefits and uncertainties when making their recommendations. These tools are also important in identifying the socioeconomic impact of the proposed OEL; although, the HSC states that this is not the over-riding determining factor (HSC, 2005a).

The use of CBA alone as a measure for assessing a proposal affecting health could be criticised for forcing monetary constraints onto issues that involve well-being and the value of life, and because of the inherent difficulties associated with ascribing monetary value to health improvements (e.g. The Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997).

5.4.2 Regulatory impact assessment

RIA is a policy tool used to assess the impact on costs, benefits and risks of any proposed regulation. It is an evidence-based process, which provides an analysis of a range of options for change, by identifying objectives, risks, alternatives to legislation, business (and other) sectors affected, equity and fairness, benefits and costs and unintended consequences (RIU, 2003).

A case study for RIA — assessing the cost-benefits of reducing an OEL

The use of RIA by government authorities in order to facilitate the setting of OELs is illustrated by the following case study[3], which examines the process used by the UK HSE to assess the costs and benefits associated with determining a new WEL for respirable crystalline silica (see also Section 5.7.9).

The current UK OEL for respirable crystalline silica is a MEL of 0.3 mg/m^3; however, when the COSHH regulations were introduced in 1989, the OEL was 0.1 mg/m^3. The MEL was introduced with the expectation that those industries already complying with an exposure level of 0.1 mg/m^3 should continue to do so. The HSC is now in the process of issuing a consultative document for a proposed new WEL of 0.1 mg/m^3 [18].

The HSC conducted a RIA and took its findings into account in reaching its proposal to lower the current MEL[18]. Four potential revised limits were considered in the RIA — 0.3 (current), 0.1 (pre-1992 limit), 0.05 or 0.01 mg/m^3. In order to determine which would be most appropriate, the critical health effects of lung cancer, fatal silicosis and silicosis were considered in terms of cost and benefit for each of the proposed limits. The benefits were identified as monetary values placed on medical costs, human costs (pain and suffering) and productivity losses. The benefits, over sixty years, from preventing cases of fatal silicosis, lung cancer and silicosis at each of the limits were assessed and the total prevented costs (benefits) can be seen in the Table 5.2, which also indicates the costs associated with implementing the four proposed new limits.

Table 5.2: Summary table of benefits and costs over 60 yrs from preventing silicosis, fatal silicosis and lung cancer for each WEL proposed for respirable crystalline silica[18]

	0.3 mg/m^3 (£ Million)	0.1 mg/m^3 (£ Million)	0.05 mg/m^3 (£ Million)	0.01 mg/m^3 (£ Million)
Benefits	39.4 to 78.8	209 to 414	340 to 671	515 to 1,015
Costs	5.1 to 5.3	638 to 650	3,453 to 3,603	12,024 to 14,663

[3] A more detailed case study can be included, if required, when the background documents are confirmed as publicly available, (HSE, 2005a; HSC, 2005b).

The recommendation of the RIA for respirable crystalline silica is that the current WEL of 0.3 mg/m^3 needs to be reduced, on the grounds of the health risks associated with this level of exposure. However, the RIA concluded that lowering the WEL to 0.01 mg/m^3 or 0.05 mg/m^3 would have major economic implications for UK industry and would not be enforceable in all instances, given limitations in current sampling and analytical methods. Therefore, the RIA recommendation for a revised WEL (8-h TWA) of 0.1 mg/m^3 was made for respirable crystalline silica on the grounds of significant health benefit at a level at which industry could meet the costs of compliance without major economic implications[18].

It should be borne in mind that the use of RIA in the process used to set OELs would only apply to regulatory authorities and governments that consider economic factors in addition to health-based factors in deriving their OELs.

5.5 Technical feasibility

The case study of silica (above) also illustrates issues about the impact of technical feasibility on OELs. The HSE RIA found that available sampling and analytical methods would not be sufficiently robust to determine compliance at the lower of the four limits considered[18].

5.6 Safety impact

5.6.1 Reducing and controlling exposures

It should be recognized that OELs, as such, do nothing to protect workers from exposure to hazardous substances in the workplace. It is only when they are applied (compliance and enforcement), as part of a broader framework of exposure control, that they have any use. There are other means to reduce worker exposure to substances that must be applied.

In the UK, for example, COSHH regulations[19] specify processes to minimize worker exposure to hazardous substances. For example, employers who undertake work that is liable to expose employees to substances hazardous to health are required to provide to employees suitable and sufficient information, instruction and training, including information about the chemicals being handled, appropriate precautions to be taken by employees to safeguard themselves and their colleagues, and the results of exposure monitoring and health surveillance activities. Principles governing control of exposure include the use of a safer substitute (where available), hygiene measures, engineering controls, controlling exposure at source and, as a final protective measure, the use of personal protective equipment. This is broadly in line with the provisions of the EU Chemical Agents Directive, which applies to all member states[20].

Recognizing that it is not possible to assign a specific OEL to every chemical in use, 'Control Banding' is being developed as a complementary approach to protecting worker health[21]. Much of the development of control banding derives from the UK HSE COSHH Essentials, which provide web-based step-wise guidance for the control of health risks from chemicals[22].

The principle of the COSHH Essentials is that, if the user follows the guidance, then it is likely that they are complying with good hygiene practice and that any relevant OELs will be complied with. It also covers control advice on the very many substances without specific OELs. Under COSHH Essentials, hazard assessment for the individual substances does not rely on specific toxicological assessment, but on 'hazard banding.' The system does not cater for carcinogens or respiratory sensitizers, for which expert advice is recommended[22]. To assist, in particular, small and medium-sized enterprises in developing countries, the ILO has been developing a Workplace Chemical Control Toolkit, using COSHH Essentials as a model[21].

In control banding, a chemical is assigned to a 'band' for control purposes, based on hazard classification and potential for exposure. Hazard classification uses the EU Risk Phrases (Health and Safety Commission, 1999), which in Europe are assigned to potentially harmful chemicals, to allocate chemicals to one of six hazard groups (A–E for inhalation and S for skin). Potential for exposure is determined by the scale of use and the ability to become airborne, including information on whether the material is a gas, vapour or dust, and handling procedures. Based on these factors, a chemical is assigned to one of four control strategies[21]:

- general ventilation (i.e. good industrial hygiene practice);
- engineering control (i.e. local exhaust ventilation);

- containment (i.e. enclosed process); or
- specialist guidance.

Employing a similar good hygiene control strategy, the AIHA (Mulhausen and Damiano, 1998) also propose a hierarchy of control:

- elimination of the process, equipment or materials giving rise to the exposure;
- substitution with a less hazardous process, equipment or material;
- engineering controls;
- work practice controls and employee training;
- administrative controls; and
- proper selection fitting and use of personal protective equipment.

In general, the two examples above demonstrate that, worldwide, there is good consensus on what constitutes good hygiene control to reduce worker exposure to hazardous substances in the workplace, although there may be subtle differences as to how OELs may be used.

5.6.2 Variability and susceptibility

Variability in the response of humans to occupational or other exposures can be due to true differences in exposure or it can be due to differences in factors such as toxicokinetic or toxicodynamic parameters, the impact of existing disease or injury, or loss of physiological function or reserve. Variability describes the normal spread of values for a biological parameter, such as lung function, or for a biological response, such as irritation. Variability may also describe factors such as age, gender, weight and genetic polymorphisms. Susceptible individuals may be those whose response to an exposure falls at the extremes of a variability distribution curve. Susceptibility may be related to immunological or genetic factors. How individuals that fall at the lower end of a variability curve or that are idiosyncratically susceptible should be treated is an important factor in risk management (IEH, 2002). These are important issues for the setting of OELs and have to be reviewed in relation to occupational groups and exposure to occupational toxicants.

5.7 Case studies

Descriptions for the establishment of OELs by five international authorities (EU SCOEL, German DFG, Netherlands DECOS, UK HSE[4] and US ACGIH) have been included, where available, for the following nine case studies of relevance to metal and mining industries: nickel and nickel compounds, palladium and palladium salts, lead, chromium metal and its tri- and hexavalent compounds, manganese, nitrogen dioxide, sulphur dioxide, sulphuric acid mists and silica. Summary tables for the setting of OELs for these case studies can be found in Annex 1.

Metals provide a unique challenge when setting OELs owing to factors related to metal speciation and health risks. Similarly gases, mists and particles of different size and physical form also add other health parameters of concern owing to different deposition and absorption characteristics in the respiratory tract and the potential for both acute and chronic sequelae.

5.7.1 Nickel and nickel compounds

Nickel (CAS No. 7440-02-0) is a silvery-white transition metal with hard, malleable and ductile properties. It is a trace element occurring in soils, air, water and the biosphere. The major use of nickel is in the production of stainless steel and other corrosion and heat-resistant alloys. Other uses include coinage, in alkaline batteries, magnets, welding rods and as catalysts for hydrogenation of fats. The soluble nickel compound, nickel sulphate (CAS No. 7786-81-4), is the most important form of nickel in ambient air and its principal use is in electroplating. Workers can be exposed to nickel dusts and fumes in a wide range of occupations spanning many industries. Exposure is associated with hypersensitivity and the induction and maintenance of contact dermatitis.

[4] UK OELs are reported herein as MELs and OESs, not as the recently adopted WELs.

