A health risk assessment of working in hypoxic atmospheres

Prepared by the Health and Safety Executive
Hypoxic atmospheres - those in which the ambient oxygen level is lower than normal – may be specifically generated in some workplaces, particularly for fire prevention. Such atmospheres potentially present a health risk to workers who are required to enter the hypoxic space. This report reviews the impact of hypoxia on human physiology, behaviour, and cognitive function, in order to provide information about the potential occupational health risks arising from working in hypoxic atmospheres.

The available evidence suggests that hypoxic environments in which the levels of oxygen are greater than 15% but below 21%, are safe for most healthy, fit individuals. However, prior to entry into such environments, risk assessments should be performed to cover: the working environment; the work and tasks undertaken; and the worker. Occupational health assessments should be in place for all workers who have a potential requirement to enter these atmospheres. Careful consideration should be given to: workers carrying out tasks that require higher levels of physical activity; and pregnant workers.

For hypoxic working environments between 12% and 15% oxygen, there is a lack of evidence-based or expert consensus-led guidance that addresses medical conditions and their severity. There is therefore an insufficient evidence-base to provide guidelines for safe working in hypoxic environments between 12-15% oxygen, other than relating to the use of supplemental oxygen.

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A health risk assessment of working in hypoxic atmospheres

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Published evidence suggests that working in hypoxic environments from below 21%\(^1\) down to 15% oxygen is safe for most healthy individuals. Much of this evidence is however, based on individuals who are sedentary so greater care needs to be taken when the levels of physical activity are increased. A risk assessment is required when any entry is made into an environment where the levels of oxygen are reduced below 21%.

For hypoxic working environments with levels of oxygen between 12-15%, published evidence is even more limited, relating to studies of highly selected volunteer populations, and therefore not directly applicable to the general working population. There is therefore an insufficient evidence-base to provide guidelines for safe working in hypoxic environments between 12-15%, other than relating to the use of supplemental oxygen.

The risk assessment should be carried out for all hypoxic facilities prior to anybody entering the environment and should include consideration of the following:

- **Working environment**
  - Degree of O\(_2\) deficit
  - Control around the set working level of oxygen *i.e.* minimum level oxygen
  - Contaminants *e.g.* dusts, carbon monoxide, carbon dioxide
  - Environmental temperature
  - Size and layout and the ease of escape from the installation
  - Means of communicating problems to the outside from inside the installation
  - Effects of a failure of the engineering system producing and controlling oxygen levels

- **Work and tasks**
  - Duration of the working time
  - Working pattern *e.g.* number of entries
  - Type and level of physical activity
  - Supervision of all workers with particular attention being paid to lone workers

- **The worker**
  - Age
  - Level of physical fitness
  - Smoking status
  - Pregnancy
  - Existing medical conditions

Occupational health assessments should be carried out on all individuals who may be required to enter the hypoxic facility. These ‘fitness to work’ assessments should take into account the working environment, including the work and tasks to be carried out by the worker. The age, level of physical fitness, whether or not they are a smoker or pregnant and any medical conditions also need to be considered. These occupational health assessments should take the form of pre-placement ‘fitness to work’ assessments with regular review.

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\(^1\) Dry air at sea level contains 20.95% O\(_2\) (Linde, 1997). For the purposes of this report the figure has been rounded up to 21%.
Hypoxic atmospheres are being installed in particular workplaces as a fire prevention measure and therefore workers may be required to work in reduced oxygen (O₂) atmospheres, which may be potentially hazardous as they can cause hypoxia (low levels of O₂ in the body). The aim of this work is to review the impact of hypoxia on human physiology, behaviour and cognitive function, and to understand the potential medical implications.

Individual physiological, behavioural and cognitive responses to hypoxia are very variable. Much of the literature refers to healthy individuals with a high level of physical fitness (e.g. mountaineers or athletes). The literature can be contradictory and it is often difficult to verify research results from multiple sources. This report attempts to reach some consensus.

**Physiological effects of hypoxia**

As hypoxia can have adverse effects, the body always tries to maintain normal levels of blood gases by a series of integrated responses of the pulmonary system, cardiovascular system and changes to the composition of the blood. This means that the body responds to hypoxia by an increase in the breathing rate and depth, and heart rate. In most healthy adults, the level of O₂ in the air can fall to 15-16% before any of these compensatory mechanisms start to take place. It is this insensitivity to low O₂ (from about 21 to 16%) that makes hypoxia potentially dangerous, as O₂ can drop to between 16 to 15% without an individual becoming breathless and therefore not appreciating that there is a problem.

**Behavioural and cognitive effects of hypoxia**

One of the main dangers of behavioural and cognitive effects of hypoxia is that they are so subtle that they often go unnoticed by an individual. As the effects of hypoxia on the body increase, the person may believe that they are more able to carry out tasks and perform the requirements of the job, than they are capable of doing.

Studies in healthy individuals have also shown that inspired (i.e. breathed in) O₂ levels of 17-18% may start to impair balance, and at levels between 13-17% O₂, finger dexterity, motor skills and steadiness can also be affected. Levels of 13% inspired O₂ can impair cognitive and neuro-behavioural functions and alter mood in healthy volunteers, the effects increasing with decreasing levels of O₂. At 12% O₂ there is also an increase in reaction time, movement components are affected and the individual becomes less cautious. These studies however did not control carbon dioxide levels which could have been a confounding factor in their findings.

**Altitude sickness: physiological and psychological effects**

There is some evidence that when exposed to low O₂ levels around 13% and below (at normal atmospheric pressure), acute mountain sickness (AMS) can develop in a proportion of a fit, healthy population, depending on the length of time spent in the environment.

**Risk assessment**

As there are physiological and psychological effects caused by hypoxia it is important that a risk assessment is carried out prior to any worker entering the environment. The risk assessment should include consideration of the following:

**Working environment**

The control of the reduced O₂ environment will vary depending on the engineering design of each installation. Therefore the risk assessment should consider the working levels of O₂ within the workplace and the potential levels of exposure depending on the tolerance of the system, i.e. the amount the O₂ fluctuates around the set point. It is also important to consider the size and
layout of the environment and how easy it would be for the workers to escape or leave if they feel unwell.

Other contaminants such as dust and other gases must also be taken into account, for example levels of carbon dioxide, carbon monoxide and nitrogen. Carbon dioxide should be carefully monitored especially if it is not being ‘scrubbed’ from the environment. As the numbers of people in the work area and their level of physical activity increases, the more carbon dioxide is produced.

The temperature of the environment is important to the assessment of the safety of the working conditions. Cold conditions can elicit shivering thus increasing the metabolic rate and carbon dioxide production and the heat can increase deep body temperature and in turn, the breathing rate. These physiological responses complicate the effects of hypoxia.

**Work and tasks**

Working patterns (e.g. number of entries into the reduced O₂ environment per day) and how long workers remain in the O₂ reduced atmosphere will vary for each workplace. Depending on the type of environment the tasks can range from climbing ladders, stacking and moving food, books or artwork and driving vehicles such as fork lift trucks. The type of task and the length of time taken to perform the task will affect the amount of O₂ required by the individual. There is a potential for the capacity for physical work to be reduced in hypoxic environments and this may limit the work that can be performed or the ability to escape from a situation of danger. There is, however, insufficient evidence in the literature to allow clear guidance to be provided in terms of the safe range of working tasks that can be carried out in workplaces with different levels of reduced O₂.

**The worker**

Aging may increase the probability of suffering from pulmonary or cardiovascular diseases and a reduction in physical fitness means that as a person ages they are more likely to suffer adverse effects from hypoxia. Smokers, as they are already suffering from a form of hypoxia due to the elevated levels of carbon monoxide in their blood, may be more at risk in a reduced O₂ environment than non-smokers. Hypoxia decreases maximal aerobic power, increases fatigue and shortens the endurance time for heavy work. The higher the level of physical fitness of an individual, the longer and higher the level of physical activity they will be able to perform in a reduced O₂ environment. It is doubtful that short intermittent exposures to reduced levels of O₂ will produce acclimatisation in the workers, as it is dose dependent (related to time and level of exposure). Therefore, it is safer to assume that workers entering a reduced O₂ environment are not acclimatised.

**Occupational health assessments**

Occupational health assessment should follow a comprehensive risk assessment taking into account the work environment, work tasks and the worker. The ‘fitness to work’ assessments should focus on excluding those individuals where an existing medical condition causes a known, or likely, additional risk to their health eg a range of pulmonary or cardiovascular diseases. They should take the form of pre-placement ‘fitness to work’ assessments with regular review.

Occupational health assessments and necessary medical exclusions for working in environments with O₂ levels from less than 21% down to 15% for largely sedentary activities can be derived from the evidence-based and expert opinion-based international guidance on ‘fitness to fly’ on commercial airlines. For hypoxic working environments with O₂ levels of less than 15%, any form of guidance on appropriate health assessment to determine appropriate ‘fitness to work’ is scant, whether evidence-based or expert-led.
Little is known about the effects of working in reduced $O_2$ environments during pregnancy; however, it is an area of concern. Most healthy women will have no adverse health effects to flying (15% $O_2$) and the foetus is able to maintain blood $O_2$ saturation levels unless the mother has significant additional health problems: for example, cardiovascular problems, sickle cell disease or severe anaemia may increase the risk of the foetal $O_2$ blood saturation levels falling. Special consideration needs to be given to pregnant women if the level of physical activity is greater than sedentary activity (low physical activity) in $O_2$ deficient environments between 17 and 15%.

**Summary**
The evidence suggests that working in $O_2$ deficient environments down to 15% $O_2$ are safe for most healthy, fit individuals if the work tasks do not require high levels of physical activity and occupational health assessments derived from ‘fitness to fly’ guidance are utilised. When the levels of physical activity are higher than sedentary, the risk to the worker increases. However, due to a lack of evidence it is difficult to specify exposure times for different levels of physical activity for the range of reduced $O_2$ conditions. Workers who are pregnant should be carefully considered before they undertake work in a hypoxic environment, especially if it involves a greater than sedentary level of physical activity to be undertaken. Any ‘health assessment’ should be based on consideration of all the risks, not just the level of $O_2$ reduction.

