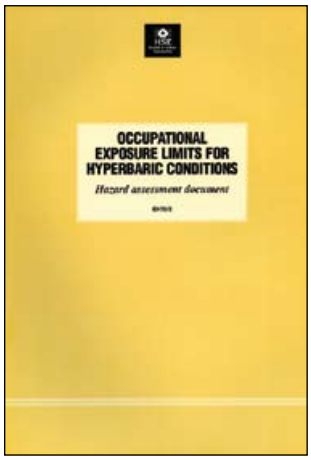
Occupational exposure limits for hyperbaric conditions

Hazard assessment document



This is a free-to-download, web-friendly version of EH75/2 (Fourth edition, published 1998). This version has been adapted for online use from HSE's current printed version.

You can buy the document at www.hsebooks.co.uk and most good bookshops.

ISBN 978 0 7176 1899 6
Price £7.50

This hazard assessment document examines the exposure to airborne contaminants under hyperbaric conditions such as diving and compressed air tunnelling work. It is aimed at a technical audience.

In Great Britain, Occupational Exposure Limits (OELs) are a potentially important element of the regulatory approach to the control of chemical exposure within these occupational settings.

The document describes the derivation of a methodology for the extrapolation of established OELs to the hyperbaric setting, taking into account of the changes in absolute pressure and exposure duration, such that the resultant Hyperbaric Occupational Exposure Limits (HOELs) represent adequate control for the hyperbaric environment.

First published 2000

ISBN 978 0 7176 1899 6

Contents

Introduction

This Hazard Assessment Document has been published by the UK Health and Safety Executive (HSE) and is aimed at a technical audience.

In Great Britain, substances which may cause harm to health are subject to the Control of Substances Hazardous to Health Regulations (COSHH) 1999. These Regulations require employers to prevent, or if this is not reasonably practical, adequately control employees' exposure to hazardous substances.

Hazard Assessment Documents are produced to facilitate the development of HSE' s regulatory position on a specific health related issue, which may relate to an individual hazardous substance or may involve consideration of more general issues related to chemicals and ill health. The documents in this series cover issues relating only to toxicological hazard; other document series address issues which involve consideration of occupational exposure and risk:

- Exposure Assessment Document - EH74 series;
- Risk Assessment Document - EH72 series

The data in Hazard Assessment Documents are assessed and endorsed by the Working Group on the Assessment of Toxic Chemicals (WATCH). WATCH makes recommendations to the Advisory Committee on Toxic Substances (ACTS) on all aspects of chemicals hazard and risk assessment and risk management issues, including recommendations for Occupational Exposure Limits and other aspects of occupational health risk management, as part of its assessment of the substance under discussion. Hazard Assessment Documents are published after their endorsement by WATCH.

Details of how to obtain HSE publications are on the back cover.

Summary

Exposure to airborne contaminants under hyperbaric conditions arises in occupations such as diving and compressed air tunnelling work. Occupational Exposure Limits (OELs) established in Great Britain are a potentially important element of the regulatory approach to the control of chemical exposure in these occupational settings. However, OELs are developed for exposures at normal pressure in air, and on the basis of an exposure pattern of 8 hours per day, 5 days per week. In the hyperbaric setting, OELs must apply to conditions of elevated pressure and, in the case of saturation diving, to periods of continuous exposure (24-hours per day for a period of days or weeks) breathing helium-oxygen mixtures. Therefore OELs which represent adequate control of exposure for conventional occupational scenarios at normal pressure will not necessarily represent adequate control under hyperbaric conditions.

There are no experimental data, in humans or animals, which explore the toxicity arising from exposure to industrial chemicals under hyperbaric exposure conditions. Limited data are available on the toxicokinetic behaviour of substances under hyperbaric conditions. Thus, there is no reliable experimental database from which to derive OELs for individual substances of concern in the hyperbaric setting. In the absence of data, it is considered appropriate to adopt a generic approach to extrapolate OELs derived for standard occupational exposure conditions to the hyperbaric environment.

However, in adopting a generic approach, the resultant hyperbaric OELs (referred to as HOELs) should, as far as possible, provide at least the same level of assurance of health protection as do the equivalent OELs under conventional occupational exposure conditions. This applies whether the OEL is a Maximum Exposure Limit (MEL) or an Occupational Exposure Standard (OES). Definitions of these two types of limits are given in the HSE publication, EH40.

The key issues involved in extrapolation of OELs to HOELs are the effects of the increase in the absolute pressure and, specifically in the case of saturation diving, the potential for extended continuous exposure to background levels of contaminants in the diving habitat.

In relation to the extrapolation of OELs to take account of the increase in absolute pressure, based on theoretical considerations and the limited experimental evidence available, it is concluded that adjustment on the basis of partial pressure is appropriate. The need for this extrapolation applies only to substances in gaseous or vapour form. The OEL (expressed in ppm units) should be linearly adjusted to ensure that the same partial pressure is maintained under all hyperbaric conditions. This can also be achieved by adherence to the OEL expressed in $mg.m^{-3}$ units.