OELs

The solubility of nickel metal and nickel salts influences the toxic effects. For this reason authorities have set separate limits for different nickel species. The ACGIH have established four separate 8-h TWAs for nickel and its inorganic compounds, including nickel subsulphide: nickel metal, 1.5 mg/m^3; insoluble nickel compounds 0.2 mg/m^3; soluble nickel compounds 0.1 mg/m^3; and nickel subsulphide 0.1 mg/m^3. All of the recommended TLVs are for inhalable nickel particulate (ACGIH, 2003b). The UK HSE MELs (8-h TWA) are 0.5 mg/m^3 for nickel metal and insoluble inorganic nickel compounds and 0.1 mg/m^3 for soluble inorganic nickel compounds. No MAK value has been established for nickel metal or nickel compounds because of evidence for carcinogenic effects from human or experimental animal studies (DFG, 2004). The German TRGS 900 limits for metallic nickel, nickel sulphide and sulphide containing ores, nickel oxide and nickel carbonate are 0.5 mg/m^3, and the limit for nickel compounds in the form of inspirable droplets is 0.05 mg/m^3. Nickel and nickel compounds are on the priority list for SCOEL but no recommendation has been made to date. DECOS have not set a health-based recommended OEL (HBR-OEL) for nickel but have published an evaluation of the effects of nickel and its compounds on reproduction.

Key studies and critical effects

The UK HSE published summary of the basis for the MELs for nickel and insoluble inorganic compounds (0.5 mg/m^3 8-h TWA) and soluble nickel compounds (0.1 mg/m^3 8-h TWA) did not provide references for the key studies used to identify the critical effects on which the MEL recommendations were based. The critical effects observed from human studies were skin sensitization, causing dermatitis — commonly known as 'nickel rash', respiratory sensitization and non-malignant lung disease. Studies in nickel refinery workers show an excess risk from lung and nasal sinus cancers at exposure levels ranging from 5–400 mg/m^3 (as nickel — specific forms stated to be unknown) but no association has been made at exposure levels up to 1 mg/m^3 (HSE, 2001).

The ACGIH recommended the TLVs for nickel (1.5 mg/m^3 inhalable nickel particulate) based on the potential for dermatitis and pneumoconiosis and for soluble compounds (0.1 mg/m^3 inhalable nickel particulate) based on the potential for pulmonary damage, dermatitis and suspected cancer risk. The key studies cited were the NTP studies on selected nickel compounds, in rats and mice (NTP, 1996a; 1996b; 1996c). However, there was no evidence of carcinogenicity following nickel sulphate inhalation (ACGIH, 2003b).

Uncertainty factors

In the rationale for the ACGIH documentation for the derivation of TLVs for nickel and soluble nickel compounds, the key studies cited were the NTP studies on nickel compounds (NTP, 1996a; 1996b; 1996c), which found biological and histological changes in rats and mice at 0.1–1.0 mg/m^3, total aerosol; however, it is not stated or apparent that an uncertainty factor was used to account for data extrapolation from animals to humans (ACGIH, 2003b).

Overview for nickel and nickel sulphate

Nickel and nickel compounds are relevant to the mining and metal industry. The toxic effects are related to the solubility of the compounds. The ACGIH and HSE have different OELs for nickel metal (1.5 and 0.5 mg/m^3 respectively) and the critical effects on which these OELs were based also differed. The ACGIH and HSE set identical OELs for soluble nickel compounds, but the critical toxic effects on which these were based differed between the two organizations, which makes a comparison of the rationale for the OELs difficult.

5.7.2 Palladium and soluble palladium salts

Palladium (CAS No. 7440-05-3) is a silvery-white, ductile metal with the lowest density and lowest melting point of all the platinum group metals (ruthenium, rhodium, palladium, osmium, iridium and platinum). The metal is known to absorb different gases, most notably, hydrogen. Extraction of palladium from ores requires complex aqueous chemical processing and the metal is usually highly disseminated with other platinum metals in ores, such as nickel sulphites. Palladium is an important, powerful catalyst in industry and is also used in dental and electrical industries[23]. Palladium salts vary in solubility from readily soluble in water, such as palladium dichloride ($PdCl_2$), to insoluble in water, such as palladium iodide (PdI_2)[24].

OELs

No OEL has been established for palladium and its compounds by the SCOEL, DFG, DECOS, HSE or ACGIH. The DFG have examined palladium and its compounds but no MAK value is set because of insufficient toxicological information from human and experimental animal studies (DFG, 2004). Consequently, this compound would be an interesting substance on which to determine whether the approaches used to set OELs by different authorities could be harmonized.

5.7.3 Lead

Lead (CAS No. 7439-92-1) is a heavy, highly ductile, bluish-grey metal, which readily dulls in air. It is highly dense, soft and malleable; it is resistant to corrosion, has a low melting point (327.5°C) and opacity to gamma and X-rays. For these reasons, lead has been used in a wide variety of applications, such as in metal sheeting, in batteries and chemical manufacture and in the production of alloys, such as solder, gun-metal and bullets. Lead is a rare metal in the earth's crust and is mined from seam deposits around the world. It also occurs as sulphite ores, the most common is lead sulphide (galena), and extraction is by smelting. As a consequence of legislation to ban the use of leaded petrol in industrialized countries, both environmental levels and blood lead concentrations in the general population have decreased. Occupational exposure to lead occurs during the mining of the metal, in the production of lead metal and its compounds, manufacture of batteries, and in the pottery, shipbuilding, construction, demolition and scrap industries (EC, 2002).

OELs

The SCOEL recommendation for lead is 0.1 mg/m^3 8-h TWA and the ACGIH TLV (8-h TWA) is 0.05 mg/m^3 (EC, 2002). On the basis of evidence of carcinogenicity for soluble lead compounds in animals and inadequate evidence in epidemiological studies, lead is assigned an A3, 'confirmed animal carcinogen with unknown relevance to humans' notation by the ACGIH (2003a). In the UK, a limit of 0.15 mg/m^3 has been set but lead is regulated separately from all other substances under the 'Control of Lead at Work' (CLAW) regulations (1998). The German DFG has not established a MAK value for lead but has assigned a carcinogenicity notation 3B because *in vitro* or animal studies have shown evidence for carcinogenic effects but no evidence for genotoxic effects (DFG, 2004). No value has been established for lead metal by the DECOS.

Key studies and critical effects

The rationale for the SCOEL recommendation was based on the critical effect of central nervous system (CNS) disturbances observed in key studies by Lai et al. (1997) and Kentner and Fischer (1993). The OEL based on avoiding CNS effects is also assumed to protect against the peripheral nervous system (PNS) and renal toxicity and possibly the risk from renal cancer (EC, 2002).

The HSE summary criteria for the OEL for lead states that the limit was set on the basis of the critical health effects of anaemia, followed by effects on the nervous system and kidney damage. However, the key studies on which these critical effects were identified were not cited in the published summary document and the critical effects were discussed in relation to blood-lead concentrations of 80 µl/l, at which point anaemia occurs, and 100 µl/l, at which point CNS effects and gastrointestinal symptoms become apparent. The rationale for the limit of 0.15 mg/m^3 for lead was set in conjunction with the blood-lead standard, and it was recognized that the relationship between airborne lead concentrations and blood-lead levels is not clearly established (HSE, 2001; 2003).

The rationale for the TLV-TWA of 0.05 mg/m^3 set by the ACGIH for lead and its inorganic compounds was based on the BEI for lead, since blood-lead concentrations are more strongly related to health effects than atmospheric lead concentrations. The ACGIH identified blood dyscrasias, reduced nerve conduction velocities, peripheral neuropathies, possible kidney dysfunction, altered spermatogenesis, impaired intellectual development in children exposed *in utero* and carcinogenicity as adverse health effects. The recommended TLV is intended to minimize the risk from these collective toxic effects; no single study was selected as key to the TLV recommendation (ACGIH, 2003b).

Uncertainty factors

The SCOEL and ACGIH have not stated the use of uncertainty factors in their documents for the basis of their occupational and biological exposure limits.

Overview for lead

The lowest OEL was set by the ACGIH, which also had a comprehensive rationale for the basis of the recommendation. The HSE and ACGIH adopted similar approaches in recommending that the airborne OEL be based on the biological exposure limit for lead because blood lead concentrations are more closely related to adverse health effects. SCOEL recommend that the setting of an OEL for lead is more difficult than other substances because only part of occupational exposure occurs via inhalation.

5.7.4 Chromium

Chromium (CAS No. 7440-47-3) occurs naturally in the earth's crust as chromite, a substance from which all chromium compounds and chromium metal are derived. Chromium exists in many oxidation states; however, in occupational use, most commonly found are the trivalent and hexavalent forms, such as chromates and dichromates. Chromium metal (0) is used in the production of stainless steel and other alloys (Arbetslivsinstitutet, 2000). Chromium (VI) compounds are used in plating and anodising solutions, in the production of pigments and dyes, tanning agents, wood preservatives, photographic sensitizers, and as catalysts in certain refractory materials. Trivalent chromium (as found in chromite ore) is a naturally occurring, essential trace element. For healthy adults, the UK Expert Vitamin and Mineral Group (EVM) for upper safety limits have recommended a guidance level of 0.15 mg/kg bw/day for dietary intake of chromium (III) and the Committee on Medical Aspects of Food and Nutrition Policy (COMA) report recommends above 0.025 mg/day for adults. Chromium (VI) compounds have variable water solubility, ranging from highly soluble to virtually insoluble, and this influences their bioavailability and hence toxic effects.

OELs

The US ACGIH and UK HSE have similar approaches and have set the same 8-h TWA TLVs or OESs for chromium metal and trivalent compounds (0.5 mg/m^3) and a lower 8-h TWA TLV or MEL of 0.05 mg/m^3 for hexavalent compounds owing to strong evidence for serious health effects (HSE, 2002). The German DFG has not established OELs for chromium and its compounds since it is not their policy to establish OELs when there is good evidence for a human cancer risk but soluble chromium (VI) compounds have been assigned with an 'S' notation because of evidence for human skin sensitization (Greim, 1996). For hexavalent chromium compounds the German TRGS 900 lists TRKs of 0.005 mg/m^3 and 0.1 mg/m^3, for specific workplaces.