For working environments where the $O_2$ has been reduced to between 12-15% $O_2$, the evidence is more limited and related to studies of highly selected volunteers and therefore not directly applicable to the general population. There is also a lack of evidence-based or expert consensus-led guidance that addresses medical conditions and their severity that may exclude the worker, which makes it difficult to define the requirements of appropriate ‘fitness to work’ assessments.
<table>
<thead>
<tr>
<th>CONTENTS PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEY MESSAGES..............................................................................4</td>
</tr>
<tr>
<td>EXECUTIVE SUMMARY......................................................................5</td>
</tr>
<tr>
<td>1. INTRODUCTION................................................................................9</td>
</tr>
<tr>
<td>1.1 Research aim.................................................................9</td>
</tr>
<tr>
<td>1.2 Objectives.................................................................9</td>
</tr>
<tr>
<td>2. IMPLICATIONS.............................................................................10</td>
</tr>
<tr>
<td>2.1 Hypoxic atmospheres down to 15% oxygen (O₂).................10</td>
</tr>
<tr>
<td>2.2 Hypoxic atmospheres below 15% O₂..................................10</td>
</tr>
<tr>
<td>3. METHODOLOGY..........................................................................11</td>
</tr>
<tr>
<td>3.1 Literature search.............................................................11</td>
</tr>
<tr>
<td>3.2 limitations and Exclusions.............................................12</td>
</tr>
<tr>
<td>4. RESULTS.........................................................................................13</td>
</tr>
<tr>
<td>4.1 Hypoxic working environment........................................13</td>
</tr>
<tr>
<td>4.2 Mechanisms and control of respiration............................13</td>
</tr>
<tr>
<td>4.3 Physiological effects of hypoxia.........................................15</td>
</tr>
<tr>
<td>4.4 Altitude sickness: physiological and psychological effects.......19</td>
</tr>
<tr>
<td>4.5 Behavioural and cognitive effects of hypoxia....................20</td>
</tr>
<tr>
<td>4.6 Gender, aging, pregnancy, smoking combined with hypoxia....22</td>
</tr>
<tr>
<td>4.7 Health assessments...........................................................24</td>
</tr>
<tr>
<td>4.8 Physiological mechanism of acclimatisation......................27</td>
</tr>
<tr>
<td>5. SUMMARY OF PHYSIOLOGICAL, PSYCHOLOGICAL AND MEDICAL IMPLICATIONS OF EXPOSURE TO DIFFERENT LEVELS OF HYPOXIC ATMOSPHERES........................................29</td>
</tr>
<tr>
<td>6. LIMITATIONS OF THE LITERATURE SURVEY.................31</td>
</tr>
<tr>
<td>6.1 Population tested or assessed..........................................31</td>
</tr>
<tr>
<td>6.2 Differences between normobaric and hypobaric hypoxia......31</td>
</tr>
<tr>
<td>6.3 Literature relating to behavioural and cognitive effects........31</td>
</tr>
<tr>
<td>7. ANNEXES.................................................................................33</td>
</tr>
<tr>
<td>7.1 Annex A: Definitions of hypoxia........................................33</td>
</tr>
<tr>
<td>7.2 Annex B: Air travel guidance.............................................34</td>
</tr>
<tr>
<td>8. REFERENCES..............................................................................36</td>
</tr>
<tr>
<td>9. BIBLIOGRAPHY..........................................................................41</td>
</tr>
<tr>
<td>10. GLOSSARY..............................................................................42</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

Hypoxic atmospheres are being more frequently installed, for example for fire prevention measures within libraries, book or art archive stores, mines, and food storage facilities. They are also used in some sports science and medical practices. As the list of uses grows, more and more workers may be asked to work in hypoxic atmospheres, which may be potentially hazardous.

Hypoxia is a general term used to describe a decrease in oxygen (O\textsubscript{2}) below normal levels (given in Table 1, page 6) in the inspired gas, alveolar air, blood or tissues of the body. It can be thought of as an imbalance between the O\textsubscript{2} requirement of the body and its supply. It has been well documented (Küpper et al, 2011) that physically fit populations such as the military, athletes and mountaineers, are exposed to environments with an O\textsubscript{2} level of less than 21%, in the short term with few ill health effects. These exposures are usually conducted under close medical supervision and the risks are well understood. Also it is often stated that because there are about 4 billion aircraft passengers who are exposed to hypoxic environments without ill effects from reduced levels of O\textsubscript{2}, then there is not an issue with healthy individuals (Küpper, et al, 2011). However, this is a different population to those who might be exposed to hypoxia at work and relates to a sedentary environment.

Therefore it is not possible to simply apply data and anecdotal findings from these situations to the working population that is not necessarily composed of fit, healthy individuals. The recent abolition of compulsory retirement ages and the introduction of the Equality Act (2010) are legislative highlights within the general trend for the working population to include both older individuals and those with pre-existing diseases. Kloss (1988) highlights the tensions between the differing views within the health and safety field ‘where the worker is chosen who fits the job that is available’ as opposed to ‘the job should be adjusted to the worker, not the worker to the job’.

It is important to understand the possible risk to the workers, including those within the working population that may be at higher risk of health effects (e.g. the pregnant worker and foetus, older worker, those with confounding medical conditions etc).

1.1 RESEARCH AIM

The aim of this work is to review the impact of hypoxic hypoxia on human physiology, behaviour and cognitive function, and to consider the medical implications. The review focuses on papers that have direct application to the typical population and work activities, although in some areas the body of evidence is limited to aviation and associated tasks.

1.2 OBJECTIVES

The objectives of the study are to provide evidence to enable informed decisions to be taken about the effects of different levels of O\textsubscript{2} that workers could be exposed to and the risks involved. The ways of mitigating these risks are also considered. This consolidated approach should allow HSE to draw conclusions about the risks arising from different hypoxic atmospheres to inform policy and enforcement positions.
2. IMPLICATIONS

2.1 HYPOXIC ATMOSPHERES DOWN TO 15% OXYGEN (O\textsubscript{2})

The evidence reviewed for this report suggests that hypoxic environments, from levels of O\textsubscript{2} below 21% down to 15%, are safe for most healthy, fit individuals. However, risk assessments should be performed covering: the working environment, work and tasks undertaken, the worker and occupational health assessments including the effects on pregnancy.

Occupational health assessments should be in place for all staff who have the potential need to enter an hypoxic environment, which can be derived from ‘fitness to fly’ guidance for sedentary tasks. These should focus on existing medical conditions known, or likely, to have an additional potential risk to a worker’s health. These pre-placement ‘fitness to work’ assessments should be reviewed regularly and if the worker’s medical situation changes. More careful consideration should be given to workers carrying out tasks requiring a higher level of physical activity, such as climbing ladders, as these may pose a greater risk. The level of physical activity undertaken by pregnant women should also be considered with care.

2.2 HYPOXIC ATMOSPHERES BELOW 15% O\textsubscript{2}

For hypoxic working environments between 12-15% O\textsubscript{2} there is a lack of evidence-based or expert consensus-led guidance that addresses medical conditions and their severity that may exclude the worker. Therefore it is difficult to define the requirements of appropriate pre-placement ‘fitness to work’ assessments or medical conditions and their severity that would lead to exclusions, to allow the employer to fulfil their ‘duty of care’.
3. METHODOLOGY

3.1 LITERATURE SEARCH

The literature search was divided into 3 work streams: physiology of hypoxia, (work stream 1); medical screening (work stream 2); and behavioural and cognitive effects (work stream 3). Work stream 4 was the consolidation of these three work streams into this document. Text books (listed in the bibliography) have been used as the reference for the basic underlying classical physiology. These have not been referenced in the text, for reasons of clarity and ease of reading, but we have ensured that the narrative included has been corroborated by at least two sources. A search of English language peer reviewed publications over the last 10 years for human subjects (excluding medical error/ negligence related hypoxia) was performed by the HSE Information Services Search Team. In addition, key references cited in reviews were also reviewed. The databases used were: Osh line, Healsafe, Thomson Reuters Web of Knowledge and Medline Embase.

Work stream 1: Physiological effects of hypoxia
A search of English language peer reviewed publications covering the health, sports, physiological and medical literature. Key words combined with the search words hypoxia, human and adult used in the search included:

- Acute hypoxia response
- Chronic hypoxia response
- Arterial oxyhaemoglobin saturation
- Oxygen dissociation curves
- Normobaric hypoxia acclimatisation
- Low altitude acclimatisation
- Isocapnic hypoxia response
- Hypoxic hypoxia

Work stream 2: Medical Screening
A search of both peer reviewed publications and international regulatory guidance were based on:

- Hypoxia or Hypoxic work environments
- Fitness to work or regulatory guidelines or guidance

Work stream 3: Behavioural and Cognitive effects of hypoxia
Key words combined with the search words hypoxia, human and adult used in the search included:

- Cognitive performance
- Perceptual-motor performance or skills
- Visual and motor performance or skills
- Psychological adaptation
- Work environment
- Reaction time
- Decision making
- Aviation/ aviators
3.2 LIMITATIONS AND EXCLUSIONS

The review focuses on identifying summary and review papers. However, because of the gap in knowledge it was necessary to consider key articles, as cited in review papers, from the primary literature. This report aims to identify key findings, however we have not quoted the source documentation in every case when they are included in a review.

This report does not include the following:

- The effects of levels of O₂ below about 10 % (equivalent to over 5500m altitude).
- The integrative physiological effects of extremes of environmental temperatures together with hypoxia.
- The composition of the contaminants, including water vapour pressure, of industrial hypoxic environments and their physiological and psychological effects.
- The effects of chronic acclimatisation.

Risk assessments are outside the scope of this report.

Without more detailed information some areas are difficult to assess:

- Acclimatisation: general outlines have been given, as this will depend on individual work patterns for each workplace, including the level of hypoxia and the length and the frequency of exposure.
- The effects of physical activity: without detailed knowledge of the type of tasks and the length of time they are performed for in the hypoxic environment it is difficult to assess the effects. Only general outlines will be given.

Scientific terminology is defined in the Glossary (Section 10).
4. RESULTS

4.1 HYPOXIC WORKING ENVIRONMENT

4.1.1 Composition of the hypoxic atmosphere

Dry air is normally composed of 20.95% O₂, 78.1% nitrogen (N₂), and 0.03% carbon dioxide (CO₂), with less than 2% of other trace gases (Linde, 1997). Partial pressures (P) will also be used as a measure of the level of O₂ and CO₂ in this report.

For the purpose of this report we have assumed that the hypoxic atmosphere is normobaric and that the O₂ has been reduced in the range of below 21 to 10%, with the difference being made up by N₂. It is also assumed that the CO₂ exhaled by the workers whilst inside the hypoxic environment does not increase the CO₂ above normal levels.

4.1.2 Control of the hypoxic atmosphere

The control of the hypoxic environment will vary depending on the engineering design of each installation. Risk assessments should therefore consider the normal working levels of O₂ and the potential levels of exposure given the design.