In relation to adjustment of 8-hour time-weighted average (TWA) OELs for continuous exposure during saturation diving, linear extrapolation on the basis of a concentration x time relationship is proposed. Thus, the OEL should be adjusted downwards to take account of 168 hours exposure per week (24 hours per day for 7 days) rather than 40 hours exposure per week (8 hours per day for 5 days). This adjustment takes account of the potential for cumulative effects to arise as a result of continuous exposure. In line with the approach currently adopted in Great Britain by the Defence Evaluation and Research Agency in relation to continuous exposure of submariners, it is proposed that the 8-hour TWA OELs be reduced by a factor of S to derive the HOEL for hyperbaric work activities involving continuous exposure.

In relation to the short-term reference period for OELs, no adjustment is necessary to take account of continuous exposure. The IS-minute reference period will apply under hyperbaric conditions as it does under standard pressure conditions, to prevent effects arising from short-term peak exposures. Thus, the only adjustment of a IS-minute STEL OEL for the hyperbaric setting will be that required to take account of the increased pressure. Similarly, for occupational hyperbaric exposures other than saturation diving, where exposures may be based on an 8-hour or shorter working shift, no additional adjustment to the 8-hour TWA OEL, other than that to take account of increased pressure, is necessary.

As a result of adopting this approach, the resultant HOELs should provide a level of control that is at least, if not more, protective of health as that provided by the relevant OEL from which it is derived.

1 Background

Exposure to airborne contaminants under hyperbaric conditions arises in occupations such as diving and compressed air tunnelling work. Occupational Exposure Limits (OELs) established in Great Britain (GB) are a potentially important element of the regulatory approach to the control of chemical exposure in these occupational settings. However, OELs are developed for exposures at normal pressure in air, and on the basis of an exposure pattern of 8 hours per day, 5 days per week. In the hyperbaric setting, OELs must apply to conditions of elevated pressure and, in the case of saturation diving, to periods of continuous exposure (24-hours per day for a period of days or weeks) breathing helium-oxygen mixtures. Therefore OELs which represent adequate control of exposure for conventional occupational scenarios at normal pressure will not necessarily represent adequate control under hyperbaric conditions.

For OELs to define adequate control in the hyperbaric setting, as far as possible they must provide at least the same level of assurance of health protection as they do under conventional occupational exposure conditions. This applies whether the OEL is a Maximum Exposure Limit (MEL) or an Occupational Exposure Standard (OES).

Ideally, the development of OELs for the hyperbaric setting (hereafter referred to as Hyperbaric Occupational Exposure Limits, HOELs) would be based on knowledge of exposure-response relationships for individual substances of concern at different pressures. However, experimental data on the effect of exposure to individual substances under hyperbaric conditions, either in animals or in humans, is extremely limited. Therefore there is little or no possibility of establishing HOELs for substances in the hyperbaric setting on the basis of actual toxicological data. An alternative approach is to adopt a position based on extrapolation of established OELs. This document describes the derivation of a methodology for the extrapolation of established OELs to the hyperbaric setting, taking account of the changes in absolute pressure and exposure duration, such that the resultant HOELs represent adequate control for the hyperbaric environment.

2 General information on exposure

2.1 Occupational activities involving hyperbaric exposure

There are two main activities which involve exposure to chemicals under hyperbaric conditions: (i) compressed air tunnelling and (ii) commercial deep diving.

Commercial deep diving takes place at considerably higher absolute pressures than compressed air work which typically involves exposure at 200-300 kPa. In addition, commercial deep diving may involve saturation dive techniques. Saturation diving requires extended periods of living and working under hyperbaric conditions; under such conditions, there is the potential for continuous exposure to chemicals for extended periods. This assessment addresses hyperbaric occupational exposures, including exposures occurring during saturation diving and so covers human health issues surrounding chemical exposures at increased absolute pressure and under conditions of continuous exposure. Although the focus of the assessment is on saturation diving, the principles of extrapolation of OELs for changes in atmospheric pressure will be generally applicable to hyperbaric exposures occurring during non-saturation dives and compressed air tunnelling work.

Commercial deep diving around the British coast involves underwater work at depths of up to (typically) 150 metres beneath the sea surface. At these depths, the total pressure experienced will be up to about 1600 kPa. Gases are compressible at these increased pressures, whereas liquids and solids are not and so gas-filled spaces in the body will be subject to compression. Therefore, so that divers are able to work at such depths, the gases in their physiological air spaces must be equilibrated to the equivalent sea water pressure. This is achieved in a hyperbaric chamber, which forms the divers' main living habitat during an operational dive. The habitat is pressurised to the required working pressure and remains at the sea surface. A mobile diving bell, similarly pressurised, is used to transport the divers to the working depth in the water.

An additional factor in relation to hyperbaric work is that air is not used as the breathing gas at depths greater than about 50 metres (600 kPa). This is because of the narcotic properties of nitrogen, which become significant at elevated pressure. For deep diving, the standard breathing gas mixture used is heliox, a mixture of helium (chosen because of its low density and low narcotic potency) and oxygen.