The DECOS have no HBR-OEL for Cr metal dust and insoluble Cr(III) compounds owing to lack of toxicological data. The 8h-TWA HBR-OEL for soluble Cr(III) and Cr(IV) compounds (as inhalable dust) are 0.06 mg/m^3 and 0.05 mg/m^3, respectively. No HBR-OEL value was set for Cr(VI) compounds although a thorough assessment of the health risks was made and an estimation of the additional cancer mortality risk was derived by the committee. All the health-based limits for chromium do not include workers sensitized to chromium, who are perceived as being at extra risk. DECOS recommend that sensitized individuals should not be placed in employment that could put them at risk of chromium exposure (Dutch Expert Committee on Occupational Standards, 1992).

Key studies and critical effects

The key study used by DECOS to derive the HBR-OEL for soluble Cr(III) compounds was a study by Johansson et al. (1987) in which a minimal observed adverse effect level (MOAEL) of 0.6 mg/m^3 was identified in rabbits. A study by Lee et al. (1989) was used to identify a LOAEL of 0.5 mg/m^3 for the critical effect of minute fibrotic pleuritis in rats exposed to Cr(IV) compounds during a 2-year inhalation study. The critical effect of Cr(VI) compounds is lung carcinogenicity, as identified in epidemiological studies, lung cancer cases listed by Langård (1990), and animal carcinogenicity studies and mutagenicity tests. DECOS used the Mancuso (1975) study to estimate an additional cancer mortality risk of 4 x 10^{-3} after 40 years of occupational exposure to 2 µg/m^3 as inhalable dust.

The UK HSE identified carcinogenicity, sensitization and the ability to cause ulcers as the critical health effects for chromium (VI) compounds and based the MEL on these and the absence of no-effect levels. Key studies were not cited in the published summary rationale for setting the limit (HSE, 2001).

The ACGIH adopted a TLV (8-h TWA) of 0.5 mg/m^3 for chromium metal in 1931, which has remained, based on the lack of adverse health effects in workers from chromium industry. However, reference was made to reviews by the IARC (1990) and the HSE (1989), which concluded that owing to inadequacies in studies, there is insufficient information to assess the carcinogenicity of metallic chromium; an A4 notation, 'not classifiable as a human carcinogen', was assigned (ACGIH, 2003a). The TLV (8-h TWA) for chromium (III) compounds is also 0.5 mg/m^3, based on reports of dermatitis in workers exposed to trivalent chromium compounds by Freget and Horsman (1964) and changes of low pathophysiological significance in animal inhalation studies by Henderson et al. (1979) and Johansson and colleagues (Johansson, 1986a; 1986b; Johansson et al., 1987). The TLV (8-h TWA) for soluble chromium (VI) compounds is 0.05 mg/m^3, based on evidence from animal studies for non-carcinogenic effects (Laskin et al., 1969) and kidney damage (Major, 1922; Hunter and Roberts, 1933). The TLV (8-h TWA) for soluble chromium (VI) compounds is 0.01 mg/m^3 on the basis of the large body of evidence for lung cancer in chromium workers (Machle and Gregorius, 1948; WHO, 1988; ATSDR, 1989; HSE, 1989; IARC, 1990). ACGIH has also adopted BEIs for chromium (VI), as total chromium in urine, of 25 µg/l at the end of shift at the end of a workweek and 10 µg/l increase during a shift (ACGIH, 2004a). More recently, the HSE has adopted a BMGV of 10 µmol chromium/mol creatinine in urine, with a post-shift sampling time (HSE, 2005b).

Uncertainty factors

DECOS applied an uncertainty factor of 10 to the HBR-OELs for soluble Cr(III) and Cr(IV) compounds. These factors were comprised of two factors of x 3 — one to allow for extrapolation from animal data to humans and one because a LOAEL or MOAEL was used as a starting point rather than a NOAEL. The use of uncertainty factors was not applicable to the risk evaluation of Cr(VI) compounds (Dutch Expert Committee on Occupational Standards, 1992).

The use of uncertainty factors was not stated and could not be inferred from the publication for the basis of the US TLV-TWA for chromium metal and chromium compounds (ACGIH, 2003a).

Overview for chromium

Chromium is an interesting substance for a case study because it has various oxidation states and solubilities, and hence various toxicities. It is therefore necessary to evaluate chromium metal, trivalent and hexavalent compounds separately and most authorities assigning OELs have addressed this important issue of speciation. There is agreement between the ACGIH TLV and the HSE OES for chromium metal and chromium (III) compounds (8-h TWA 0.5 mg/m^3). There is also agreement between the limits for chromium (VI) compounds (8-h TWA 0.05 mg/m^3) although the USA also has a separate, lower TLV (8-h TWA) of 0.01 mg/m^3 for insoluble compounds. The lack of a DFG MAK value is based on the genotoxicity of chromium (VI) compounds and the absence of threshold effects associated with lung carcinogenicity. Given that there is no threshold for a carcinogenic substance, DECOS has taken the approach of deriving an additional cancer mortality risk estimate for Cr(VI) compounds.

5.7.5 Manganese

Manganese (CAS No. 7439-96-5) is a Group VIIb transition metal; it exists in several oxidation states (II, III, IV, VI and VII) and forms a range of inorganic and organometallic compounds. Most OELs consider the inorganic forms of the metal. Manganese occurs naturally and is mined for use in the production of ferrous and non-ferrous metal alloys, including those essential to steel making. Iron and steel production account for 85–95% of the manganese market. Manganese is an essential element; it is involved in bone formation and amino acid, cholesterol and carbohydrate metabolism; it is a component of several enzymes and activates others. For healthy adults, estimated acceptable or adequate dietary intakes range from 1–12.2 mg manganese/day (IEH, 2004).

OELs

Current OELs (8-h TWA) in the USA, Germany, and UK are 0.2, 0.5 and 0.5 mg/m^3, respectively (HSE, 2003). A recently published criteria document for inorganic forms of manganese, which was produced for consideration by the SCOEL, proposed a limit of 0.1 mg/m^3 for respirable manganese, with an additional limit of 0.5 mg/m^3 for inhalable manganese (IEH, 2004).

Key studies and critical effects

The key studies used to make the recommendation in the IEH (2004) criteria document for SCOEL were by Roels et al. (1992), in which subtle neurological effects were observed in approximately 15% of workers exposed to 0.2 mg/m^3, Gibbs et al. (1999), in which no effect was observed at an average respirable concentraion of 0.04 mg/m^3, and Myers et al. (2002), in which no effect was observed at 0.2 mg/m^3 (equivalent to 0.04–0.08 mg/m^3 respirable concentration). The criteria document concluded that limiting exposure to 0.1 mg/m^3 for respirable manganese would prevent most workers from developing small, non-clinical decrements in motor neurobehavioural function. The 0.5 mg/m^3 limit for inhalable manganese was proposed as a safeguard against significant exposures from gastrointestinal routes, subsequent to inhalation. However, it was noted that there was insufficient evidence to evaluate the effects over a working lifetime. It was also considered that measurements of workplace concentrations in air should be possible at the level proposed, and that neither a short-term limit nor skin notation was necessary (IEH, 2004).

Derivation of the German MAK value was also based on the critical toxic effects to the CNS found in the studies by Roels and Lauwerys (Roels et al., 1987a; 1992) and in studies by Wennberg, Iregren and colleagues (Iregren, 1990; Wennberg et al., 1991; 1992) and Mergler et al. (1994). The lowest average concentration shown to cause slight neurotoxic syptoms was approximately 0.25 mg/m^3. However, given concerns about different sampling and measurement techniques in different locations, the MAK value was set at 0.5 mg/m^3 for total dust (Greim, 1999). The German OELs for the inhalable fraction of manganese have been classified with a pregnancy risk group rating C; that is, no reason to fear a risk of damage to the embryo or fetus when MAK and BAT values are observed (DFG, 2004).

The HSE replaced the 2002 OES (8-h TWA) of 5 mg/m^3 for manganese and its inorganic compounds with an MEL of 0.5 mg/m^3 (8-h TWA) in 2003 (HSE, 2003). The rationale for the OES was withdrawn but to date no documentation has been published to replace this.

The rationale for the 0.2 mg/m^3 ACGIH TLV-TWA for manganese was also based on CNS effects and manganism, from the same studies as those considered by IEH and Germany, and lung and reproductive effects (Lauwerys et al., 1985; Roels et al., 1987a; 1992). ACGIH concluded that the lowest exposure concentration of manganese at which early effects on the CNS could be detected was unknown and therefore the TLV was chosen as the recommended level at which the potential for pre-clinical adverse effects in the lungs and CNS and adverse effects on the fertility of male workers are reduced (ACGIH, 2003b).

Uncertainty factors

In the IEH (2004) criteria document, no uncertainty factor was used to derive the proposed levels because the recommendations were based on human data and non-clinical endpoints only detectable using specific test procedures. Similarly no uncertainty factor was used in the German MAK evaluation (Greim, 1999), and ACGIH (2003b) gives no information on the use of uncertainty factors in the derivation of the TLV.

Overview for manganese

In summary, manganese has been chosen as a case study because of its essentiality and because it has a threshold, albeit the subject of debate, for its neurotoxic effects. The OELs for Germany, UK, and the USA, and in the recent criteria document for SCOEL are comparable, with similar criteria being used in their derivation. The IEH criteria document for manganese gave the clearest rationale for a limit of 0.1mg/m^3 and may be used as a basis for a forthcoming SCOEL recommendation.