4.1.3 Temperature of the hypoxic environment

The temperature of the environment is important to the assessment of the safety of the working conditions. For example, cold or hot temperatures can affect the physiological response to hypoxic exposure. It must also be remembered that the body temperature and physiology of the person can also be affected by environmental conditions in which they work. For example, a fall in core temperature or a cold skin temperature will elicit shivering and increase the metabolic rate. Also an increase in deep body temperature can increase ventilation rate (Whipp and Wasserman, 1970; Petersen and Vejby-Christensen, 1973) which may also affect the hypoxic pulmonary ventilatory response. These physiological responses may complicate the effects of hypoxia.

4.1.4 Working pattern and tasks performed in hypoxic atmosphere

Working patterns (e.g. number of entries into the hypoxic environment per day) and how long workers remain in the hypoxic atmosphere will vary for each workplace. Depending on the type of environment the tasks can vary from climbing ladders, stacking and moving food, books or artwork and driving vehicles such as fork lift trucks. However, the full range of potential tasks that may be required in hypoxic environments remains unknown. The type of task and the length of time the task is performed will affect the amount of O₂ consumed by the tissues of the worker (Table 4, page 10).

4.2 MECHANISMS AND CONTROL OF RESPIRATION

4.2.1 Levels of O₂ throughout the body

As the individual inhales, inspired air mixes with the exhaled air and also becomes saturated with water vapour, resulting in the P O₂ (partial pressure of O₂) falling from 21.2 to 13.33 kPa (159 to 100 mm Hg). The O₂ diffuses down its concentration gradient from the alveolar air into the arterial blood (Table 1). Most of the O₂ carried in the blood is in combination with
haemoglobin (97%) with the remainder (3%) dissolved in the plasma. The $P_{O_2}$ in arterial blood varies from person to person around about 12.97 kPa (97 mmHg) falling to around 7.00 kPa (52 mmHg) in capillary blood (due to mixing and use) which then diffuses down a concentration gradient to give a tissue concentration of 0.1 to 5.3 kPa (1 to 40 mmHg).

<table>
<thead>
<tr>
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<th>Mean partial pressure of $O_2$</th>
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<tbody>
<tr>
<td></td>
<td>kPa</td>
</tr>
<tr>
<td>Environmental air</td>
<td>21.1</td>
</tr>
<tr>
<td>Tracheal air</td>
<td>19.9</td>
</tr>
<tr>
<td>Alveolar air</td>
<td>13.3</td>
</tr>
<tr>
<td>Arterial blood</td>
<td>12.7</td>
</tr>
<tr>
<td>Mean capillary blood</td>
<td>7.0</td>
</tr>
<tr>
<td>Tissues</td>
<td>0.1 - 5.3</td>
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<tr>
<td></td>
<td>depending on the tissue</td>
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**Table 1**: Mean $P_{O_2}$ in males showing the decrease from the level in the environmental air to the tissues ($O_2$ cascade). These values will differ between individuals.

### 4.2.2 Oxygen-haemoglobin dissociation curve

The oxygen-haemoglobin dissociation curve is key to the understanding of how the different levels of hypoxia affect the body and the mechanisms that control the uptake and delivery of $O_2$. This association and dissociation of haemoglobin (Hb) and $O_2$ curve is ‘S’ shaped (Figure 1). Hb binds readily with the $O_2$ to form oxy-haemoglobin (HbO$_2$) at the lungs, where the $P_{O_2}$ is higher in the alveolar air than in the blood. When blood reaches the tissues, the low $P_{O_2}$, higher tissue temperature and acidity (higher concentration of hydrogen ions [H+] due to the higher levels of CO$_2$ in the metabolising cells ie low pH) causes the HbO$_2$ to dissociate and give up its $O_2$ to the tissues. The affinity of Hb for $O_2$ is so high that $O_2$ would not be readily released from Hb without the higher acidity, increased $P_{CO_2}$ and the formation of the metabolite 2,3-diphosphoglycerate (DPG). Due to the ‘S’ shaped curve, Hb releases most of the bound $O_2$ in a narrow range between about 2.7 and 5.3 kPa (20 and 40 mmHg).

As blood passes through the lungs CO$_2$ is lost and pH levels increase, both of which cause the curve to shift to the left and upwards and $O_2$ combines with Hb. As blood reaches the metabolising muscles and tissues, the increased levels of CO$_2$ and decreased pH levels cause the dissociation curve to shift to the right and downwards, facilitating the release of $O_2$ from the blood to the tissues (Table 2). This effect is increased during physical activity as exercising muscles produce more CO$_2$ and DPG.

<table>
<thead>
<tr>
<th>Shift of the curve to the left Hb has increased affinity for $O_2$</th>
<th>Shift of the curve to the right Hb has decreased affinity for $O_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased [H+], increased pH</td>
<td>Increased [H+], decreased pH</td>
</tr>
<tr>
<td>Decreased $P_{CO_2}$</td>
<td>Increased $P_{CO_2}$</td>
</tr>
<tr>
<td>Decreased temperature</td>
<td>Increased temperature</td>
</tr>
<tr>
<td>Decreased 2,3 DPG</td>
<td>Increased 2,3 DPG</td>
</tr>
</tbody>
</table>

**Table 2**: Factors which shift the HbO$_2$ dissociation curve, where [H+] is the concentration of hydrogen ions.
Figure 1: The normal HbO₂ dissociation curve, at a pH of 7.4, which shows that as Pₐ increases the O₂ saturation of Hb increases. The blood leaving the lungs is usually about 97% saturated (13 kPa, 97 mmHg) with O₂ and venous blood returning is about 75% saturated (5.3 kPa, 40 mmHg). The bound O₂ is released to the tissues in a narrow range between 2.7 and 5.3 kPa (20 and 40 mmHg) (shaded area). Factors that shift the curve to the left and right are also included. Taken from Law and Bukwirwa (1999).

4.2.3 Central and peripheral chemoreceptors

Central and peripheral chemoreceptors sense changes in blood levels of Pₐ, PₐCO₂ and H⁺ and attempt to maintain Pₐ, PₐCO₂ and the acid-base balance of the blood at a constant level. They have effects on both the respiratory and cardiovascular systems. The chemoreceptors are, in general, more sensitive to changes in PₐCO₂ than Pₐ. However, if low levels of Pₐ or hypoxia are combined with an elevated level of CO₂ or hypercapnia, the physiological effects are augmented.

4.3 PHYSIOLOGICAL EFFECTS OF HYPOXIA

Hypoxia can have adverse effects on the body. However, the body always tries to maintain homeostasis of the blood gases and the blood acid-base balance by a series of integrated responses of the pulmonary system, cardiovascular system and changes to the composition of the blood. Some of these responses are acute (short term) and others chronic (longer term) leading to acclimatisation. The type of hypoxia being discussed in this report is hypoxic hypoxia caused by a decrease in the Pₐ in the arterial blood and body tissues. The other types of hypoxia, caused by diseases, are important, as they will exacerbate the additional effects of hypoxic hypoxia. The various forms of hypoxia are defined in Annex A, Section 7.1.

In hypoxia, the importance of the HbO₂ dissociation curve, in healthy individuals, is shown in Table 3 as the level of O₂ in inspired air can fall to between about 15 and 16% before the arterial
O₂ saturation level also falls. This in part may explain the lack of significant effects on the healthy body until about 15% O₂ is reached.

O₂ Normobaric and sea level

<table>
<thead>
<tr>
<th>%</th>
<th>mmHg</th>
<th>kPa</th>
<th>mmHg</th>
<th>KPa</th>
<th>mmHg</th>
<th>kPa</th>
<th>mmHg</th>
<th>kPa</th>
<th>ml (STPD)</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>20.9</td>
<td>148</td>
<td>19.7</td>
<td>103</td>
<td>13.7</td>
<td>95</td>
<td>12.6</td>
<td>40</td>
<td>5.3</td>
<td>20.5</td>
<td>97</td>
</tr>
<tr>
<td>15.4</td>
<td>108</td>
<td>14.3</td>
<td>64</td>
<td>8.5</td>
<td>56</td>
<td>7.4</td>
<td>38</td>
<td>5.1</td>
<td>18.8</td>
<td>93</td>
</tr>
<tr>
<td>13.6</td>
<td>80</td>
<td>10.7</td>
<td>44.7</td>
<td>6.0</td>
<td>43</td>
<td>5.7</td>
<td>35</td>
<td>4.7</td>
<td>16.9</td>
<td>84</td>
</tr>
<tr>
<td>11.9</td>
<td>69</td>
<td>9.2</td>
<td>39.5</td>
<td>5.2</td>
<td>37</td>
<td>4.9</td>
<td>30</td>
<td>4.0</td>
<td>15.7</td>
<td>78</td>
</tr>
<tr>
<td>10.4</td>
<td>63</td>
<td>8.4</td>
<td>-</td>
<td>-</td>
<td>32</td>
<td>4.3</td>
<td>28</td>
<td>3.7</td>
<td>14.5</td>
<td>72</td>
</tr>
<tr>
<td>9.7</td>
<td>57</td>
<td>7.6</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>3.9</td>
<td>26</td>
<td>3.5</td>
<td>13.2</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 3: Indicative values for healthy, fit individuals of O₂ and CO₂ partial pressures of inspired gas, arterial blood and corresponding O₂ saturation levels at STPD (standard temperature and pressure, dry). [O₂] denotes concentration of O₂. It should be noted that there is a lot of variation in these values within the normal population.

4.3.1 Effects of hypoxia on pulmonary ventilation

If the hypoxic stimulus is great enough, the body responds to the lack of O₂ within a few seconds by increasing pulmonary ventilation. However, as previously stated (Section 4.2.3), the body’s mechanisms for detecting a lack of O₂ are relatively insensitive. When O₂ falls to between about 15 to 16% most individuals show either a small increase in pulmonary ventilation (both the tidal volume and ventilation rate), or no response at all (Iwasaki et al., 2006). It should however be noted that this makes hypoxia dangerous as O₂ can drop to dangerously low levels before an individual becomes particularly breathless. Only when the O₂ falls to 10% and below is there a marked increase in pulmonary ventilation. This is augmented if CO₂ levels in the atmosphere are also high. The increase in pulmonary ventilation corresponds to the steep part of the HbO₂ dissociation curve (Section 4.2.2) attempting to maintain arterial PO₂ at normal levels.