During hyperbaric exposure, the chemically inert gas constituents of the breathing gas (nitrogen in the case of air breathing, or helium in the case of heliox) dissolve into the blood and tissues; the longer the time spent at pressure, the more gas becomes dissolved, until the blood and tissues reach saturation. During decompression, the opposite process occurs, and dissolved gas comes out of solution in the blood and tissues; if the decompression is too rapid, gas bubbles form in blood and tissues, which can have severe and potentially fatal consequences. The various physiological consequences of bubble formation are termed decompression illness. The appropriate rate of decompression is determined by the degree of saturation of the blood and tissues with inert gas, which in turn depends on the time spent at pressure and the absolute pressure reached. Once the tissues reach saturation, a fixed time period for decompression will be required, regardless of how much subsequent time is spent at pressure. Decompression times are long relative to compression times and time to reach saturation. For this reason, for longer duration operations at high pressure, the

most efficient means of completing the work is to operate saturation diving techniques, in which the divers remain at pressure for an extended period, living and working under these hyperbaric conditions. A saturation dive may involve exposure under hyperbaric conditions for up to four weeks; decompression from such dives requires several days.

3 Extrapolation of OELs to take account of increased absolute pressure

3.1 Basic principles

Extrapolation of OELs to take account of an increase in absolute pressure applies only to substances in the gas or vapour state. This is because gases are compressible at the increased pressures associated with hyperbaric exposures, whereas liquids and solids are not. The physical behaviour of substances in the gaseous state is therefore dependent on absolute pressure, whereas that of solid particulates and liquid aerosols is not. Thus, adjustment of GELs for particulates and aerosols to take account of a change in absolute pressure is unnecessary; the numerical value of the OEL ($mg.m^{-3}$) will be appropriate regardless of the pressure conditions.

A brief discussion of the principles underlying the behaviour of gases at increased absolute pressure is given below.

3.1.1 Partial pressure

Gases expand to fill the available space in which they are contained and in doing so, exert a pressure which is related to the number of molecules, or mass of gas, present in that volume. If a single gas is present in a fixed volume, then the total pressure will be the pressure exerted by that gas as it expands into the volume. The pressure is therefore determined by the amount of gaseous substance per unit volume. If a mixture of gases is present in a fixed volume, then the total pressure will be the sum of the pressures exerted by each individual gas in the mixture.

Partial pressure is the term given to the pressure exerted by an individual gas in a mixture and is directly related to the proportion of the gas in the mixture (Dalton's Law):

partial pressure = total pressure x proportion of gas present

For example, air is made up primarily of 78% nitrogen and 21% oxygen. The total pressure exerted by air at sea level is 101.3 kPa. The partial pressure of these two individual components of air is:

nitrogen partial pressure = 101.3 kPa x 78/100 = 79 kPa

oxygen partial pressure = 101.3 kPa x 21/100 = 21 kPa

If another gas or vapour is present in the atmosphere, then this will also exert a partial pressure according to its proportion in the atmosphere. Thus, for example, 20 parts per million (ppm) hexane (where ppm represents a vol/vol concentration) at standard atmospheric pressure (101.3 kPa) exerts a partial pressure of:

101.3 kPa x 20/1 000 000 = 2 Pa

Similarly, any OEL can be expressed as a partial pressure on the basis of its proportion in the atmosphere i.e. its vol/vol concentration. Thus, the 8-hour TWA OES for hexane is 20 ppm, which, as indicated above, equates to a partial pressure of 2 Pa under standard atmospheric pressure conditions.

3.1.2 Pressure changes

In relation to commercial deep diving, the habitat and bell are compressed to the required working pressure by the addition of heliox. As long as the volume of the working space is fixed, then the partial pressure of each of the individual gas components will be related to the number of molecules, or mass of each gas component in that volume. If the habitat at normal atmospheric pressure contains a mixture of 80% helium, 20% oxygen, the partial pressure of each of these individual gas components is:

helium partial pressure = 101.3 kPa x 80/100 = 81 kPa

oxygen partial pressure = 101.3 kPa x 20/100 = 20 kPa

If the chamber is then pressurised to 500 kPa by the addition of further heliox in the same relative proportions, then the partial pressures of the individual gases increase by 5-fold:

helium partial pressure = 500 kPa x 80/100 = 400 kPa

oxygen partial pressure = 500 kPa x 20/1 00 = 100 kPa

If the chamber at standard atmospheric pressure contains 20 ppm hexane, its partial pressure is 2 Pa. However, at 500 kPa, 20 ppm of hexane will exert a partial pressure of 10 Pa (500 kPa x 20/1 000 000).

Since the partial pressure of an atmospheric component is related to the number of molecules, or mass per unit volume, then an increase in partial pressure represents an increase in the mass of hexane present per unit volume. Thus, at 101.3 kPa absolute pressure, 20 ppm hexane, with a partial pressure of 2 Pa, is equivalent to 72 $mg.m^{-3}$. At 500 kPa absolute pressure, 20 ppm hexane with a partial pressure of 10 Pa, is equivalent to 360 $mg.m^{-3}$.