5.7.6 Nitrogen dioxide

Nitrogen dioxide (NO_2; CAS No. 10102-44-0) is a reddish-brown gas that is produced naturally by bacteria, volcanic activity, lightning and oxidation of nitric oxide (NO) in the atmosphere. Sources of NO_2 from human activity include diesel exhaust, cooking/heating with non-vented gas appliances and tobacco smoke (Dutch Expert Committee on Occupational Standards, 2004). NO_2 is mainly used as an intermediate in the formation of NO, but also as a nitrating or oxidising agent, for example in rocket fuels, and as a catalyst for sulphuric acid. The route of exposure most relevant to the mining industry is during the use of dynamite, but workers from the chemical and gas welding industries are also exposed (Dutch Expert Committee on Occupational Standards, 2004).

OELs

The UK HSE OES for NO2 of 5.7 mg/m^3 (8-h TWA) and 9.6 mg/m^3 (15-min STEL) were withdrawn in 2003 (HSE, 2002; 2003) on the grounds that they were 'unsafe' owing to 'evidence to show that inhalation exposure at that level on a day to day basis would cause various degrees of harm to workers' health'[25]. It is not clear if the HSE have plans to introduce a new WEL for NO_2. However, the US ACGIH TLV-TWA (8-h) of 5.6 mg/m^3 and STEL of 9.4 mg/m^3 are similar to the HSE, which suggests that perhaps the TLVs need review.

The standards recommended by DECOS are 0.4 mg/m^3 (8-h TWA) and 1.0 mg/m^3 (15-min STEL), which are considerably lower than the ACGIH TLVs (Dutch Expert Committee on Occupational Standards, 2004). The German DFG has not established a MAK for NO_2 and has classified it with a 3B notation. The rationale for the DFG evaluation is based on genotoxic effects in vitro, suspected genotoxicity in vivo, tumour promoting activity and the analogy to the mechanism of action of ozone (DFG, 2005a; 2005b).

Key studies and critical effects

The database used to derive the DECOS, 8-h TWA HBR-OEL lacked epidemiological data so the committee used the large number of animal studies as a basis for the recommended limit. The critical effect involved the respiratory tract and includes increased airway resistance, enhanced susceptibility to bacterial or viral airway infections and long-term irreversible damage to the lung tissue. The lowest-observed-effect level (LOEL) from robust animal studies was 0.96 mg/m^3, although a LOEL of 0.65 mg/m^3 was identified in less robust studies showing morphological changes to the lungs. The 15-min HBR-OEL for NO_2 was based on the complete set of human data from single-exposure studies, which determined significant toxicological effects on lung function and increased airway resistance at concentrations as low as 2.9 mg/m^3 (Frampton et al., 1991). However, taking the collection of studies as a whole, the recommended STEL was based on the NOAEL of 1 mg/m^3 (Dutch Expert Committee on Occupational Standards, 2004).

The key studies used to derive the ACGIH TLV were early studies in humans and animals. In particular, Kosmider et al. (1972) reported slight changes in pulmonary vital capacity in workers exposed to NO_2 at 0.4–2.7 ppm (0.8–5.2 mg/m^3). The ACGIH (2003b) assigned the A4, 'not classifiable as a human carcinogen', notation to NO_2, based on a lack of evidence for carcinogenicity in animal studies by Wagner and colleagues and Freeman and colleagues (Wagner et al., 1965; Freeman et al., 1966; 1968).

Uncertainty factors

There was no stated use of uncertainty factors in the published rationales for the ACGIH TLV.
No overall uncertainty factor was used by DECOS to derive the 8-h TWA HBR-OEL because the uncertainty from intraspecies differences is counterbalanced by the uncertainty arising between the continuous exposure of the experimental animals in studies used to derive the OEL and the shorter duration of exposure for a worker (8h/day, 5d/week). No uncertainty factor for interspecies differences was used because the NOAEL derived from animal studies was within a narrow concentration range for three different species. No uncertainty factor for intraspecies differences was used for the STEL HBR-OEL because the NOAEL used to derive the limit came from a large and consistent database of human studies (ACGIH, 2003b; Dutch Expert Committee on Occupational Standards, 2004).

Overview for nitrogen dioxide

There is a lack of consistency in both the value and the approach used to set OELs for NO_2 and the issue of what was practical for industry has guided the establishment of historical values. The limit set by DECOS represents the most robust rationale for a health-based limit.

5.7.7 Sulphur dioxide

Sulphur dioxide (SO_2; CAS No. 7446-09-5) is a water-soluble, non-flammable, colourless gas or liquid with a pungent, suffocating odour. The presence of SO_2 in the atmosphere results from anthropogenic activity and natural sources. Anthropogenic sources include the burning of coal and fuel oils, production, refining and use of natural gas and petroleum, and natural sources include sea spray, volcanic activity, decomposition of biological matter and anaerobic microbiological activity. SO_2 is mainly used as a catalyst or as a reducing or oxidising agent in many different commercial uses including the pulp and paper, petroleum and food industries. In the mineral industry, SO_2 has several applications: as flotation depressants for sulphide ores; to pre-reduce ferric to ferrous ions during the electro-winning of copper from leach solutions containing iron; to initiate precipitation of metallic selenium from selenous acid; as a by-product of copper metallurgy; and to reduce hexavalent chromium to its less toxic trivalent form in chrome waste disposal. Workplace exposures to SO_2 relevant to the metal industry arise in the production of steel, copper, nickel, zinc, cobalt, aluminium and other metals, when sulphidic ores or sulphuric impurities of the ores are sintered, roasted or melted (IARC, 1992b).

OELs

The UK HSE 8-h TWA OES of 5.3 mg/m^3 and the 15-min STEL OES of 13 mg/m^3 were withdrawn in 2003 (HSE, 2002; 2003) on the grounds that they were 'unsafe' owing to 'evidence to show that inhalation exposure at that level on a day-to-day basis would cause various degrees of harm to workers' health[25]. It is not clear if the HSE have plans to introduce a new WEL for SO_2. The US ACGIH 8-h TWA-TLV of 2 ppm (5.3 mg/m^3) and 15-min STEL of 5 ppm (13 mg/m^3) are identical to the withdrawn HSE OELs, which suggests that perhaps the TLVs need review.

DECOS recommends a 15-min STEL of 0.7 mg/m^3 (no 8-h TWA HBR-OEL has been established for SO_2, owing to lack of long-term exposure animal studies and epidemiological studies) and identifies workers with asthma and, possibly, workers with ischaemic heart disease as 'at risk' groups (Dutch Expert Committee on Occupational Standards, 2003b).

The German DFG has set a MAK value of 1.3 mg/m^3 for SO_2 (DFG, 2005b; 2005c).

Key studies and critical effects

The DECOS HBR-OEL STEL (15-min TWA) of 0.7 mg/m^3 was based on the critical effect of an increased susceptibility to airway infections and chronic irritation. The key studies used to identify a NOAEL of 2.0 mg/m^3 were short-term inhalation studies in humans by Stacy et al. (1983) and Schachter et al. (1984). In both studies, the participants took moderate exercise sessions and lung function tests were performed before and after exposure for four hours and 40 minutes, respectively (Dutch Expert Committee on Occupational Standards, 2003b).

The German MAK value is based on human data that show no effect on lung function in volunteer studies after 2-hour exposures to 0.5 ppm (Schachter et al., 1984) or in workers exposed to long-term average concentrations of 0.67 to 0.78 ppm (Broder et al., 1989; Kremer et al., 1994; 1995).

The critical effect used to derive the ACGIH TLV for SO_2 was a human study, reported in a publication by the US Department of Health, Education and Welfare, in which bronchoconstriction occurred following inhalation at 5 ppm or more (DHEW, 1969). The ACGIH assigned an A4, 'not classifiable as a human carcinogen' notation to SO_2, based on evidence for cocarcinogenic action, although Laskin et al. (1976) reported an absence of squamous cell carcinomas in the respiratory tract of rodents (ACGIH, 2003b).

Uncertainty factors

DECOS (Dutch Expert Committee on Occupational Standards, 2003b) used an uncertainty factor of 3 to adjust for interindividual differences owing to the limited number of participants in the key studies (Stacy et al., 1983; Schachter et al., 1984) and data showing variation in studies by Islam et al. (1992; 1994). There is no mention of the use of uncertainty factors in the rationale for the basis of the ACGIH TLVs for SO_2 (ACGIH, 2003b).

Overview for sulphur dioxide

The OELs for SO_2 differ between authorities. The ACGIH TLV recommendation was based on data from before 1977. More recent studies have shown that this limit may be unsafe and the UK HSE has withdrawn its comparable OES for SO_2. The DECOS has the most comprehensive rationale for the HBR-OEL for SO_2 but this is a STEL (15-min TWA) only. The database for health effects in both humans and animals is limited, particularly regarding long-term exposures and long-term concentration–response relationships. These data are required to establish an 8-hr TWA OEL.

5.7.8 Sulphuric acid mists

Sulphuric acid (H_2SO_4; CAS No. 7664-93-9) is a dense, oily, odourless liquid that is colourless when pure but may be dark brown. It is a strongly corrosive, non-flammable, dehydrating reagent that reacts exothermically with water and alcohol (ACGIH, 2001). Sulphuric acid is used in a diverse range of industries, such as in the manufacture of food, glue, dyestuff, parchment and petroleum, and it is used as a battery electrolyte and for electroplating. Of greater relevance to the mining and metal industry, sulphuric acid is used in nonferrous metallurgy, copper, zinc, iron and steel production and as a leaching agent during the extraction of uranium and copper from ore[26].