The responses to hypoxia are very variable across the population (Angerer and Nowak, 2003) and are initiated at different levels of O₂ in different people. If O₂ levels fall to between 15 and 11% and elicit a physiological response, this takes place in three phases:

- **Increase in pulmonary ventilation**: This occurs in the first 10 seconds to 10 minutes and causes P<sub>CO₂</sub> levels to also fall.
- **Hypoxic ventilatory decline**: After 20 to 30 minutes there is a reduction in ventilation back to normal levels and P<sub>CO₂</sub> increases. The mechanism for this effect remains unclear.
- **Respiratory acclimatisation**: During this final stage there is a further increase in the pulmonary ventilation. This can occur between 30 minutes and several days after exposure to the hypoxic environment, and decreases over a period of two weeks (Section 4.8) if the hypoxia is continuous.
4.3.2 Effects of hypoxia on the cardiovascular system

The primary cardiovascular response to hypoxia is initiated by the chemoreceptors and the secondary response is from the stretch receptors in the lungs and the heart. When 17% \( O_2 \) is inspired the cardiovascular effects are initiated. When inspired \( O_2 \) levels fall to below about 15%, hypoxia causes an increase in pulmonary ventilation which stimulates the stretch receptors in the lungs and increases the heart rate. The stimulation of the chemoreceptors causes the stroke volume of the heart to increase and blood vessels in the body (except the skin) to vasoconstrict. These effects combine to increase cardiac output and blood pressure. In severe hypoxia (below about 11% \( O_2 \)), the cardiovascular responses are different, the heart rate slows and the blood pressure starts to fall as the peripheral blood vessels respond to local tissue hypoxia by vasodilating.

4.3.3 Effects of hypoxia on cerebral cortex

The brain or neural tissue requires a constant and high level of \( O_2 \) supply and so is particularly sensitive to hypoxia. Cerebral blood flow does not increase until the \( O_2 \) levels fall to about 10%. This is presumably because the body is able to preserve cerebral tissue \( O_2 \) saturation until environmental \( O_2 \) levels fall to about 10%. At this level of hypoxia it is likely that there is a reduction in \( O_2 \) saturation of cerebral tissue (Foster et al., 2005). As the cerebral blood flow is also very sensitive to changes in \( P_{CO2} \) any experimental results where \( P_{CO2} \) is uncontrolled may have effects on the cerebral blood flow and therefore \( O_2 \) saturation of the cerebral tissue. This makes research results reported in the literature difficult to interpret where levels of \( P_{CO2} \) are uncontrolled.

4.3.4 Combined pulmonary and cardiovascular effects of hypoxia

An hypoxic environment reduces the difference between the alveolar \( P_{O2} \) and the venous \( P_{O2} \) reducing the \( O_2 \) diffusion gradient. Therefore less \( O_2 \) diffuses into the arterial blood. The increase in heart rate and cardiac output also leads to a reduction in the capillary transit time (the blood flow through the vessels is increased). Both these effects reduce the \( O_2 \) saturation of the arterial blood exacerbating the effects of hypoxia (Schoene, 2001).

4.3.5 Effects of physical activity

4.3.5.1 Effects of physical activity in a normoxic environment

All cells of the body require \( O_2 \) and when the body is undertaking physical exercise the demand for \( O_2 \) from the muscles increases. The higher the level of physical activity (Table 4) of the person and the longer the task is performed, the higher their oxygen consumption.

This increased \( O_2 \) demand and \( CO_2 \) production increases the tidal volume and the ventilation rate increasing the pulmonary ventilation. The mechanism for this response is unknown, but it is more closely related to the levels of arterial \( P_{CO2} \) than \( P_{O2} \). The body tries to maintain \( O_2 \), \( CO_2 \) and [\( H^+ \)] in the blood at roughly the same levels as when at rest. However exercise in healthy individuals, reduces the \( O_2 \) saturation levels in the blood and at maximum physical activity these fall from 97% to about 90%. As previously stated, exercise shifts the HbO\(_2\) saturation curve to the right, decreasing affinity for \( O_2 \) so that more \( O_2 \) can be released to the more rapidly metabolising tissues, but less is transported from the lungs to the tissues.

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2 Chemoreceptors are chemical sensitive structures located centrally and near the aortic and carotid arteries that detect changes in arterial \( P_{CO2} \) and \( P_{O2} \).
Physical activity also has an effect on the cardiovascular system increasing the heart rate and stroke volume and therefore increasing the cardiac output. The blood vessels in the exercising muscles vasodilate to increase the blood flow through the tissues, increasing the amount of available O₂.

<table>
<thead>
<tr>
<th>Level of work</th>
<th>Oxygen uptake Litres/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Light</strong></td>
<td>Up to 0.5</td>
</tr>
<tr>
<td><em>e.g.</em> Resting, sitting at ease</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>0.5-1.0</td>
</tr>
<tr>
<td><em>e.g.</em> Light manual work (writing, typing, use of small bench tools, inspection, assembly or sorting of light materials) Driving a vehicle in normal conditions Standing doing light work Casual walking (up to 3.5 km/hour)</td>
<td></td>
</tr>
<tr>
<td><strong>Heavy</strong></td>
<td>1.0-1.5</td>
</tr>
<tr>
<td><em>e.g.</em> Intermittent handling of moderately heavy material Pushing or pulling lightweight carts or wheelbarrows Walking (speeds from 3.5 to 5.5 km/hour)</td>
<td></td>
</tr>
<tr>
<td><strong>Very heavy work</strong></td>
<td>1.5-2.0</td>
</tr>
<tr>
<td><em>e.g.</em> Carrying heavy material Walking (speeds from 5.5 to 7.0 km/hour) Pushing or pulling heavily loaded carts or wheelbarrows</td>
<td></td>
</tr>
<tr>
<td><strong>Extremely heavy work</strong></td>
<td>Over 2.0</td>
</tr>
<tr>
<td><em>e.g.</em> Climbing stairs, ramp or ladder Walking quickly with small steps Walking (at a speed greater than 7.0 km/hour)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: An estimate of oxygen consumption at different levels of activity. It should be borne in mind that these values are affected by individual variability (gender, physical fitness and anthropometric characteristics), differences in work equipment, clothing worn, work speed, technique and skill. Modified from Astrand and Rodahl (1986) with additional information from EN ISO 8996:2004.

4.3.5.2 Working pattern and tasks performed in hypoxic atmosphere

The type of task and the length of time the task is performed affect the metabolic rate and the O₂ consumed by the tissues. As the level of physical activity increases, the O₂ demand of the tissues, especially the muscles, increases. Therefore in a hypoxic environment the supply of O₂ reaching the tissues may be less than the amount required for tissue metabolism and there may be a potential for physical work capacity to be reduced as a consequence.

4.3.5.3 Effects of hypoxia on the ability to perform physical activity

Hypoxia decreases maximal aerobic power and shortens the endurance time for heavy work. These decreases are due to:

- **Increase in the heart rate, cardiac output and stroke volume**: For any given level of submaximal physical activity the cardiac output is greater in a hypoxic environment at 15% O₂ than in a normoxic environment (Haufe et al, 2008). Heart rate, stroke volume and therefore cardiac output are elevated above that expected for any given level of physical activity, so exercise endurance time is reduced and fatigue develops earlier when hypoxia and physical activity are combined.
- **Reduction in the arterial O2 saturation:**
  - The elevated cardiac output reduces the capillary transit time, reducing the time for O2 from the lungs to diffuse into the blood.
  - The lowering in the ventilation perfusion ratio (the gradient between the O2 in the atmosphere and the O2 blood levels) at the lungs, which increases the resistance to O2 diffusion at the lungs.

Therefore the amount of O2 that enters the blood is reduced and less is available at the tissues, reducing the ability to perform physical activity (Favret and Richalet, 2007; Peltonen *et al*, 2001).

There is also some limited evidence in the literature that physical activity in a hypoxic atmosphere (approximately 16% O2 and below) causes levels of blood lactate to increase faster than it would if exercising at the same level in a normoxic environment. This suggests that there is a switch from aerobic to anaerobic metabolism when exercising in hypoxic environments at approximately 16% and below (Hermansen and Saltin, 1967). These elevated levels of lactate when exercising in hypoxic environments also account for the lower endurance times and also a feeling that the level of work being performed is higher than in normal O2 levels (Astrand and Rodahl, 1986). This change from aerobic to anaerobic metabolism is also demonstrated in patients with chronic obstructive pulmonary disease (which also causes hypoxic hypoxia) who also show a reduction in body mass as the metabolic pathways become less efficient (Raguso *et al*, 2004).

### 4.3.5.4 Effect of physical fitness and the ability to exercise in an hypoxic environment

Exercise performance in healthy individuals is limited by pulmonary ventilation. Therefore by increasing physical fitness and respiratory muscle performance, the individual can increase their ability to perform exercise in hypoxic environments. Therefore the higher the level of physical fitness of an individual the longer and the higher the level of physical activity they will be able to perform in a hypoxic environment (Astrand and Rodahl, 1986).

### 4.3.6 Effects of hypoxia on temperature regulation

DiPasquale *et al* (2002) found that when they exposed volunteers to normobaric hypoxia at 13% O2 the peripheral sweat rate was depressed from a level of 5.5 ± 3.0 g/m²/min at 21% O2 to 4.6 ± 2.6 g/m²/min. They found that the hypoxia was having local effects on the sweat glands rather than modifying any central thermoregulatory pathways. This might suggest that there may be an increase in the susceptibility of individuals to heat stress in hypoxic environments, however we found no evidence in the literature to support this hypothesis.

### 4.4 ALTITUDE SICKNESS: PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS

The three stages of altitude sickness are described by the Lake Louise Consensus (1991) which includes acute mountain sickness (AMS) and the cerebral and pulmonary types of oedema. AMS symptoms include headache, nausea and vomiting, dizziness, fatigue, and difficulty sleeping. These symptoms can progress to High Altitude Cerebral Edema (oedema) (HACE) or High Altitude Pulmonary Edema (oedema) (HAPE) which can be life threatening. HACE can cause psychological effects such as a change in the mental state and physiological effects such as ataxia. It is difficult to predict who will develop AMS.
Though the incidence of developing AMS when exposed to hypobaric hypoxia is greater than with normobaric hypoxia, it is still possible to develop the illness. It is the opinion of Angerer and Nowak (2003) after reviewing the limited evidence on the normobaric hypoxic state in their review that normobaric hypoxia (15-13%) ‘may cause AMS in a considerable proportion of exposed people’, depending on the level of O$_2$ in the hypoxic environment and the time spent within it. They recommend that the time of exposure should be limited to 6 hours or even less if the person complains of the symptoms such as headache, nausea or lassitude. We have however found no evidence from the literature, including the papers quoted in Angerer and Nowak (2003) that AMS occurs in normobaric O$_2$ until levels of approximately 13% and below are reached. Angerer and Nowak (2003) also hypothesised that some of the high degree of individual variability found in cognitive testing could be explained by AMS and that it could in some way correlate with cognitive decline.