Thus, to maintain the same mass/vol concentration of hexane in a chamber pressurised to 500 kPa as at standard pressure, the partial pressure must be maintained at 2 Pa. The atmospheric vol/vol concentration of hexane must therefore be reduced by a factor proportional to the increase in absolute pressure. At 500 kPa, a partial pressure of 2 Pa hexane is equivalent to 4 ppm. In terms of the OEL, to maintain the same partial pressure, the OEL of 20 ppm (8-hour TWA) under standard pressure conditions would be equivalent to 4 ppm (8-hour TWA) at 500 kPa.

Alternatively, given that partial pressure is dependent on mass/vol concentration, an OEL expressed in $mg.m^{-3}$ could be applied without adjustment for absolute pressure to maintain a constant partial pressure under all hyperbaric conditions.

3.2 Toxicological response to chemicals under hyperbaric conditions

The effect of increased absolute pressure on toxicity has not been explored for industrial chemicals. However, there is a relatively extensive database relating to

the effects of oxygen, nitrogen and carbon dioxide at increased pressure and it is known from experimental observations in humans that the effects of exposure to these gases under hyperbaric conditions are related to partial pressure: the toxic and narcotic effects of oxygen under hyperbaric conditions are related to partial pressure, as are the narcotic properties of nitrogen and carbon dioxide (e.g. Balentine, 1982; Bennett, 1993; Clarke, 1993). On the basis of these observations, it seems reasonable to propose that the effect of exposure to industrial chemicals under hyperbaric conditions will be similarly related to partial pressure.

There is a limited amount of experimental data on the toxicokinetic behaviour of substances under hyperbaric conditions which gives some support to the proposal that toxicity will be related to partial pressure. This information is summarised briefly below. It is also possible to consider the theoretical basis for a relationship between toxicity and partial pressure, in relation to both systemic and local effects; this is addressed in section 3.2.2.

3.2.1 Experimental data on the toxicokinetic behaviour of substances under hyperbaric conditions

The effect of hyperbaria on the toxicokinetics of toluene has been investigated in male Sprague-Dawley rats (Nilsen *et al*, 1987). Absorption and distribution of toluene under different pressure conditions and after various exposure durations was investigated in two male rats per group. Animals were exposed whole body by inhalation to 0.28 or 3.75 $mg.l^{-1}$ toluene vapour (equivalent to a partial pressure of about 7 or 100 Pa respectively) for 0.5-8 hours at standard atmospheric pressure (101.3 kPa) or at 1100, 2100, 3100 or 4150 kPa. The elimination of toluene from blood and tissues under hyperbaric conditions was investigated in groups of 2 male rats exposed to 3.75 $mg.l^{-1}$ toluene for 2 hours at standard atmospheric pressure and then maintained for 0.5-8 hours at standard atmospheric pressure or at 1100 or 4150 kPa. The pressure was increased by the addition of helium to the chamber. Oxygen partial pressure was 20 kPa at standard atmosopheric pressure and 50 kPa for all hyperbaric exposures. These conditions were designed to be comparable to actual diving exposure conditions.

Absorption of toluene was assessed by measurement of the total volume of toluene added to the chamber to maintain a constant chamber concentration during the exposure period. Following exposure, in each of the absorption and elimination studies, animals were sacrificed immediately after a 5 second decompression period and blood, brain, liver, kidney, testes and perirenal fat samples analysed for toluene. Blood and tissue samples were stored in sealed head space vials within 20 minutes from the start of decompression.

Hyperbaria reduced the absorption of toluene compared with that at standard atmospheric pressure. At 0.28 $mg.l^{-1}$, uptake was reduced by about 30% at all pressures; at 3.75 $mg.l^{-1}$, uptake was reduced by about 18-27%, with the greatest reduction at 1100 kPa. This reduction in uptake was reflected in the blood and tissue concentrations of toluene, which were generally lower under hyperbaric conditions; the lowest mean concentrations were generally found at 1100 kPa. There was no apparent effect of hyperbaria on the pattern of distribution of toluene into the various tissues and blood. Toluene was measured in all tissues sampled, with the highest concentrations found in the perirenal fat at both exposure concentrations. Tissue:blood ratios ranged between about 50 and 105 at all pressures for perirenal fat, compared with ratios of about 1.5-6 for other tissues. In most tissues, toluene concentration generally increased towards a plateau after about 1-2 hours following exposure to 0.28 $mg.l^{-1}$ toluene, and after about 6-8 hours following exposure to 3.75 $mg.l^{-1}$, at all pressures. An exception to this general pattern was the concentration of toluene in perirenal fat, for which the time

to reach steady-state concentration was longer or not achieved within the period of exposure: a plateau in tissue concentration appeared after about 4-8 hours exposure to 0.28 $mg.l^{-1}$; at 3.75 $mg.l^{-1}$, the concentration in perirenal fat continued to show an increase at 8 hours, the longest exposure duration. In addition, after 8 hours exposure to 3.75 $mg.l^{-1}$, the mean concentrations of toluene in perirenal fat measured at 3100 and 4150 kPa exceeded the concentration measured at 1100 kPa, by 12%.

Elimination of toluene was found to be similar at standard atmospheric pressure and 1100 kPa. However, at 4140 kPa, there was some evidence for a slightly increased rate of elimination during the 4-8 hours post-exposure. Elimination from perirenal fat was slower than for other tissues and blood, under all pressure conditions.