OELs

Current 8-h TWA OELs in Germany and the USA are 0.1 and 0.2 mg/m^3, respectively. The UK HSE 8-h TWA OES of 1 mg/m^3 was withdrawn in 2003 (HSE, 2002; 2003). It is not clear if the HSE have plans to introduce a new WEL for sulphuric acid.

Key studies and critical effects

The MAK value classification was based on the critical effect of changes to mucociliary clearance, in humans, at concentrations of 0.3 mg/m^3. Owing to the lack of data in humans on the effects of long-term exposure, the MAK value was reduced to 0.1 mg/m^3. Based on studies in mice and rabbits (actual studies unspecified), the NOEL for embryotoxic effects is 5 mg/m^3; therefore the MAK value is thought to be sufficient to protect against prenatal toxic effects. There is no experimental evidence to suggest mutagenicity, genotoxicity, carcinogenicity or tumour-promoting effects and no evidence to suggest sensitizing effects from sulphuric acid mists (Greim, 2001).

DECOS have classified sulphuric acid mists as carcinogenic, based on evidence from the available epidemiological studies showing an association between workers exposed to inorganic mists containing sulphuric acid and laryngeal cancer (Dutch Expert Committee on Occupational Standards, 2003a). DECOS considered supporting evidence from animal studies was limited, since a lifetime study in hamsters exposed to 100 mg/m^3 showed no carcinogenic effects. The committee concluded that sulphuric acid mist acts as a non-stochastic genotoxic carcinogen and therefore recommended that an exposure limit be derived using a threshold model; however, a limit is yet to be set.

The US ACGIH TLV (8-h TWA) of 0.2 mg/m^3 (thoracic particulate mass; ACGIH, 2004b) is based on altered tracheobronchial particle clearance mechanisms among normal and asthmatic volunteers (Leikauf et al., 1981; Lippmann et al., 1982; Leikauf et al., 1984; Lippmann et al., 1987; Spektor et al., 1989) and on pulmonary function changes among asthmatic individuals at levels above about 350 µg/m^3 (Koenig et al., 1985; Utell et al., 1989). The ACGIH have issued sulphuric acid with a TLV carcinogenicity notation of A2, 'suspected human carcinogen', based on the possibility of an association between laryngeal cancer and exposure to sulphuric acid, and strongly recommend that further studies be considered (ACGIH, 2003a).

Uncertainty factors

The German MAK value appears to have incorporated an uncertainty factor of 3 to allow for lack of knowledge about long-term effects (Greim, 2001). No other authority used uncertainty factors in the process to establish OELs.

Overview for sulphuric acid mists

The German MAK value and US TLV are similar and both are based on changes to mucociliary clearance in humans.

5.7.9 Silica (crystalline)

Quartz is found in almost all types of rock, sands, clays, gravels and shales and is, therefore, particularly relevant to the mining and quarrying industries, such as black coal and ore mining. Many different forms of crystalline silica exist in the occupational setting including crystalline cristobalite (CAS No. 14464-46-1), crystalline quartz (CAS No. 14808-60-7), crystalline tridymite (CAS No. 15468-32-3) and crystalline tripoli (CAS No. 1317-95-9). Exposure to crystalline silica has been identified as the cause of the lung disease silicosis, a slowly progressive, irreversible disease that takes years to develop and which causes fibrous nodules to develop in the lungs. Much recent debate has centred around the evidence as to whether silica is able to cause lung cancer in non-silicotics as well as silicotics and in which occupational settings such risks may occur (IARC, 1997).

OELs

There is no German MAK value for crystalline silica (respirable quartz, cristobalite and tridymite dust). Quartz has been classified in carcinogenic category 1, and the DFG propose that reducing silicosis among workers would decrease the incidence of lung cancer (Greim, 2000).

DECOS have set an health-based limit (HBR-OEL 8-h TWA) for crystalline silica (quartz, cristobalite and tridymite) of 0.075 mg/m^3 (Dutch Expert Committee on Occupational Standards, 1992).

The UK HSE 8-h TWA MEL for respirable crystalline silica dust is 0.3 mg/m^3 (HSE, 2002). The rationale for setting this limit was influenced by the level reasonably practicable for industry. However, this level is currently under review by ACTS because current evidence suggests that an MEL of 0.3 mg/m^3 is not sufficient to protect workers from lung disease. The WEL for respirable crystalline silica remains at 0.3 mg/m^3 until a proposal to reduce the value to 0.1 mg/m^3 (8-h TWA) has been formally agreed but HSE believes that the new WEL is reasonably practicable for industry to meet.

In 2002, the SCOEL issued a recommendation to the EC that, to control against silicosis, the OEL for respirable crystalline silica should be reduced to 0.05 mg/m^3 (8-h TWA; HSC, 2005b).

The ACGIH had evaluated four substances containing crystalline silica separately and assigned a TLV at 0.05 mg/m^3 (8-h TWA) for cristobalite (respirable particulate fraction), quartz (respirable) and tridymite (respirable particulate fraction) and at 0.1 mg/m^3 of contained respirable quartz particulate (8-h TWA) for tripoli. However, the documentation and TLV for tripoli were withdrawn in the 2005 NIC and crystalline silica (quartz and cristobalite) is subject to an NIC. Furthermore, the ACGIH have assigned the carcinogenicity notation A2, 'suspected human carcinogen' (ACGIH, 2003a). The NIC for quartz and cristobalite is 0.025 mg/m^3 as respirable fraction. Australia after long debate has adopted an OEL of 0.1 mg/m^3 (Klerk et al., 2002).

Key studies and critical effects

In support of the German MAK classification, an evaluation of nine relevant epidemiological studies found evidence for an excess of deaths in workers exposed to respirable dust of crystalline silica compared to the general population. Although it was concluded that an association between exposure to quartz or cristobalite is associated with increased relative lung cancer risk, the mechanism for this was unclear. It was proposed that impaired pulmonary clearance in workers with silicosis could promote the development of lung cancer because of inadequate clearance of other lung toxins. Evidence to support the carcinogenicity of crystalline silica was provided by studies in rats, where exposure to quartz via inhalation has been associated with an increase in the incidence of lung tumours but a similar effect has not been produced in studies using other rodents, such as hamsters and mice (Greim, 2000).

DECOS has designated quartz silica as a non-stochastic genotoxic carcinogen, with the implication that quartz has a threshold of effect (Dutch Expert Committee on Occupational Standards, 1998). The critical health effects have been identified as silicosis and lung cancer. The key study that identified a NOAEL of 0.075 mg/m^3 for silicosis was a mortality study of granite workers by Costello and Graham (1988). A significantly increased incidence of lung cancer was associated with long-term exposure to respirable quartz at 0.16 mg/m^3 but not at 0.05 mg/m^3 (Guènel et al.,

1989). The HBR-OEL (8-h TWA) for respirable quartz dust was set at 0.075 mg/m^3 on the basis of the NOAEL for silicosis. This limit for quartz is also used for tridymite and cristobalite because DECOS state that data for these substances are too limited to derive separate limits (Dutch Expert Committee on Occupational Standards, 1992).

The UK HSE MEL for respirable crystalline silica dust is based on the critical human health effect of silicosis although a NOEL has not been established. Exposures to a level of 1 mg/m^3 are associated with health effects that may start as silicosis but then progress to massive fibrosis (HSE, 2001; 2002; 2003).

The critical effects for the ACGIH TLV-TWA of 0.05 mg/m^3 for crystalline silica (quartz, cristobalite and tridymite) were fibrosis and silicosis. The TLV is set in recognition that fibrosis in workers exposed at levels near 0.1 mg/m^3 is not detectable by X-ray analysis and concern that fibrosis from silicosis is a risk factor for lung cancer, as identified in key studies by Hnidzo and colleagues (Hnizdo and Sluis-Cremer, 1993; Hnizdo et al., 1993). The ACGIH assigned crystalline silica with the carcinogenicity notation A2, 'suspected human carcinogen', owing to the lack of epidemiological evidence for an increased risk of lung cancer among workers without silicosis and the lack of strong evidence for carcinogenicity in animals. The only positive finding came from inhalation studies in rats, which the ACGIH noted are a poor model for effects in humans (ACGIH, 2003b). The quartz OEL, in particular, was based on the concept that the magnitude of toxicity is proportional to the quantity of quartz in the dust. The ACGIH rationale also recognizes that this TLV is subject to uncertainties regarding the quality of the epidemiological database and advises that exposures should be as low as possible below this limit.

Uncertainty factors

The DECOS and ACGIH have not stated the use of uncertainty factors in their documents for the basis of deriving OELs for crystalline silica.

Overview for crystalline silica

The US TLV of 0.05 mg/m^3 is the lowest limit for crystalline silica, based on data from studies published in 1993. The Dutch HBR-OEL of 0.075 mg/m^3 has a rationale published in 1992 and therefore does not consider the data used by the ACGIH. While current HSE OELs are based on past feasibility of measurement, new recommendations are in place and a new standard is under review[27]. The absence of a MAK value is in keeping with the DFG policy on carcinogenic substances.

In summary, there is some discrepancy between the values and rationales used to set these OELs although there is a trend amongst authorities to reduce exposures to the lowest level reasonably practicable. Silicosis is a key feature in the evaluations of all standard setting organizations reviewed above.

5.7.10 Overall summary on case studies

The case studies review the approaches used by five different authorities to derive OELs for substances of particular relevance to the mining and metal industries. The UK HSE, German DFG and EU SCOEL set legally binding OELs, and in setting them a review committee takes into account economic and technical feasibility factors as well as health-based recommendations. The Netherlands DECOS and US ACGIH set health-based OELs, but in the Netherlands, for example, the Ministry of Social Affairs and Employment evaluates the DECOS HBR-OELs in conjunction with feasibility data from the Social Economic Council, before legally binding OELs are set. Consequently, OELs are practical limits, a fact that contributes further to variability between different countries.