We have found four papers that demonstrate AMS when fit healthy volunteers are exposed to normobaric hypoxia of 13% and 11% O$_2$ and these are included in Sections 4.4.1 and 4.4.2.

4.4.1 AMS and hypoxic atmospheres between 13-11% O$_2$

AMS symptoms developed in a third of subjects exposed to 13% O$_2$ after about 11 hours. Five out of thirteen subjects reported symptoms of cerebral AMS and four out of these also reported pulmonary AMS (Shukitt et al., 1988). AMS symptoms were also seen in twelve healthy young men confined for 15 days in a submarine in normobaric O$_2$ at 13% with higher than normal levels of CO$_2$ (0.9%). Five out of twelve of the submariners (42%) had AMS symptoms (without cerebral or pulmonary oedema) on day 1. The symptoms of AMS were monitored by a 67-point environmental questionnaire, and the subjects were also examined by physicians morning and evening to ensure that symptoms were not due to any other illnesses (Knight et al., 1990). Again Kolb et al. (2004) exposed subjects to five nocturnal 8-hour normobaric sessions at about 14% O$_2$ and saw symptoms associated with AMS on nights 1 and 2 when assessed by the Lake Louise AMS score.

Nine healthy males had been exposed to normobaric hypoxia at about 12% O$_2$. After 6 hours 2 (22%) of the subjects developed AMS symptoms (measured on the Lake Louise AMS score) and after 9 hours, a further subject (total 33%) had developed AMS symptoms (Roach et al., 1996).

4.5 BEHAVIOURAL AND COGNITIVE EFFECTS OF HYPOXIA

There is much debate about the relationship between levels of hypoxia and the detection of psychological effects. It appears that the threshold for performance decrements and the magnitude of the effects vary with the difficulty and the complexity of the task being assessed. One of the main problems and dangers of behavioural and cognitive effects in the work place is that changes often go unnoticed, especially by the person affected, as they are so subtle. The person often believes that they are more capable of carrying out the tasks due to an increasing feeling of well being as the effects of hypoxia increase (Rainford and Gradwell, 2006).

Angerer and Nowak (2003) reviewed some 27 papers that considered the behavioural and cognitive effects of hypoxia. This comprehensive review concluded that, at altitudes greater

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3 Assessment of AMS symptoms including headache, nausea, vomiting, fatigue, dizziness, difficulty sleeping, change in mental status, ataxia and peripheral oedema.
than 4000m or equivalent atmospheres of less than 13% O₂ at sea level, several cognitive and neuropsychological functions are impaired and mood is altered. The severity of impairment increased with decreasing PO₂. However other researchers have found conflicting evidence of the level of hypoxia and its effects on behaviour and cognition. Fowler et al (1985) when reassessing the minimum altitude for detecting performance decrements, concluded that 2438m (approximately 15% O₂) may be too conservative and that 3048m (approximately 14% O₂) may be more appropriate.

At 17% O₂ there were no measured effects on mental arithmetic (Knight et al, 1990); spatial orientation, visual reaction time or parallel processing motor skills (Gustafsson et al, 1997); reaction time, spatial orientation or psychomotor performance (Blogg and Gennser, 2006). When exposed to normobaric hypoxic levels above about 15.5% O₂, there is little or no evidence in the literature reviewed, of any effects on the battery of test measures used to measure cognitive performance. This may be because the saturation of the cerebral arterial blood only falls by 0.3-0.5 kPa (2-4mmHg) (Blogg and Gennser, 2006) which is unlikely to have any measurable and repeatable cognitive effects. This is backed up to some extent by Piehl Aulin et al (1998) who also found no effect of hypoxia on mood state at approximately 16 or 14% O₂.

Between about 15.5% and 13% O₂, researchers have found contradictory effects on cognition. McCarthy and Miller (1997) found that subjects were less accurate on the memory test part of a signal detection test. In another study there was an increase in error rate, which may be explained by impaired critical judgement, but this was not associated with a reduction in performance or a decrease in the rate of learning (Gustafsson et al, 1997). Elmenhorst et al (2009) found that at about 13% hypoxia, the decrement in performance for single reaction time and an unstable tracking task was equivalent to having a Blood Alcohol Concentration (BAC) of 0.6%⁴. However care must be taken when interpreting these results as the testing was carried out when some of the subjects were also sleep deprived and there were large individual variations in the data. This is contrasted with the experimental data of Knight et al (1990) who found 13% hypoxia had no effects on mental arithmetic tests.

There was a decline in performance when interacting with a computer, which Shukitt et al (1988) explained by an increased level of sleepiness and dizziness in subjects when exposed to a hypoxic atmosphere of 13% O₂ for 8 hours. However, AMS affecting behaviour and mood may explain these changes rather than direct cognitive effects of the hypoxia. Below 13% O₂ studies relating to the effects of hypoxia are less contradictory and the effects on performance more marked. As already stated, hypoxia can make the affected individual believe they are more able to carry out tasks than they are capable of. This is supported by McCarthy and Miller (1997) who demonstrated that when subjects were assessing signal detection at a normobaric hypoxic level of about 12% O₂, they were more likely to report the presence of a signal, suggesting that less caution was exercised.

McCarthy and Miller (1997) found that at about 12% O₂ performance ability on decision making tests was reduced. Tests carried out on military instructor pilots showed that at 11% O₂ there was a significant performance degradation of 53% in precision slow flight tasks such as altitude and airspeed control (Temme et al, 2010). In the experiments by Elmenhorst et al (2009) using a battery of tests to measure performance at 11.5% O₂, there was a significant impairment of the single reaction time and unstable tracking task and this was further impaired when the level of O₂ was decreased to 10%. In another study at 10% O₂, accuracy and vigilance were slightly affected; however, there was a large variability in the data (Blogg and Gennser, 2006).

⁴ BAC drink driving limit is 0.08%
Fowler et al (1987) tried to explain which components of a serial choice response task were affected by breathing 11% O₂. The results indicate that hypoxia disrupts reaction time and the movement time components of serial choice response task performance, but did not affect cognitive processes.

At these levels of hypoxia, it is likely that there is a reduction in O₂ reaching the brain caused by a reduction in the O₂ saturation of cerebral tissue (Foster et al., 2005). Blogg and Gennser (2006) found that cerebral blood flow did not increase until the inspired O₂ levels had fallen to 10%, so there could be a mismatch between supply and demand of O₂. However it should also be noted that cerebral blood flow is also very sensitive to changes in P CO₂, so if this variable is uncontrolled in the experimental design it could explain the variability in the results in the literature.

### 4.5.1 Effect of hypoxia on motor performance

When people stand upright there is an acute response of the cardiovascular system (heart rate and blood pressure) which helps maintain the blood flow to the heart by reducing blood pooling in the legs. There is some evidence that when individuals are exposed to normobaric hypoxia at O₂ levels of about 14.5% and below, the heart rate response to the orthostatic stress is reduced but the blood pressure response remains unchanged. This orthostatic stress could be exacerbated if the individual is also suffering from dehydration and could lead to dizziness, sweating and nausea in susceptible individuals (Rickards and Newman, 2002).

Wagner et al (2011) used computerised dynamic posturography (CDP) as a measure of degradation of balance under hypoxic conditions. Standing balance sway scores decreased compared to baseline at hypoxic levels of between 15 and 16% O₂. Reaction time scores to unexpected movements in the support surface for the motor control subset also increased compared to baseline, and ability was impaired even at 17.8% O₂. The study indicated degradation of balance measured by this technique as the level of hypoxia increased. It should be noted that the levels of blood P CO₂ were not controlled and could have had a significant impact on cerebral perfusion and therefore the results.

Sclichting and Knight (1988) suggested from their limited data that hypoxia at 13 and 17% had some effects on motor skills when finger dexterity and steadiness were assessed. They suggest, with other evidence from the literature, that fine finger dexterity and arm steadiness is more sensitive to hypoxia than cognitive tests. Results from a cognitive experiment which was trying to elucidate the mechanisms that affect a serial choice response task, conducted on students aged 20-27 years, found that hypoxia between about 12 and 11% O₂ which lasted 1 hour, affected reaction and movement times (Fowler et al., 1987) (Section 4.5).

### 4.6 GENDER, AGING, PREGNANCY, SMOKING COMBINED WITH HYPOXIA

We have been unable to find conclusive evidence of any behavioural and cognitive effects when these factors are combined with hypoxia, so only physiological effects are discussed here.

#### 4.6.1 Gender differences

Table 5 shows that females have fewer red blood cells (rbcs) than males, so less Hb and O₂ can be carried from the lungs to the tissues. This is compensated by the fact that females have a
higher concentration of DPG, so Hb has a reduced affinity for O₂ and more of the O₂ carried by Hb can be released at the tissues.

Though there are gender differences in the rbc count between males and females, research has shown that the pulmonary ventilatory response to 11% hypoxia is the same in healthy women as in healthy men, with a mean age of 27.2 to 27.4 years respectively (Loeppky et al 2001). This suggests that males and females may be affected by hypoxia in a similar way, although we have found little or no evidence to support this conclusion.

### Table 5: Gender differences in the red blood cell (rbc) count, Hb and the capacity of the blood to carry O₂ (Lee et al, 1993).

<table>
<thead>
<tr>
<th></th>
<th>Red blood cells</th>
<th>Hb</th>
<th>O₂ carriage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number/mm³ whole blood</td>
<td>g/100ml whole blood</td>
<td>ml/100ml whole blood</td>
</tr>
<tr>
<td>Male</td>
<td>5,200,000 (±300,000)</td>
<td>16 (± 2)</td>
<td>21</td>
</tr>
<tr>
<td>Female</td>
<td>4,700,000 (±300,000)</td>
<td>14 (± 2)</td>
<td>19</td>
</tr>
</tbody>
</table>

#### 4.6.2 Effects of aging

The number of rbcs falls from birth until the age of about 3 months. It then slowly increases and reaches the adult level between 13 and 20 years after which it slowly starts to decline with age. Though there is no other corroborating evidence, Smith et al (2001) demonstrated that the ventilatory response to hypoxia in a group of active male subjects with a mean age of 73.4 years is similar to that of a group of healthy younger men with a mean age of 29.8 years. The reducing numbers of rbcs, coupled with the increase in the probability of suffering from pulmonary or cardiovascular diseases and a tendency for the level of physical fitness to decline with age, means that as the person ages they are more likely to suffer adverse effects from hypoxia.