Overall, although limited in terms of the small numbers of animals investigated per group, this study indicates that increased pressure appears to reduce the absorption of toluene, to a moderate extent and in an irregular manner, but appears not to influence significantly subsequent tissue distribution nor elimination (there were only small changes at very high pressures of 3100 and 4150 kPa). Whilst it is possible that some absorbed toluene may have been lost to analysis due to the time taken to collect and seal the samples post-decompression, this is unlikely to explain the pattern of results seen, as any such loss would affect the results for all hyperbaric exposures in a similar manner. Hence the pattern of results is probably real. The reasons for the reduction in the uptake of toluene at increased absolute pressure are not clear; the influence of various factors, other than the change in pressure alone, may be involved. The change in gas composition, oxygen partial pressure and ambient temperature may have some influence on partitioning and absorption into tissues, as well as on physiological parameters such as ventilation rate and blood flow; the relative importance of these factors may vary at different hyperbaric conditions, which could result in the differing pattern of uptake seen.

A recent review of the available evidence for the effects of hyperbaria or hyperoxia on the distribution of pharmacological agents is available (Rump *et al*, 1999). This identified a number of studies, in both animals and humans, in which the effect of exposure to pharmacological agents on various toxicokinetic parameters has been investigated during exposure up to 600 kPa, breathing air or 100% oxygen. Overall, these studies have found no effect of hyperbaria itself (i.e. increased pressure with normal oxygen partial pressure) on any of the measured toxicokinetic parameters, namely elimination half-time, clearance rate or volume of distribution.

Limited additional information that metabolism or elimination is generally unaffected by pressure is available from studies of anaesthesia under hyperbaric conditions.

Halsey *et al* (1978) investigated the effects of pressure on anaesthesia in groups of 10-12 male rats exposed by intravenous infusion to each of four barbiturate agents at up to 10^4 kPa. Although not specifically designed to investigate metabolism of these agents, the authors suggested that some information on metabolism could be derived from the results. The level of anaesthesia was estimated by the percentage of animals responding to an electrical stimulus at each anaesthetic dose. The dose required to maintain a particular level of anaesthesia for each agent was shown to be increased at increased pressure. However, the slope of the dose-response curve (i.e. percentage of animals responding to the stimulus at each anaesthetic dose) was unaffected by hyperbaria. In addition, the time to recover consciousness from a defined level of anaesthesia following cessation of the anaesthetic infusion was the same at high pressure as at normal atmospheric pressure. Both these findings were interpreted by the authors to indicate that metabolism of each agent was not affected by the increase in pressure. However,

this conclusion is uncertain, given that the extent to which metabolism is involved in the anaesthetic action is unknown.

In a study of pressure reversal of one anaesthetic agent in humans, the potential for changes in the elimination of the agent from the blood was investigated by measurement of plasma levels of the anaesthetic at various time points during administration via an in-dwelling intravenous catheter (Dundas, 1998). Based on data from three volunteers at 2100 kPa and from two volunteers at 1100 kPa, there was no evidence for a change in elimination rate of the anaesthetic agent at increased pressure.

3.2.2 Theoretical considerations

3.2.2.1 Systemic toxicity

In relation to passive uptake of substances into the body, the partial pressure of a gas determines its dissolution into tissues, fats, blood and water. The relationship between partial pressure and solubility into liquid media is expressed by Henry's Law:

$$V = k \times p$$

where V = volume of dissolved gas; k = solubility coefficient; p = gas partial pressure.

Maintaining the same partial pressure of a substance under different hyperbaric conditions should therefore result in the same degree of dissolution into the tissues and blood following exposure by the main routes of occupational relevance, inhalation and dermal exposure. Therefore, the amount of substance absorbed under hyperbaric conditions will depend on the partial pressure. If the partial pressure of a substance in the atmosphere is constant under all hyperbaric conditions, then the absorbed dose of that substance should also be constant for a given set of exposure parameters under all hyperbaric conditions. Assuming that the subsequent toxicokinetic behaviour and toxicodynamic response is unaffected by pressure itself, then the systemic toxicity of a substance should be determined by its partial pressure under any hyperbaric exposure conditions.

Although limited, the experimental toxicokinetic data summarised in section 3.1.1 suggest that at a constant partial pressure, absorption may be reduced under hyperbaric exposure conditions. However, once absorbed, there is no indication from the available data that the subsequent toxicokinetic behaviour of a substance, in terms of distribution, metabolism and elimination, is significantly affected by hyperbaria.

Thus, on this basis, maintaining a constant partial pressure under hyperbaric exposure conditions should result in equivalent or lower uptake of a substance and equivalent subsequent metabolism, leading to an expected level of systemic toxicity comparable to that at normal atmospheric pressure.

3.2.2.2 Local toxicity

Local toxicity, such as sensory irritation, is related to the local tissue concentration of a substance at the site of contact. Therefore if the local tissue concentration is the same under hyperbaric conditions as under normal pressure conditions, the potential for local toxicity should be same. Local tissue concentration is a reflection of the number of molecules per unit volume, or mass per unit volume. In

a hyperbaric chamber, maintaining a constant mass of substance per unit volume will maintain its partial pressure. Therefore, by ensuring the same partial pressure of a substance under all hyperbaric conditions, the local tissue concentration of the substance will also remain constant and the potential for local toxicity will be unchanged.