No one authority has more or less conservative OELs and the use of key studies, critical effects and uncertainty factors is very variable. There is a lack of transparency in some of the published rationales. Often, the limits themselves and the supporting documents are several years old, and some might be reviewed in the light of more recent data. The case studies, therefore, illustrate the need for greater transparency and a more consistent approach when deriving health-based limits.

For countries within the EU, OELs should comply with EU legislation, which is based on recommendations from SCOEL. SCOEL recommendations could be used as a foundation for steps towards harmonization between authorities on a global scale. Historically, both within and outside the EU, there has been a degree sharing of both OELs and approaches in the setting of OELs. For example, the Australian NOHSC has made use of the ACGIH TLVs and is cognisant of the approaches used by the UK HSE and German DFG in deriving their national limits (NOHSC, 1999).

6

A Harmonized Approach

6. A Harmonized Approach

6.1 Initiatives on harmonization

Harmonization does not mean standardization; that is, it is not to be expected that all jurisdictions should use identical approaches and generate identical standards, rather differences in approaches should clearly reflect identifiable differences in scientific policy or scientific judgement, which should be communicated in a transparent manner. (e.g. Haber and Maier, 2002).

6.1.1 Harmonizing review activities

The work of the NEG (Section 5.2.4, above), in preparing scientific criteria documents to underpin OEL setting, already exemplifies a harmonized approach to the evaluation of scientific data between the five countries concerned. Implementation of proposals, for example between NEG, DECOS and the US NIOSH, to write joint criteria documents would further promote harmonization at this level (Lundberg, 1991). This only involves seven countries, but this principle could be extended to encompass many others. In practice, there is already intensive interaction between the different European national committees, the SCOEL and the US TLV committee. For example, members of DECOS are also members of the German DFG committee, members of the DFG committee attend the TLV committee and members of the major European national committees are members of SCOEL. The result is an extensive exchange of original publications and documents so that the data from which the different committees derive their OELs are more or less the same.

6.1.2 Initiatives on a minimum data set

Requirements for a minimum data set for the development of OELs have been discussed. While it might be thought that the absence of a minimum data set would reduce confidence in the ability to provide any meaningful guidance, the absence of any OEL, even one based on limited information, is not helpful in the occupational situation. It has been proposed that a strategy for communicating the strength of the evidence used in deriving an OEL could be helpful (Haber and Maier, 2002).

6.1.3 Harmonizing approaches to developing occupational exposure limits for sensory irritants

Most OEL setting groups in Europe and the ACGIH appear to use similar approaches to dealing with sensory irritants, and there have been recent efforts to further harmonize approaches (Paustenbach, 2001; Triebig, 2002), including a recent workshop sponsored by the MAK[28]. SCOEL has established a set of criteria to help ensure greater consistency in approaches to setting OELs for sensory irritants (Meldrum, 2001). As sensory irritation will continue to be an important aspect of OEL setting for many substances, at least for short-term exposure limits, this could be one area where harmonization would be extremely helpful.

6.2 Benefits of harmonization

The value of harmonizing approaches to setting OELs is becoming increasingly apparent with industrial globalization, yet OELs set in various regions and jurisdictions are often different. In the review by Haber and Maier (2002) the need for harmonization, using mining and metal compounds as case studies, was addressed. Four reasons for harmonization were identified, as follows.

- Increased transparency of health-based OELs, clarifying their uses and limitations
- Enhanced confidence in the process used to derive OELs by communicating key scientific criteria
- Pooling of resources among OEL setting bodies, increasing coverage of substances with no OEL, decreasing time to update OELs
- Increased provision for similar levels of worker health protection globally by increasing consistency in scientific criteria used as basis for deriving OELs

Clearly, there may be many other benefits of harmonizing activities in the setting of OELs, but the above are considered to represent a good starting list.

Haber and Maier (2002) reviewed the different approaches to, for example, uncertainty factors and carcinogenicity used by the ACGIH, DECOS and the DFG, for chromium and its compounds, and for copper, lead, manganese and silica. As a result, they made the following recommendations to facilitate harmonization.

- Improve transparency and completeness of OEL documentation and identify strengths and weaknesses
- Provide greater accessibility to grey literature
- Increase dissemination/publication of studies that evaluate several endpoints but find no effect
- Develop approaches for characterizing the overall confidence in OELs
- Harmonize the consideration of severity in the identification of the POD
- Harmonize definition of minimum data set for development of OEL
- Harmonize approach for interspecies extrapolation
- Harmonize default uncertainty factors used in developing OELs
- Harmonize approach for consideration of speciation and essentiality of metals

6.3 Good practice in identifying and handling hazards

It is worth noting that OELs are only one tool that can be used to control exposure to hazardous substances in the workplace (see also 5.6.1) and, even then, they are only part of a broader control framework that involves compliance with the OEL, by good practice and measurements and inspection by regulators. The control banding approach to controlling exposure to chemicals, currently being developed, shifts the paradigm towards more control by following good practice with less reliance upon OELs and occupational hygiene measurement. Nonetheless, it is recognized that soundly based and well respected OELs will continue to be an important and fundamental cornerstone of good occupational hygiene control of occupationally-used substances.

6.4 Recommendations for harmonization

6.4.1 Reviewing the literature

As currently practiced between some standard setting bodies (e.g. Lundberg, 1991), although on a limited basis, the production of reviews of the literature on scientific data as background documentation for setting OELs, including data on physicochemical properties, occupational hygiene data, toxicological and mechanistic data and human health data, could be a shared activity, with one review produced for and used by all organizations setting OELs. Such reviews could be evaluated and adopted on behalf of all standard setting bodies by an independent expert group.

Whether or not such an approach to produce single review documents is appropriate, or would be currently acceptable, reviews of scientific data pertinent to setting OELs should all be prepared to a set of agreed basic criteria for inclusion and analysis of data and studies, such as the criteria adopted in the EU (CEC, 1992).

All such background documentation should also be evaluated, whether by an independent expert group acting for all or several standard setting bodies or by individual standard setting bodies, according to predefined and consistent criteria, and all reviews that underpin OELs should be in the public domain.

The background documentation should clearly identify all elements of the process of evaluating the scientific literature and should identify key health impacts for setting OELs and/or determining that no health-based OEL can be set (e.g. for substances with an effect for which no threshold can be reliably identified) and key studies to be used in setting OELs for threshold substances.

The process to set an OEL must be efficient. Ideally an OEL review, including a literature review and preparation of a report, peer review by the scientific community and consideration by the social partners and regulators, should be completed within one year.

One advantage of establishing a centralized expert group to oversee and evaluate collation and review of data pertinent to setting OELs would be more timely evaluations of new OELs and re-evaluations of existing OELs than are currently possible. This would be even better facilitated if a centralized financial resource could be made available for such activities.

6.4.2 Risk assessment

An evaluation of the pertinent scientific data should, therefore, result in the identification of critical health effects and key studies for the development of OELs.

Where uncertainty factors are then applied in developing OELs, these should be clearly described. As has been recommended (Risk Assessment and Toxicology Steering Committee, 1999a), although uncertainty factors are often presented as single numbers, scientific and non-scientific influences on decisions about uncertainty factors should be clearly described when chemical risk assessments are made publicly available. Transparency would be improved if individual components of a composite risk factor were to be clearly identified.

All non health-based influences that impact on the OEL should also be described, such as issues of technical feasibility and socioeconomic benefit and risk.

All elements of the decision making process should be documented and, as with the background scientific review, all documentation, including the finally adopted OELs, should be readily available in the public domain.

Where appropriate all documentation, including the initial literature review, should be published together.

6.5 Proposed code of practice for setting occupational exposure limits

- Literature review of relevant scientific data according to standardized criteria
- Evaluation of literature review according to standardized criteria
- Selection of critical health endpoint(s)
- Determination of whether critical effects are threshold/non-threshold
- Selection of key studies for OEL
- Selection of POD
- Selection of factors influencing uncertainty
- Application of individual uncertainty factors to each such influencing factor
- Determination of composite uncertainty factor
- Identification of non-scientific influences on development of OEL
- OEL
- Discussion on the availability and accuracy of sampling technology
- Documentation and publication of all key steps, above

Proposals put forward, separately, by ICMM member companies can be found in Annex 2.

Annexes

Annex 1
Case Studies

A comparison of OELs and how they were set for selected case studies of compounds that are particularly relevant to the metals and mining industry is presented in Tables A1–A9.