#### 4.6.3 Effects of pregnancy

During pregnancy the maternal O₂ consumption increases and this together with the growing uterus and foetus pressing on the diaphragm increase the ventilation rate in order to maintain oxygenation of the maternal blood. Therefore, pregnant women have an elevated ventilation rate so any hypoxia may increase this still further.

As foetal blood leaves the placenta it has a P₀₂ of 4 kPa (30mmHg), compared with about 7 kPa (50 mmHg) for the maternal blood. The foetus receives adequate O₂ because of the combined effects of:

- The HbO₂ saturation curve for foetal Hb is shifted to the left of the maternal HbO₂ curve i.e. so that foetal Hb can remove O₂ from the maternal Hb.
- Foetal Hb is also less reactive to DPG than normal maternal Hb so that the foetal Hb has an increased affinity for O₂. This means that foetal Hb carries about 20-30% more O₂ than maternal Hb at the same P₀₂.
- The foetus also has about 50% more Hb than the mother, again increasing the O₂ carrying capacity of the foetal blood.

In normal pregnancy, the maternal physiological effects of hypoxic environments are an increase in heart rate, increased blood pressure and decrease in transtcutaneously measured arterial O₂ saturation. This means that the foetus is able to maintain O₂ saturation levels when the mother is exposed to hypoxic environments of 15% O₂ (Hezelgrave et al, 2011).
4.6.4 Effects of smoking

The carbon monoxide (CO) in cigarette smoke combines irreversibly with Hb to form carboxyhaemoglobin. Paradoxically smokers appear to be slightly more resistant to the effects of hypoxia than non-smokers as they show the symptoms at a lower O\textsubscript{2} level. This may be because smokers are acclimatised to hypoxia and therefore show a blunted response, which may not be beneficial as they are unaware of the effects (Yoneda and Watanabe, 1997). Some authors (reviewed in Nesthus et al., 1997) believe that smoking and hypoxia are additive and that smokers should be considered physiologically to be at an altitude of between 600 and 2000m (approximately 20 and 16% O\textsubscript{2} respectively). Therefore smokers will be more at risk in hypoxic environments than non-smokers as they are already suffering from a degree of hypoxaemia depending on the number of cigarettes smoked per day.

4.7 HEALTH ASSESSMENTS

‘Medical assessment’ of prospective and current employees is designed to give an indication of either the effects of work on the individual or the suitability of the individual to do particular work. Kloss (1998) defines four general goals for such assessments as:

- The early pre-symptomatic detection of disease
- The evaluation of the effectiveness of engineering controls and personal protection
- The detection of health effects previously unknown or unsuspected
- Suitable job placement

HSE identifies formal Health Surveillance as those regular procedures that address the first two bullet points, primarily early disease detection and fitness to continue work with the secondary goal of evaluating the overall effectiveness of control measures. However, due to the nature of hypoxic work places, the focus of any medical assessment would be ‘suitable job placement’ or ‘fitness to start work’ in such a facility. This would likely take the form of ‘pre-placement medical assessments’, with regular reassessments to exclude those individuals with pre-existing or new conditions where there is a known or likely additional risk to their health through hypoxic working. It would also be good practice for such health assessments to be accompanied by simple worker symptom or incident reporting systems specifically for the hypoxic environment, and an explanation to the staff about the nature of hypoxic atmospheres and the possible physiological changes that they may notice.

The health assessment needs to take into account all the risk factors not just the level of hypoxia and existing medical conditions. For example the nature of the working environment, work and tasks and the characteristics of the worker such as physical fitness, pregnancy and smoking all need to be carefully considered.

4.7.1 Hypoxic atmospheres down to 15% O\textsubscript{2}

There is some evidence-based and expert opinion-led guidance related to the degree of hypoxia that can be used as source material in developing ‘fitness to work’ criteria for work in a hypoxic facility.

‘Fitness to fly’ criteria for civil aviation is a well-appraised and documented area. Flying is commonplace within the general population, including the elderly or those with specific medical conditions. However, the aircraft cabin provides a relatively alien, restrictive environment, with
a number of hazards including the issue of hypobaric hypoxia that may have a deleterious effect on passengers’ health.

In Europe, the UK and USA the cabins of commercial passenger aircraft should be pressurised to an equivalent maximum altitude of 2438m (8,000ft) or lower (equivalent to about 15% O\textsubscript{2} under normobaric conditions) which should not be exceeded even at the highest flying altitudes (European Aviation Safety (EASA); US Government 1986).

A number of guidelines (Aerospace Medical Association, 2003; British Thoracic Society Standards of Care Committee, 2002 and 2011; Simpson \textit{et al}, 2004; UK Civil Aviation Authority, 2007; Working Group of the British Cardiovascular Society, 2010) have been developed concerning a passenger’s ‘fitness to fly’ that address issues of specific pulmonary and cardiovascular diseases and the additional risk that hypoxia up to the maximum altitude (equivalent to approximately 15% O\textsubscript{2}) may present.

The American and British Thoracic societies together with the Aerospace Medical Association have recommended that for individuals who cannot maintain an in-flight P\textsubscript{O\textsubscript{2}} above 6.7-7.3 kPa (50-55 mmHg) or O\textsubscript{2} saturation of 85% and above, supplementary O\textsubscript{2} should be available. The British Thoracic Society guidelines (2011) actually acknowledge that these figures have little supporting evidence but are generally accepted as reasonable. At the maximum altitude (equivalent to about 15% O\textsubscript{2}) P\textsubscript{O\textsubscript{2}} falls to the equivalent of breathing roughly 15% normobaric O\textsubscript{2}. In healthy passengers, arterial P\textsubscript{O\textsubscript{2}} is influenced by both age and pulmonary ventilation and will fall to between 8.0-10.0 kPa (60-75 mmHg) and O\textsubscript{2} saturation (measured by pulse oximetry) to 89-94%. These levels of arterial P\textsubscript{O\textsubscript{2}} and O\textsubscript{2} saturation could be even lower when undertaking physical activity (British Thoracic Society Standards of Care Committee, 2011). Thus, altitude exposure (or equivalent decrease in %O\textsubscript{2} in air at sea-level) may exacerbate hypoxaemia in those with lung disease and particular caution seems justified in those hypoxaemic at sea level. The physiological compensations for acute hypoxia at rest are mild to moderate hyperventilation and moderate tachycardia. Someone with pre-existing pulmonary disease may not be able to increase his or her pulmonary ventilation or tolerate hypoxic vasoconstriction. Moreover if their P\textsubscript{O\textsubscript{2}} or O\textsubscript{2} saturation is already reduced at normobaric normoxic conditions, then working in normobaric but reduced O\textsubscript{2} concentrations can shift the individual onto the steep part of HbO\textsubscript{2} dissociation curve with the physiological consequence of a very low O\textsubscript{2} saturation. It should be stressed that air travel guidelines concern a largely sedentary situation. Even at mild exertion levels, a metabolic rate increase of 30-60W, at 14.5% O\textsubscript{2} or less causes abrupt decreases in O\textsubscript{2} saturation below 90% and hypoxic symptoms (Smith, 2007). This reinforces the principle that physical activity accelerates hypoxia onset and has the effect of lowering the altitude at which symptoms can occur (Pickard, 2002; Gradwell, 2005).

‘Fitness to fly’ guidelines present recommendations concerning the presence of medical conditions that would indicate exclusion from flying, or the need for additional supplementary O\textsubscript{2} to be available for the normobaric equivalent of 15% O\textsubscript{2} atmospheres \textit{i.e.} additional risk (for examples see Section 7, Annex B, Tables 8 and 9). They also discuss blood gas status in individuals that indicate minimal hypoxic risk within flight and the sort of pre-existing medical conditions where pre-flight health assessment should be necessary in individuals. The nature of any pre-flight assessment, including a hypoxia challenge test if necessary, are also described in Dine and Kreider (2008) and Mohr (2008).

There had been considerable interest in whether resting blood gas measurements (normobaric, normoxic) could accurately predict the extent of hypoxaemia during air travel for those with respiratory disease. However, the most recent guidance (British Thoracic Society Standards of Care Committee, 2011) in reviewing the evidence stated that neither resting measurements at sea level of O\textsubscript{2} saturation or forced expiratory volume in 1 second (FEV\textsubscript{1}) reliably predict
hypoxaemia or complications during or after air travel in those with respiratory disease. These recent guidelines suggest further research is necessary to determine whether a symptom-based approach or exercise testing (i.e., walk test) might be more reliable in screening for ‘fitness to fly’, but highlight the better predictive value of the hypoxic challenge test rather than resting blood gas measurements in screening those with some degree of respiratory disease.

Notwithstanding the issues of levels of physical activity, work patterns, potential contaminants and the nature of the environment, consensus guidelines from expert panels concerning ‘fitness to fly’ may form the best evidence base for appropriate health assessment for workers prior to their working in a normobaric hypoxic enclosure controlled to 15% O₂ or above. Such guidelines refer to situations where changes in hypoxic atmospheres are relatively rapid, not assuming acclimatisation, and must take account of variable patterns of flying both in duration and frequency (British Thoracic Society Standards of Care Committee 2002 and 2011; Aerospace Medical Association (2003); Working group of the British Cardiovascular Society (2010).

4.7.2 Hypoxic exposure below 15% oxygen

Where workers may be potentially required to work in atmospheres of less than 15% O₂, appropriate guidance (evidence-led or consensus expert-led) is scant. A report of the Medical Commission of the Union Internationale des Associations d’Alpinisme (UIAA MedCom) (Küpper et al., 2009) suggests that for exposure to altitude equivalents of 2,700-3,800m (approximately 15 to 13% O₂), in addition to excluding workers with significant cardiopulmonary disease, blood counts, ergometry (physical work activity) and spirometry (maximum O₂ uptake assessment) should be performed. Workers are also advised to take a normoxic break of 15 minutes every 2 hours and for exposure to less than 13.2% O₂, such normoxic breaks are extended to 30 minutes. Capability criteria for the former blood and physiology tests are not explicit and the rest break advice does not appear evidence-based.

This paper also advises workers ‘to leave hypoxic areas if he/she does not feel well’ and that ‘if symptoms recover completely after ¼ to ½ hour the person (sic worker) can re-enter’, if there is no recovery within the ½ hour, then the worker ‘should be advised to consult a physician who is a specialist in altitude medicine’. This implies that the worker should be aware of their symptoms and make their own decision to leave the working area. Such guidance seems at odds with UK Health and Safety good practice. At less than 12% O₂ (equivalent to above 4,500m) this report states employees should be observed for safety by a rescue person outside the windowed facility, with additional safety through availability of mask-administered O₂ and a specialist high altitude physician on call.