3.3 Summary and conclusions

Partial pressure is the conventional unit used to describe airborne concentrations of gases and vapours under hyperbaric exposure conditions. The partial pressure of a gaseous component of the atmosphere will be a determinant of its uptake into the body and once absorbed, the available evidence, although limited, suggests that the subsequent toxicokinetic behaviour is unaffected by hyperbaria. There is no information on the toxicological response to industrial chemicals under hyperbaric exposure conditions. However, experimental observations in humans show that the toxicological response to oxygen, nitrogen and carbon dioxide under hyperbaric exposure conditions is related to the partial pressure of these gases. Thus, in relation to systemic' toxicity, it seems reasonable to conclude that the potential for toxicity will be related to partial pressure.

In relation to local effects, local tissue concentration will be the key determinant of toxicity. Again, there is no experimental information on the local effects of exposure to industrial chemicals under hyperbaric conditions. However, local tissue concentration (mass per unit volume concentration) is related to partial pressure, such that if partial pressure is constant, the tissue concentration will be also be constant under all hyperbaric conditions. The potential for local toxicity is therefore predicted to be determined by partial pressure.

Overall, adjustment of OELs based on maintaining a constant partial pressure under all hyperbaric exposure conditions is an appropriate approach, in the absence of experimental data on the toxicity of individual chemicals at high atmospheric pressures. Thus, the numerical value of the OEL expressed in ppm units must be linearly adjusted in proportion to the increase in absolute pressure. Since partial pressure is determined by the mass of gas per unit volume, rather than converting OELs in ppm units, adherence could be to the OEL in mg.m-3 units under all hyperbaric conditions.

In relation to OELs for particulates and aerosols, since the physical behaviour of substances in this state is unaffected by changes in ambient pressure, adjustment of the OELs to take account of a change in pressure is unnecessary. Thus, for OELs which apply to substances in particulate or aerosol form, the OEL value (in $mg.m^{-3}$) should apply under all hyperbaric exposure conditions.

4 Extrapolation of OELs to take account of increased exposure duration

4.1 Introduction

Exposure to toxic substances during commercial deep diving could occur in a number of ways, for example, as a result of suit contamination whilst working in the water, which is subsequently transferred to the diving bell from the diver's clothing. Each time the diver transfers between the diving bell and the habitat, there will be a mixing of the atmosphere between the two chambers. Thus, during saturation diving, any contamination of the atmosphere of the diving bell may be transferred to the habitat atmosphere. Another potentially important source of contamination is off-gassing from materials within the habitat. A programme of monitoring for atmospheric contaminants in the diving habitat has been undertaken by the diving industry. A list of substances which have been detected in the atmosphere of a diving bell and habitat is attached at Appendix A.

The breathing gas supply to the diving bell and surface habitat is re-circulated following removal of carbon dioxide and replenishment of oxygen. Therefore if contamination of the breathing gas supply occurs, there is the potential for continuous exposure to the substance in the re-circulated gas supply within the habitat. Since 8-hour TWA OELs are derived for 'standard' work shifts of 8-hours per day, 5 days per week, their application to the hyperbaric situation must take account of this potential for continuous exposure. In a worst case situation, if contamination occurs early in the duration of the dive period, then continuous exposure could occur for up to 4 weeks.

For occupational hyperbaric exposures other than saturation diving, where exposures may be based on an 8-hour or shorter working shift, no additional adjustment to the 8-hour TWA OEL, other than that to take account of partial pressure considerations, is necessary.

4.2 Adjustment of 8-hour TWA OEL

4.2.1 Mathematical models

Various mathematical models of varying complexity have been developed to derive OELs for 'unusual' work shifts. However, no model has been developed specifically for continuous exposure scenarios. A review of the various models which have been published in the scientific literature is given by Paustenbach (1994).

The accurate adjustment of 8-hour TWA OELs to take account of non-standard exposure periods requires an understanding of the toxicokinetics of the substance, its toxicological effects and the underlying mechanism for those effects and the basis on which the OEL was derived. The better the understanding and awareness of each of these factors, the more precise will be any adjustment, because it can be better tailored to take account of these various elements.

The most accurate mathematical models which have been developed to adjust OELs for non-standard work shifts are those which take account of

the toxicokinetic behaviour of the substance in question. These so-called pharmacokinetic models take into account the influence of biological half-life in determining the resultant body burden of a substance arising from a particular exposure regime. A number of pharmacokinetic models have been developed, although all are relatively similar in their approach and resultant outcome (Paustenbach, 1994).

Information on various toxicokinetic parameters is required to use these models. For many substances, the required toxicokinetic information may not be available. For this reason, and because of the potential complexity of pharmacokinetic models, this approach to the adjustment of OELs is not readily applicable to many substances. For this reason, simpler approaches have been developed. These are discussed below.