Abbreviations

ACGIH
American Conference of Governmental Industrial Hygienists
BAT
Biological Tolerance Value
BEI
Biological Exposure Indices
CNI
Central Nervous System
DECOS
Dutch Expert Committee on Occupational Standards
DFG
Deutsche Forshungsgemeinschaft
EU
European Union
HBR-OEL
Health Based Recommended Occupational Exposure Level
HSE
Health and Safety Executive
LOAEL
Lowest Observed Adverse Effect Level
MAK
Maximale Arbeitsplatzkonzentrationen
MEL
Maximum Exposure Limit
MOAEL
Minimal Observed Adverse Effect Level
NOAEL
No Observed Adverse Effect Level
OEL
Occupational Exposure Limit
OES
Occupational Exposure Standard
PNS
Peripheral Nervous System
SCOEL
Scientific Committee on Occupational Exposure Limits
STEL
Short Term Exposure Limit
TLV
Threshold Limit Value
TWA
Time Weighted Average

Table A1.1: Nickel metal

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			On priority list but no recommendation to date
German DFG	No MAK set			Has been evaluated but no MAK value assigned because classified as a carcinogen
The Netherlands DECOS	HBR-OEL, 8-h TWA, 0.05 15-min TWA, 0.1			Fertility and developmental toxicity publication but HBR-OEL publication in Dutch
UK HSE	MEL, 8-h TWA, 0.5 (HSE, 2002)	Sensitization, cancer (key studies not provided)	Uncertainly factor: none stated NOAEL not identified but 0.004 mg/m³ produced minimal effects in animals *In vitro* evidence for clastogenicity	Published basis for this OEL lacking transparency
USA ACGIH	8-h TWA, 1.5 (I) (ACGIH, 2003a)	Dermatitis, pneumoconiosis		Insufficient data to recommend a STEL or 'Skin' or 'Sensitization' notations; TLV-TWA expressed as inhalable nickel particulate rather than 'total' nickel particulate as it is a respiratory hazard

* mg/m³ unless otherwise stated

Table A1.2: Nickel sulphate

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			On priority list but no recommendation to date
German DFG	No MAK set			Has been evaluated but no MAK value assigned because classified as a carcinogen
The Netherlands DECOS	HBR-OEL, 8-h TWA, 0.05 15-min TWA, 0.1			Fertility and developmental toxicity publication but HBR-OEL publication in Dutch
UK HSE	MEL, 8-h TWA, 0.1 (HSE, 2002)	Sensitization, cancer (key studies not cited in rationale)	Uncertainty factor: none stated NOAEL not identified but 0.004 mg/m³ produced minimal effects in animals. *In vitro* evidence for clastogenicity	Published rationale for this OEL lacking transparency
USA ACGIH	8-h TWA, 0.1 (I) (ACGIH, 2003a)	NTP Studies in rats and mice identified pulmonary damage, CNS, irritation, dermatitis as the critical effects (NTP, 1996a; 1996b; 1996c)	Uncertainty factor: None stated Evidence for inflammatory changes in rats and mice at 0.06 and 0.11 mg/m³; no evidence for carcinogenicity via inhalation of nickel sulphate	TLV-TWA expressed as inhalable nickel particulate rather than 'total' nickel particulate because of the association between nickel exposure and sinus cancer

* mg/m³ unless otherwise stated

Table A2: Palladium metal and salts

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			
German DFG	No MAK value			
The Netherlands DECOS	No HBR-OEL			
UK HSE	No OEL			
USA ACGIH	No TVL			

* mg/m³ unless otherwise stated

Table A3: Lead metal

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	8-h TWA, 0.1 Biological limit value, 30 µg/dl (EC, 2002)	CNS, PNS, kidney (Kentner and Fischer, 1993; Lai et al., 1997)	Uncertainty factor: none stated Based on the LOAEL for neurobehavioural effects of 40 µg/dl; assumption that avoiding CNS effects will protect against other toxic effects on the PNS and kidneys (including renal cancer); no NOAEL can be derived using available data	Other routes of exposure contribute to blood-lead and so lead is more difficult to set an OEL for than other substances Minimize exposure of women at childbearing age to lead
German DFG	No value set	N/A	Uncertainty factor: N/A Based on potential carcinogenic effects	Published rationale
The Netherlands DECOS	HBR-OEL, 8-h TWA, 0.06 for men and 0.04 for women			HBR-OEL evaluation (1980) in Dutch
UK HSE	8-h TWA, 0.15 No STEL Biological limits for workers, 50 µg/dl, 25 µg/dl for women of reproductive age, 40 µg/dl for child <18 y (HSE, 2001; 2003)	Anaemia, nervous system effects and kidney damage (key studies not cited)	Uncertainty factor: None stated Based on critical health effects observed as blood-lead concentrations	Lead has its own Control of Lead at Work Regulations (1998) and therefore is not regulated by COSHH (2002)
USA ACGIH	8-h TWA, 0.05 BEI, 30 µg/dl at non-critical sampling time Women of child-bearing age at risk if blood-lead exceeds 10 µg/dl (ACGIH, 2003a)	CNS, blood, kidney; reproductive effects (key studies not cited in the TLV recommendation)	Uncertainty factor: none stated Based on critical health effects observed as blood-lead concentrations	Blood lead concentration rather than air lead concentration is the principal method of monitoring lead exposure in the workplace; all sources of lead-exposure are therefore covered Lead has A3 notation, Confirmed Animal Carcinogen with Unknown Relevance to Humans but insufficient information to recommend 'Skin' or 'Sensitization' notations

* mg/m³ unless otherwise stated

Table A4: Chromium

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			Unpublished risk assessment approach
German DFG	Cr: No value CrIII: No value CrVI: (sol and insol) No value	Cancer	Uncertainty factor: N/A	Based on cancer classification and lack of threshold effects
The Netherlands DECOS	Cr: No value CrIII: 8-h TWA, 0.06 CrIV: 8-h TWA, 0.05 CrVI (sol and insol): No value	 Lung toxicity (Johansson et al., 1987) Lung toxicity (Lee et al., 1989) Lung Cancer	No HBR-OEL due to lack of data MOAEL and uncertainty factor (x10) NOAEL and uncertainty factor (x10) No HBR-OEL because genotoxic carcinogen	The Netherlands has 8-h or 15-min TWA Maximal Accepted Concentration (MAC) OELs for Cr and all Cr compounds despite the lack of DECOS HBR-OELs (Dutch Expert Committee on Occupational Standards, 1992)
UK HSE	Cr and CrIII: OES, 8-h TWA, 0.5 CrVI: MEL, 8-h TWA, 0.05 (HSE, 2002)	 Ulceration, sensitization, cancer (key studies not cited)	Uncertainty factor: none stated No NOAEL could be identified; basis for limit unclear	No published rationale for Cr metal and CrIII Rationale lacking transparency; substances were not distinguished between solubility on the basis that it would be impracticable to distinguish them in practice (HSE, 2001)
USA ACGIH	Cr and CrIII: 8-h TWA, 0.5 CrVI (sol): 8-h TWA 0.05 CrVI (insol): 8-h TWA 0.01 (ACGIH, 2003a) CrVI (urine): BEI increase, (end shift) 10 µg/l, (endweek) 30 µg/l (ACGIH, 2004a)	Irritation, dermatitis (Fregert and Horsman, 1964; Henderson, 1979; Johansson, 1986a; 1986b; Johansson et al., 1987) Liver, kidney, respiratory (Laskin et al., 1969) Cancer, irritation (Machle and Gregorius, 1948; WHO, 1988; ATSDR, 1989; HSE, 1989; IARC, 1990)	Uncertainty factor: none stated Cr metal TLV based on historical limit; LOAEL for CrIII salts 0.5 mg/m³ (ACGIH, 2003a)	A1 notation, confirmed Human Carcinogen' for CrVI (sol and insol)

* mg/m³ unless otherwise stated

Table A5: Manganese

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			
German DFG	MAK, 8-h TWA, 0.5 BAT (blood, end shift(s)), 20 µg/l (DFG, 2004)	CNS effects (Roels et al., 1987b; Iregren, 1990; Wennberg et al., 1991; 1992; Mergler et al., 1994)	No uncertainty factors used LOAEL 0.25 mg/m³ observed from critical studies in Sweden equivalent to 0.5 mg/m³ using dust monitoring equipment in Germany	No 'Sensitization' notation
The Netherlands DECOS	No HBR-OEL set			Effects on reproduction — publication but no OEL recommendation; currently under evaluation
UK HSE	MEL, 8-h TWA, 0.5 (HSE, 2003)			No published rationale available since the alteration of an OES to an MEL
USA ACGIH	TLV, 8-h TWA, 0.2 (ACGIH, 2003a)	CNS effects (manganism), lung toxicity (Lauwerys et al., 1985; 1987a; Roels et al., 1992), reproductive effects (Lauwerys et al., 1985)	Uncertainty factor: none stated LOAEL unknown; OEL based on evidence for a worsening of pre-clinical neurological symptoms after exposure ends	Insufficient data to recommend 'Skin', 'Sensitization' or 'Carcinogenicity' notations

* mg/m³ unless otherwise stated

Table A6: Nitrogen dioxide

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			
German DFG	No MAK value			DFG evaluation and category 3B carcinogen but no MAK value set
The Netherlands DECOS	8-h TWA, 0.4 15-min STEL, 1.0 (Dutch Expert Committee on Occupational Standards, 2004)	Pulmonary effects, fibrosis (Kubota et al., 1987; Miller et al., 1987; Frampton et al., 1991)	No overall uncertainty factor used although the use of uncertainty factors was discussed HBR-OEL based on animal data due to a lack of human data; NOAEL of 0.38 mg/m³ in animal studies was rounded to 1 decimal place to give the HBR-OEL	Transparent, robust rationale
UK HSE	OES, 8-h TWA, 5.7 (withdrawn) OES, 15-min STEL, 9.6 (withdrawn) (HSE, 2003)			
USA ACGIH	8-h TWA, (3 ppm) 5.7 15-min STEL, (5 ppm) 9.6 (ACGIH, 2003a)	Irritation, pulmonary oedema (Wagner et al., 1965; Freeman et al., 1966; Kosmider et al., 1972)	Uncertainty factor: none stated	A4 notation, not classifiable as a Human Carcinogen