Therefore, if there is a need to expose workers to less than 15% O₂ without supplementary O₂, employers and occupational physicians would need to implement far more stringent ‘fitness to work’ criteria, including the likely impact of the level of physical activity, the length of exposure to such atmospheres, monitoring and the escape capabilities needed for the hypoxic facility. Given the increased risk of adverse effects, including AMS, at lower O₂ levels, thought may have to be given to the nature of any health surveillance or routine monitoring of staff, as well as health assessments based on ‘pre-placement’ and regular reviews of ‘fitness to work’.

Unlike atmospheres at 15% O₂ and above, there appears little appropriate guidance that can be used to underpin a working system that confirms a duty holder’s due duty of care to such employees working in atmospheres below 15%.
4.7.3 Pregnancy

The Management of Health and Safety at Work Regulations 1992 puts a duty of care on employers to provide a safe system of work to all women of reproductive age and their unborn children. Thus pregnancy needs to be specifically considered in the context of hypoxic working.

Van Dyke (2010) highlights that there is much more research data on the effects on pregnancy in acclimatised women, while very little is known about the effects of transiting through high altitudes, with regard to air travel. Van Dyke also states that ‘the precise effect of cabin pressurisation in a pregnancy with compromised uteroplacental perfusion is currently unknown, but potentially is of concern’.

In normal pregnancy, maternal physiological compensatory responses to hypoxic environments means that the foetus is able to maintain O₂ saturation levels when the mother is exposed to environments of 15% O₂, so that the foetus is protected during routine flight conditions (Hezelgrave et al., 2011). The same paper states that most healthy women will have no adverse health effects to flying but those with pre-existing cardiovascular problems, sickle cell disease or severe anaemia (haemoglobin less than 8.5 g/dl) may be at risk. This lack of risk in the normal pregnancy is confirmed within air travel guidelines (Aerospace Medical Association 2003; UK Civil Aviation Authority 2007); some air carriers allow flight attendants and pilots to fly through the first two trimesters of pregnancy. It should be borne in mind that air travel is a sedentary activity (low physical activity) so this gives no guide to the effects of higher levels of physical activity in hypoxic environments.

Specific advice has been offered by the American Pregnancy Association (www.americanpregnancy.org/pregnancyhealth/travel.html); namely ‘travel on major airlines with pressurized cabins and avoid smaller private planes. If you must ride in smaller airplanes, avoid altitudes above 7000 feet’. This altitude is equivalent to about 16% normobaric oxygen.

In relation to exercise and pregnancy, Van Dyke (2010) in a recent review noted that only a couple of studies were found pertaining to exercise and unacclimatised pregnant women at altitude. They concluded that at about 1800m (approximately 17% O₂), unacclimatised pregnant women were tolerant to sub-maximal exercise but significantly less tolerant to maximal exercise levels. Entin and Coffin (2004) state that careful monitoring of maternal Hb and adopting a more conservative stance regarding physical activity during pregnancy for both acclimatised and non-acclimatised women at altitudes greater than 1600m (approximately 17% oxygen or lower) is recommended.

4.8 PHYSIOLOGICAL MECHANISM OF ACCLIMATISATION

Acclimatisation to low levels of atmospheric P₀₂ is complex and has several stages. It should be remembered that much of the physiology literature about acclimatisation is based on the effects of altitude, including cold and low atmospheric pressures, together with the effects of very low levels of P₀₂. Also, the group of subjects studied tend to be physically fit, highly motivated, have an understanding of the risks and acclimatise over periods of weeks.

The first observed response to hypoxia is hyperventilation which increases arterial P₀₂ and decreases P₇ CO₂. The decrease in P₇ CO₂ causes alkalosis which has a secondary effect inhibiting any increases in pulmonary ventilation. This alkalosis, caused by an increase in bicarbonate, is reversed after 2-3 days as the excess bicarbonate is excreted by the kidneys, returning the acid-
base balance of the body back to normal. This means that pulmonary ventilation can increase again.

Hypoxia, when O₂ levels reach about 15%, induces the release of the hormone erythropoietin (EPO) that increases the rate of rbc production (polycythemia) so that the O₂ carrying capacity of the blood is increased. The increase in rbc production is a slow process and does not reach a new steady state level for weeks or even months. Polycythemia causes an increase in the circulating blood volume and the viscosity of the blood. This increase in viscosity of the blood is not necessarily a physiological advantage as it may cause the blood flow through the whole body to slow causing a decrease in venous return to the heart.

The alveolar hypoxia causes vasoconstriction of the pulmonary blood vessels increasing pulmonary arterial pressure and the work of the right side of the heart. The increased viscosity of the blood, caused by the polycythemia, further exaggerates this hypertension. The increased pressure in the pulmonary arterial system can cause pulmonary oedema (Section 4.4).

It is unclear from the literature as to whether intermittent bouts of acute hypoxia experienced by workers in fire prevention atmospheres induce acclimatisation or not. According to Mackensie, Watt and Maxwell (2008) there is a dose related effect of hypoxia, which depends on P₀₂, duration of exposure and the intensity of exercise undertaken while breathing the low O₂. Mackensie et al (2008) conclude from the weight of evidence from the literature that the optimal threshold for erythropoietin release in response to hypoxia is below about 16.5% O₂. Therefore, workers in hypoxic atmospheres above about 16% are unlikely to acclimatise, as it is doubtful that EPO will be released. They also conclude from the weight of evidence that more than 2 hours exposure is needed unless the person undergoes moderate intensity exercise (50% V₀₂max). Morton and Cable (2005) concluded after reviewing 20 years of research that there was no acclimatisation until O₂ falls below 10%. The differences may be due to the dose relation mentioned earlier where time in the hypoxic environment and exercise intensity affect the degree of acclimatisation that occurs.

Acclimatisation to hypoxia appears to be a dose dependent effect (time and level) and it is doubtful that short intermittent exposures to reduced O₂ will cause any acclimatisation in the workers. Therefore, it is prudent to assume the workers entering a hypoxic environment are not acclimatised.
5. SUMMARY OF PHYSIOLOGICAL, PSYCHOLOGICAL AND MEDICAL IMPLICATIONS OF EXPOSURE TO DIFFERENT LEVELS OF HYPOXIC ATMOSPHERES

Table 6 summarises the major physiological, medical and psychological effects at the different levels of normobaric O₂ and matches them with the recommended medical monitoring required for a fit, healthy population. This table must be used in conjunction with the rest of the information contained in this document.
Table 6: Effects of exposure to different levels of O₂ on a fit, healthy individual. It should be noted that individual responses to hypoxia are very variable. At any given level of hypoxia all the effects in the boxes above the %O₂ should also be taken into account. Where ↑ = increase and ↓ means decrease. This table does not take into account the effects of:
- Individual variability, physical fitness, age, gender, pregnancy
- Temperature effects
- Physical activity
- Hyperbaric/hypobaric effects

<table>
<thead>
<tr>
<th>% O₂ normobaric</th>
<th>Physiological effects</th>
<th>Behavioural and cognitive</th>
<th>Recommended medical monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Normal ambient air O₂ levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-19</td>
<td>No evidence of any adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Possible ↑ reaction time to unexpected movements in a support surface or floor, may be due to uncontrolled CO₂ levels</td>
<td>‘Fitness to work’ assessments (including regular reviews) and exclusions on medical grounds can be based on aviation guidelines for commercial air-travel, but modified by the extent of work activity likely to be performed and the nature of the specific hypoxic work place.</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Possible motor and steadiness effects, may be due to uncontrolled CO₂ levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Headaches start to develop ↑ Standing balance sway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>↑ Pulmonary ventilation (small effect) ↑ Heart rate ↑ Stroke volume ↑ Cardiac output ↑ Vasoconstriction ↑ Blood pressure</td>
<td>↓ Accuracy of memory test</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Acute Mountain Sickness can develop in some people Fatigue, dypnoea and confusion</td>
<td>↓ Single reaction task, visual reaction time task corresponding to psychomotor vigilance and unstable tracking tasks. Mood altered</td>
<td>Insufficient evidence to advise on ‘fitness to work’ and medical exclusions.</td>
</tr>
<tr>
<td>12</td>
<td>Submaximal exercise causes greater ↑ in cardiac output than in normoxic conditions</td>
<td>↓ Reaction time ↓ Control of movement ↓ Psychomotor tasks affected by physical activity ↓ Ability to discriminate ↑ Willingness to report signal detection i.e. less cautious</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>↓ Significant impairment of reaction time task and unstable tracking task ↓ Ability to perform precision slow flight tasks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Nausea, vomiting and syncope ↑ Pulmonary ventilation (greater effect)</td>
<td>↓ Accuracy and vigilance</td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>Convulsions, coma and death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. LIMITATIONS OF THE LITERATURE SURVEY

6.1 POPULATION TESTED OR ASSESSED

Much of the literature refers either to mountaineers, climbers or athletes, which are a different population to the workers that could be exposed to hypoxia for fire prevention or other reasons in the workplace. The former population are likely to be more physically fit and have fewer underlying health problems. Climbers and mountaineers also have a higher pulmonary ventilatory response to hypoxia and hypercapnia than other elite athletes and therefore, almost certainly the rest of the population. Also most of the subjects assessed in the laboratory studies reviewed were non-smokers (smokers have higher levels of carboxyhaemoglobin) so the effects of hypoxia in smokers are less well quantified. (Also see Section 4.6.4)

6.2 DIFFERENCES BETWEEN NORMOBARIC AND HYPOBARIC HYPOXIA

Much of the literature covers hypoxia in hypobaric conditions and not normobaric hypoxia and it is important to differentiate between the two as they have different physiological effects. Savourey et al (2003) demonstrated that hypobaric hypoxia (12% O₂, equivalent to 4500m) led to greater hypoxaemia (lowered O₂), hypocapnia (lowered CO₂) and lower arterial O₂ saturation than normobaric hypoxia of the same ambient PO₂, concluding that the ventilatory drive is less in hypobaric hypoxia than normobaric hypoxia.

The work of Grant et al (2002) suggests that limited information can be gained about the physiological response to hypoxia at sea level compared with the response measured at altitude. This may be due to the lower barometric pressure affecting P CO₂ and the less dense air reducing the metabolic work of respiration. It is also possible that subjects studied at altitude are dehydrated, producing haemoconcentration of the blood, due to the increased water vapour loss and greater energy expenditure especially if they are mountaineering. Therefore, experimental findings of the physiological responses to hypoxia at altitude should only be applied and interpreted with caution to normobaric hypoxia conditions.

Gustafsson et al (1997) concluded that there is a difference between the cognitive effects of normobaric and hypobaric hypoxia experimental data due to the differences in barometric pressure, P CO₂, physical activity, AMS effects, climate, undisturbed test conditions and anxious, naive test subjects.