4.2.2 Linear adjustment

The simplest adjustment to an 8-hour TWA OEL to take account of an extended exposure period is to assume that the toxicological response is related to the body burden; this in turn is a function of exposure concentration x time ($c \times t$; Haber' s rule). Thus, an 8-hour TWA OEL specifies a particular exposure concentration for an 8-hour exposure period. This can be linearly adjusted to ensure the same body burden ($c \times t$) for a 24-hour exposure period:

OEL (24-hour TWA) = OEL (8-hour TWA) x 8/24

= OEL/3

A similar approach to the calculation of exposure in any 24-hour period in relation to the 8-hour reference period is approved by the Health and Safety Commission (EH40).

However, as this is based on adjustment for a single, daily exposure, it does not address the potential for substances to accumulate in the body over a longer period of continuous exposure. Nor does it take account of the absence of an exposure-free period during continuous exposure, which could normally provide the potential for recovery from any toxic insult.

In recognition of this, an alternative is to adjust the OEL on the basis of a weekly dose, assuming 'that the OEL applies to a 40-hour working week. Thus, for a 24-hour continuous exposure for a 7-day week (168 hours), the adjustment would be:

OEL (24-hour TWA) = OEL (8-hour TWA) x 40/168

= OEL/4.2

This latter approach would be more appropriate for the hyperbaric situation, as it takes at least some account of the potential for cumulative effects as a result of continuous exposure over a prolonged period.

An approach based on the assumption of a $c \times t$ relationship, either for daily or weekly exposure, has advantages over the use of pharmacokinetic models in that it requires no information on toxicokinetic parameters and can be applied generically. It is possible that for many substances (for example, substances with a very short or very long biological half life) the $c \times t$ adjustment will be more conservative than adjustment based on a pharmacokinetic model, because of the over-simplification involved. This can be demonstrated by comparison of the simple $c \times t$ model with a

more complex pharmacokinetic model for an individual substance (Paustenbach, 1994).

There are uncertainties surrounding the general applicability of the c*x*t relationship, and not all substances will behave according to a c*x*t relationship. For example, the c*x*t relationship will not apply to substances for which irritation of the mucous membranes is the lead or only toxicological effect; for such substances there will be a clear concentration threshold below which there will be no irritation effects regardless of the exposure duration. Nevertheless, adjustment of OELs on the basis of a simple c*x*t relationship would provide a simple, generic approach to deriving HOELs. If this generic approach is adopted, then given that in a worst-case scenario, exposure could be continuous for a period of up to 4 weeks, it is considered that the more conservative of the c*x*t adjustment approaches would be appropriate i.e. adjustment based on 24 hour/day, 7 days/week exposure.

This adjustment, based on OEL/4.2 is the starting basis for the approach currently adopted by the Defence Evaluation and Research Agency (DERA) to adjust GB OELs to derive Continuous Exposure Standards (CESs) for application in the submarine environment. During operational duty, submariners are exposed continuously to the submarine atmosphere and any contaminants in it, for periods of several weeks. The CESs derived by DERA are derived on the basis of the OEL/5, rather than 4.2, which provides a small additional uncertainty factor.

In terms of the potential for continuous exposure to atmospheric contaminants, the submarine environment is comparable to saturation diving. It therefore seems appropriate to ensure a consistency of approach in relation to extrapolation of GB OELs for application in a continuous exposure situation. Thus it is proposed that the approach currently adopted by DERA to derive CESs is also adopted as a generic approach to adjust HOELs for continuous exposure. Thus, following adjustment for elevated pressure, HOELs would be derived as follows:

$$\text{HOEL (24-hour TWA)} = \text{OEL (8-hour TWA; mg.m}^{-3}\text{)}/5$$

However, it should be noted that this is a generic approach, and there may be some substances for which the biological half-life is such that this approach does not represent an adequate adjustment of the HOEL. Where appropriate, consideration should be given to the need to apply a larger adjustment factor for continuous exposure, where toxicokinetic and toxicological information indicates a particular concern for the effects of continuous exposure.

4.3 Adjustment of 15-minute STEL OEL

The 15-minute reference period is normally specified to prevent effects arising from short-term peak exposures. The need to prevent such effects will be the same under hyperbaric conditions as at normal ambient pressure. Thus, no time-related adjustment of a 15-minute STEL OEL is necessary for the hyperbaric setting.

5 Overall summary and conclusions

There are no experimental data, in humans or animals, which explore the toxicity arising from exposure to industrial chemicals under hyperbaric exposure conditions. Only limited data are available on the toxicokinetic behaviour of substances under hyperbaric conditions. Thus, there is no clear basis from which to derive HOELs for individual substances of concern for the hyperbaric setting. In the absence of such data, it is considered appropriate to adopt a generic approach to extrapolate OELs derived for standard occupational exposure conditions to the hyperbaric environment.

However, in adopting a generic approach, the resultant HOELs should, as far as possible, provide at least the same level of assurance of health protection as do the equivalent OELs under conventional occupational exposure conditions. This applies whether the OEL is a Maximum Exposure Limit (MEL) or an Occupational Exposure Standard (OES).

The key issues involved in extrapolation of OELs to HOELs are the effects of the change in the absolute pressure and, specifically in the case of saturation diving, the potential for continuous exposure to background levels of contaminants in the diving habitat.