* mg/m³ unless otherwise stated

Table A7: Sulphur dioxide

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			
German DFG	MAK, 1.3 (DFG, 2004)	Lung function (Broder et al., 1989; Kremer et al., 1994; Kremer et al., 1995)		Category 3B carcinogen
The Netherlands DECOS	15-min STEL, 0.7 (Dutch Expert Committee on Occupational Standards, 2003b)	Respiratory irritation (Stacy et al., 1983; Schachter et al., 1984)	Uncertainty factor of 3 used to account for intraspecies differences (Islam et al., 1992; Islam et al., 1994) NOAEL of 2 mg/m³ for short-term exposure and uncertainty factor used to derive STEL	No 'Skin' or 'Sensitization' notation DECOS recognizes need for 8-h TWA HBR-OEL but insufficient data for long term exposure
UK HSE	OES, 8-h TWA, 5.3 (withdrawn) OES, 15-min STEL, 13 (withdrawn) (HSE, 2003)			
USA ACGIH	8-h TWA, 2 ppm 15-min STEL, 5 ppm (ACGIH, 2003a)	Respiratory irritation, bronchoconstriction (Speizer and Frank, 1966; DHEW, 1969; Amdur, 1969)	Uncertainty factor: none stated Based on bronchoconstriction at 5 ppm	A4 notation, not Classifiable as a Human Carcinogen (Laskin et al., 1976)

* mg/m³ unless otherwise stated

Table A8: Sulphuric acid mists

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	8-hTWA, 0.05 15-min STEL, 0.1** (proposed; SCOEL, 2005)	Irritancy, laryngeal cancer		Unpublished
German DFG	MAK, 8-h TWA, 0.1 (DFG, 2004)	Decreased mucociliary clearance, lung function (key studies not cited)	Uncertainty factor of 3 used to extrapolate effects to long-term exposures (Greim, 2001) LOAEL 0.3 mg/m³; laryngeal cancer assumed to be caused by severe local irritation because of absence of genotoxic effects (Greim, 2001)	Category 4 carcinogen; no 'Sensitization' or 'Skin' notation (Greim, 2001)
The Netherlands DECOS	No HBR-OEL set	Cancer	EU category 1, carcinogenic to humans	Classified as carcinogenic but no HBR-OEL evaluation available
UK HSE	OES, 8-h TWA, 1 (withdrawn) (HSE, 2003)			
USA ACGIH	TLV, 8-h TWA, 0.2 (ACGIH, 2004b)	Changes in mucociliary clearance (Leikauf et al., 1981; Lippmann et al., 1982; Leikauf et al., 1984; Lippmann et al., 1987; Spektor et al., 1989) and pulmonary function (Koenig et al., 1985; Utell et al., 1989)	Uncertainty factor: none stated	A2 notation, suspected Human Carcinogen

* mg/m³ unless otherwise stated
** Desirable but suitable measurement technique currently not available

Table A9: Silica (crystalline)

Country/Region	OEL mg/m³*	Key study/Critical effect	Risk assessment process	Comments
EU SCOEL	No recommendation			
German DFG	No MAK set (DFG, 2004)	Nine key cohort studies (Cherry et al., 1988; Costello and Graham, 1988; Guènel et al., 1989; Merlo et al., 1991; Chen et al., 1992; Costello et al., 1995; Dong et al., 1995; Checkoway et al., 1997) critical effects were silicosis, lung cancer	Uncertainty factor: N/A Silica was evaluated but no MAK value assigned because classified in Carcinogen category 1 (Greim, 2000)	DFG recommend preventing silicosis to reduce cancer risk based on increased incidence of lung cancer in workers with silicosis
The Netherlands DECOS	HBR-OEL, 8h-TWA, 0.075 (respirable quartz, cristobalite and tridymite)	Silicosis and lung cancer (Costello and Graham, 1988; Guènel et al., 1989)	Limit based on the NOAEL for silicosis following exposure to respirable quartz Uncertainty factor: none used	
UK HSE	MEL, 8-h TWA, 0.3 (HSE, 2002) Proposed WEL, 8-h TWA, 0.1	Silicosis (key studies not cited; HSE, 2001)	Uncertainty factor: none stated No NOAEL established; MEL based on level reasonably practicable by industry	
USA ACGIH	TLV, 0.05 (respirable quartz, cristobalite and tridymite; ACGIH, 2003a)	Lung fibrosis, silicosis, cancer (Hnizdo and Sluis-Cremer, 1993; Hnizdo et al., 1993)	Concern for role of fibrosis as a risk factor for lung cancer prompted ACGIH to reduce TLV from 0.1 to 0.05 mg/m³	A2 notation, suspected Human Carcinogen; a notice of intent to lower the TLV further to 0.025 mg/m³

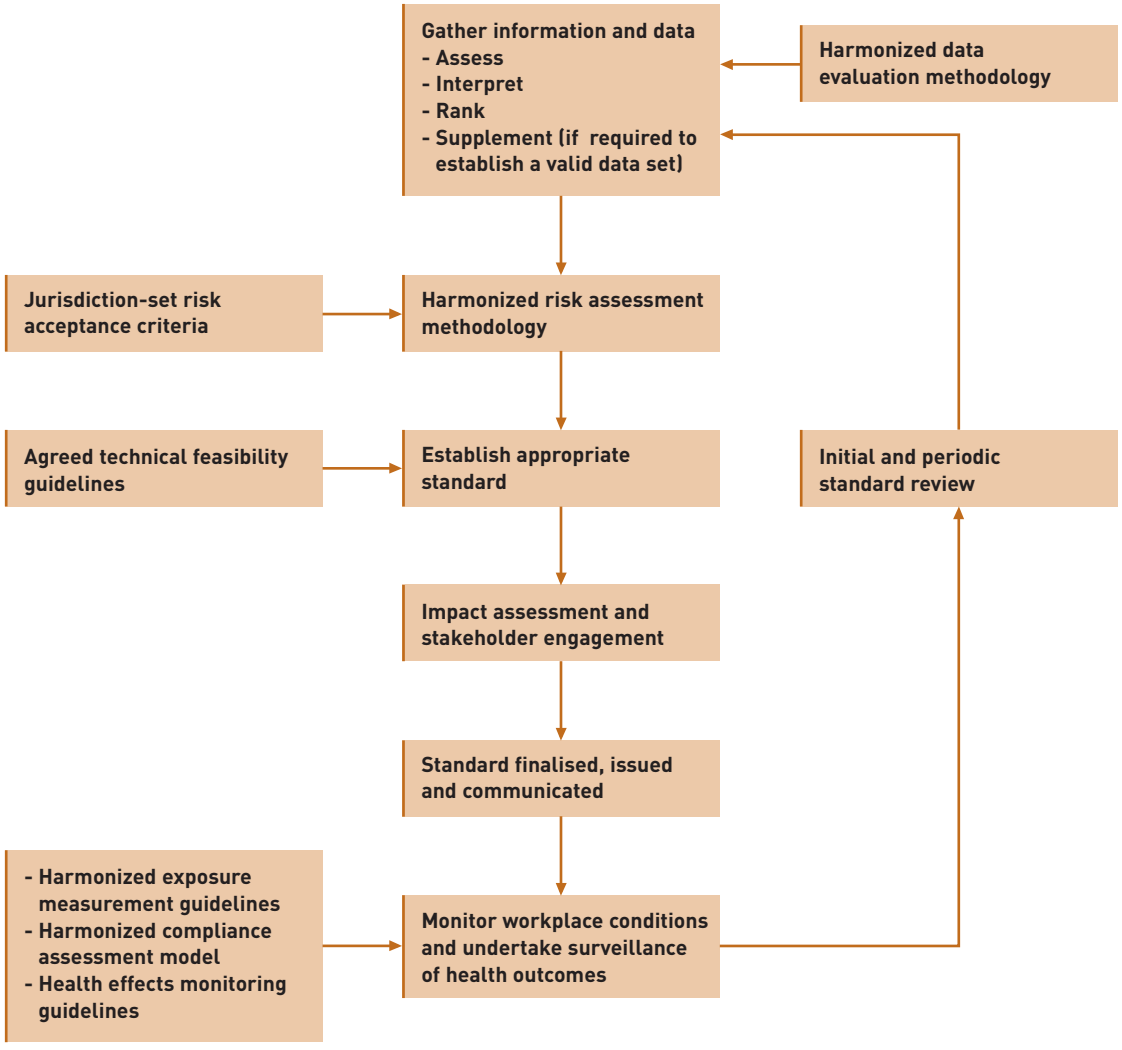
* mg/m³ unless otherwise stated

Annex 2
Industry Proposal for Harmonization in Setting OELs

As practitioners, representatives from the ICMM member companies have proposed a point from which a harmonized approach to the setting of OELs can be established.

Their approach, outlined in Figure A2.1, focuses on:
- a commonly-adopted process
- evidence-based decision making
- transparent risk acceptance criteria
- robust stakeholder engagement

Table A2.1: ICMM proposals for a harmonized approach to setting OELs



The approach seeks to achieve harmonization and agreement for the science-based elements of OEL setting, such as the collection and evaluation of data, and provides OEL-setting organizations with the opportunity to apply risk acceptance criteria consistent with their respective community norms.

Specific elements of the model relate to:

Harmonized data evaluation methodology
A proposal to develop and agree a systematic methodology by which data and evidence can be evaluated, assessed and agreed.

Harmonized risk assessment methodology
A proposal to establish, through wide stakeholder engagement a standardized approach to undertaking risk assessments on exposures and health effects.

Jurisdiction-set risk acceptance criteria
Recognition that risk acceptance criteria will vary between national and community groups dependent on their cultural acceptance of risks.

Agreed technical feasibility guidelines
Recognition that current scientific methods limit the lower levels of detectablity of agents in the workplace.

Impact assessment and stakeholder engagement
Recognition that the impacts, costs and benefits of changed exposure standards need to be understood and that a wide range of stakeholders need to be engaged.

Exposure measurement and compliance guidelines
A proposal to establish and agree guidelines to ensure that all stakeholders understand how exposures are to be measured and compliance is to be assessed.

Periodic reviews of OELs
Recognition that reviews or changes to existing OELs need to follow the same harmonized approach and should consider the results of worker health surveillance where available.

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