Based on theoretical considerations and the limited experimental evidence available, it is concluded that adjustment of OELs on the basis of partial pressure is appropriate. The need for this extrapolation applies only to substances in gaseous or vapour form. The OEL (expressed in ppm units) should be linearly adjusted to ensure that the same partial pressure is maintained under all hyperbaric conditions. This can be achieved by adherence to the OEL expressed in $mg.m^{-3}$ units.

In relation to adjustment of 8-hour TWA OELs for continuous exposure, pharmacokinetic models are available which could be used to derive an GEL for continuous exposure based on predictions of toxicokinetic behaviour. However, such models are potentially complex to apply and require information on a number of toxicokinetic parameters. Such information may not be available for the majority of substances of relevance to the hyperbaric setting. A simpler approach, which can be applied generically, is to extrapolate OELs on the basis of a concentration x time relationship. To allow for the potential for cumulative effects, this should be based on consideration of continuous 24 hour/day exposure over a 7-day period. In line with the approach currently adopted by DERA in relation to continuous exposure of submariners, it is proposed that HOELs should be derived on the basis of the 8-hour TWA OEL/5.

Thus, for example, using this approach, the HOEL for hexane at 500 kPa would be derived as follows:

Exposure conditions	(H)OEL (8-hour TWA)		
	ppm	$mg.m^{-3}$	Pa
101.3 kPa; 8 hours/day	20	72	2
500 kPa; 8 hours/day	4	72	2
500 kPa; 24 hours/day	0.8	14.4	0.4

In relation to the short-term reference period for OELs, no further adjustment to take account of continuous exposure is necessary. The 15-minute reference period will apply under hyperbaric conditions as at normal ambient pressure, to prevent effects arising from short-term peak exposures. Similarly, for occupational hyperbaric exposures other than saturation diving, where exposures may be based on an 8-hour or shorter working shift, no additional adjustment to the 8-hour TWA OEL, other than that to take account of partial pressure considerations, is necessary.

As a result of adopting this approach, the resultant HOELs should provide a level of control that is at least, if not more, protective of health as that provided by the relevant OEL from which it is derived.

6 References

Balentine ID (1982)
Oxygen intolerance. *In*: Pathology of Oxygen Toxicity. Ed. ID Balentine. New York: Academic Press.

Bennett PB (1993)
Inert gas narcosis. *In:* The Physiology and Medicine of Diving 4th Edition. Ed. P Bennett & D Elliott. London: WB Saunders Ltd.

Clarke JM (1993)
Oxygen toxicity. *In*: The Physiology and Medicine of Diving 4th Edition. Ed. P Bennett & D Elliott. London: WB Saunders Ltd.

DEA Ltd (1986)
Suggested limits for contaminants in hyperbaric chambers.
Offshore Technology Report OTH 86 262, Department of Energy.

Dundas CR (1998)
Anaesthesia at hyperbaric pressure.
Offshore Technology Report OTO 98 826, HSE.

Halsey MJ, B Wardley-Smith and CJ Green (1978)
Pressure reversal of general anaesthesia - a multi-site expansion hypothesis.
British Journal of Anaesthesia **50**; 1091-1097.

Nilsen A, K Zahlsen and OG Nilsen (1987)
Hyperbaric toxicology. Uptake, distribution, accumulation and elimination of toluene in the rat.
Sintefreport no: STF23 A87103. ISBN: 82-595-4754-6.

Paustenbach DJ (1994)
Occupational exposure limits, pharmacokinetics, and unusual work schedules.
In: *Patty's Industrial Hygiene and Toxicology, Third Edition, Volume 3, Part A*. Edited by RL Harris, LJ Cralley and LV Cralley. ISBN 0-471-53066-2.
John Wiley & Sons, Inc.

Rump APE, U Siekmann and G Kalff (1999)
Effects of hyperbaric and hyperoxic conditions on the disposition of drugs: theoretical considerations and a review of the literature.
General Pharmacology. **32**; 127-133.

Appendix

Trace volatile organic compounds detected in the atmosphere of a diving bell and habitat

The following volatile organic compounds (VOCs) have been detected in trace amounts in the atmosphere of a diving bell and habitat during a programme of monitoring of typical operational dives over a period of 9 months, in 1998/99. The samples were collected on Tenax tubes with subsequent thermal desorption and analysis by gas chromatography-mass spectrometry .

Benzene
Butoxyethanol
Cl 1- Alkanes
Cl 2- Alkanes
C9-Aromatics
Chloroform
Cyclohexane
Dichloromethane
Ethylbenzene
2-Ethylhexanol
Eucalyptol
Iso-Heptanes
Iso-hexane
Limonene
Methyl-1,3-butadiene
Methylchloroform
Methylcyclohexane
Methylcyclopentane
n-Decane
n-Heptane
n-Hexane
n-Nonane
n-Octane
Octanol
Pentane
Pinene
Tetrachloroethylene
Toluene
Trichloroethylene
Xylenes

Further information

For information about health and safety, or to report inconsistencies or inaccuracies in this guidance, visit www.hse.gov.uk/. You can view HSE guidance online and order priced publications from the website. HSE priced publications are also available from bookshops.