6.3 LITERATURE RELATING TO BEHAVIOURAL AND COGNITIVE EFFECTS

The initial search of the literature identified only one review paper (Angerer and Nowak, 2003) that included a consideration of the behavioural and cognitive effects of hypoxia. Initially, this paper was accepted as representing the research literature up to 2003, and papers identified by the search from 2003 to 2011 were reviewed to provide a complete summary of the literature. However, as the physiology workstream progressed it became apparent that the difference between hypobaric and normobaric experimental conditions might be critical. The Angerer and Nowak paper included both experimental conditions and, while they provided details of the experiments wherever possible when discussing papers, in their conclusions they did not make a distinction; therefore additional effort was made to identify key papers that were focused on normobaric experimental conditions.
The study populations are very different, often with naive subjects which can create apprehension, conditions that vary (including CO₂ levels), study design and, importantly, the assessments used to test changes in psychological performance. Even if all these factors could be normalised, variations in the physiological response to the different levels of hypoxia would also cause large variations in the psychological responses. Some workers have also found that it makes a difference to the results if a task is learnt in normobaric normoxic environments or hypobaric hypoxic environments (McCarthy et al, 1995). Henderson and McCarthy (1995) also reviewed the literature related to mild hypobaric hypoxia, and concluded that there were many contradictions in the literature related to the time effects of hypoxia. Therefore the literature is very contradictory and it is difficult to draw any conclusions that can be verified by multiple sources, however we have attempted to draw some consensus.
7. ANNEXES

7.1 ANNEX A: DEFINITIONS OF HYPOXIA

Table 7: Classification of hypoxic conditions gives the definitions of the different types of hypoxia. Hypoxic hypoxia is the type covered in this report but the other types are important in disease.

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Characteristics</th>
<th>Examples of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic hypoxia</td>
<td>Decreased volume and tension of O\textsubscript{2} in arterial blood. Chemoreceptor activation by diminished P\textsubscript{O2}, cyanosis when Hb concentration is adequate</td>
<td>Any condition that leads to lowered arterial P\textsubscript{O2} – lowered inspired P\textsubscript{O2}, respiratory obstruction, decreased alveolar ventilation, asphyxia, reduced permeability of the alveolar membranes</td>
</tr>
<tr>
<td>Anaemic hypoxia</td>
<td>Arterial O\textsubscript{2} content low but P\textsubscript{O2} normal. Chemoreceptors are not simulated and cyanosis is absent</td>
<td>Anaemia, CO poisoning and drugs that cause methaemoglobin</td>
</tr>
<tr>
<td>Stagnant hypoxia (ischaemic)</td>
<td>Subnormal arterial blood supply either to specific areas (local) or whole body (general)</td>
<td>Arterial embolus, thrombosis (local) Circulatory collapse, cardiac failure (general)</td>
</tr>
<tr>
<td>Stagnant hypoxia (congestive)</td>
<td>Impediment to venous return (local) or high systemic venous pressure (general)</td>
<td>Thrombosis (local) Perhaps congestive heart failure or polycythaemia (general)</td>
</tr>
<tr>
<td>Over utilisation hypoxia</td>
<td>Convulsions, O\textsubscript{2} debt in exercise, angina</td>
<td>Demand for O\textsubscript{2} increased above supply</td>
</tr>
<tr>
<td>Histotonic hypoxia</td>
<td>Reduction or inactivation of cellular oxidative systems Failure to metabolise</td>
<td>Poisoning by cyanide and other substances</td>
</tr>
</tbody>
</table>
### ANNEX B: AIR TRAVEL GUIDANCE

Table 8: Recommendations of the Aerospace Medical Association (Aerospace Medical Association, 2003) with special regard to influence of hypoxic atmospheres in commercial aviation

<table>
<thead>
<tr>
<th>Cardiovascular conditions</th>
<th>Pulmonary conditions</th>
<th>Other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated myocardial infarction within 2-3 weeks</td>
<td>Asthma, severe, labile or required recent hospitalisation</td>
<td>Anaemia (haemoglobin less than 8.5 g/dl)</td>
</tr>
<tr>
<td>Complicated myocardial infarction within 6 weeks</td>
<td>Asthma less severe</td>
<td>May need medical O₂. Notes that degree of compensation for anaemia may influence outcome.</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Chronic obstructive pulmonary disease, including chronic bronchitis and emphysema</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Congestive heart failure, severe, decompensated</td>
<td>Bronchiectasis, cystic fibrosis</td>
<td>Not considered hazardous to the normal pregnancy-mother or foetus</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>Interstitial lung disease, severe</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass graft within 10-14 days</td>
<td>Pulmonary infections</td>
<td></td>
</tr>
<tr>
<td>Cerebro-vascular accident (CVA) (not defined in paper) within 2 weeks</td>
<td>Pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled ventricular or supraventricular tachycardia</td>
<td>Pulmonary vascular disease</td>
<td></td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td>Other cardiovascular diseases associated with known baseline hypoxemia</td>
<td></td>
</tr>
<tr>
<td>Severe symptomatic valvular heart disease</td>
<td>Use of oxygen at baseline altitude</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure NYHA (New York Heart Association) classes III-IV or baseline PaO₂ less than 70 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angina CCS (Canadian Cardiovascular Society) class III-IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyanotic congenital heart disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other cardiovascular diseases associated with known baseline hypoxemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of oxygen at baseline altitude</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indications for medical oxygen during commercial airline flights</td>
<td></td>
</tr>
</tbody>
</table>

#### Cardiovascular conditions

| Contra-indication to commercial air flight but noted as guidelines and to be ‘tempered by clinical judgement’ |

#### Pulmonary conditions

| Contraindication to commercial air flight |
| Reminder to hand carry necessary medication on board |
| Pre-flight evaluation important -pulmonary function tests, P02, hypoxic challenge test, ability to walk & climb stairs |
| Appropriate medication and medical support necessary |
| Possible indications for medical O₂ during commercial airline flights; less severe cases tolerate the hypoxia well |
| Unsuitable for travel due to infectivity. |
| Absolute contra-indication for air travel |
| Indications for medical O₂ during commercial airline flights |

#### Other conditions

| May need medical O₂. Notes that degree of compensation for anaemia may influence outcome. |
| Not considered hazardous to the normal pregnancy-mother or foetus |
**Table 9: UK CAA guidelines on assessing ‘fitness to fly’ (UK Civil Aviation Authority, 2007)**

<table>
<thead>
<tr>
<th>Cardiovascular conditions</th>
<th>Pulmonary conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>No problem</td>
</tr>
<tr>
<td>Myocardial infarction, uncomplicated</td>
<td>May travel after 7-10 days</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>May travel if fully recovered</td>
</tr>
<tr>
<td>Uncomplicated percutaneous coronary interventions e.g. angioplasty with stent placement</td>
<td>May travel after 5 days, but should be medically stable and assessed prior to travel</td>
</tr>
<tr>
<td>Myocardial Infarction, uncomplicated within 7 days</td>
<td>Contraindication to fly, within periods stated</td>
</tr>
<tr>
<td>Myocardial infarction, complicated within 4-6 weeks</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
</tr>
<tr>
<td>Decompensated congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass graft within 10 days</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident within 3 days</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled cardiac arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Severe symptomatic valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Hypertension, treated with satisfactory control</td>
<td>Able to fly but with their medication</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>No specific additional risk, although subject should have medication on hand</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Susceptible to in-flight hypoxia depending on baseline P_{O_2}</td>
</tr>
<tr>
<td></td>
<td>Walk test or hypoxic challenge test may be appropriate</td>
</tr>
<tr>
<td>Bronchiectasis and cystic fibrosis</td>
<td>Appropriate antibiotic therapy, adequate hydration and medical O_{2} may be required</td>
</tr>
<tr>
<td></td>
<td>Medication to decrease sputum viscosity helpful due to low humidity in aircraft cabins</td>
</tr>
<tr>
<td>Pneumonothorax</td>
<td>Contraindication to fly until 2 weeks after successful drainage</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>No problem up to 36 weeks in uncomplicated pregnancy</td>
</tr>
<tr>
<td>Surgical conditions</td>
<td>Issues of anaemia and internal gases expanding by 30%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No problems, medication to hand</td>
</tr>
<tr>
<td>Haematological disorders; Hb &lt; 8g/dl and sickle cell anaemia</td>
<td>May need supplemental O_{2}</td>
</tr>
<tr>
<td>Use of oxygen at sea-level; CHF (Congestive Heart Failure) NYHA class III-IV or baseline P_{O_2} &lt; 9.33kPa (70mm Hg); Angina CCS III-IV; cyanotic congenital heart disease; primary pulmonary hypertension; other CVD (Cardiovascular Disease) associated with hypoxaemia.</td>
<td>Need for supplemental O_{2}</td>
</tr>
</tbody>
</table>
8. REFERENCES


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10. GLOSSARY

**Acclimatisation:** A physiological process where the body’s response to a stimulus is changed by repeated or prolonged exposure to that stimulus. Acclimatisation usually results in an increased tolerance to the stimulus.

**Acid:** Donor of hydrogen ions, which has a pH less than 7.

**Acid base balance:** Complex array of mechanisms regulating the concentration of hydrogen ions [H\(^+\)] in body fluids.

**Acute:** Short term.

**Acidosis (respiratory):** This is a disturbance of the acid-base balance in the body fluids that has resulted from hypercapnia (elevated CO\(_2\) levels). The homeostatic systems of the body always try to restore the pH back to the normal levels. In respiratory acidosis, the kidneys respond by retaining HCO\(_3^-\) (bicarbonate ions) and increasing the concentration of HCO\(_3^-\) in the plasma which restores the pH back to normal levels.

**Alkalosis (respiratory):** This is a disturbance of the acid-base balance in the body fluids that has resulted from hypocapnia (reduced CO\(_2\) levels) often as a result of hyperventilation.

**Aerobic metabolism:** In presence of O\(_2\).

**Alveolar:** The region of the lungs where the majority of the O\(_2\) and CO\(_2\) gas exchange takes place.

**Alveolar-arterial difference:** This is the difference in the partial pressures of gases (O\(_2\), CO\(_2\)) between the alveolar gas and the arterial blood.

**Alkalosis (respiratory):** This is a disturbance of the acid-base balance in the body fluids that has resulted from hypocapnia (reduced CO\(_2\) levels). The homeostatic systems of the body always try to restore the pH back to the normal levels. In respiratory acidosis, the kidneys respond by excreting HCO\(_3^-\) (bicarbonate ions) and decreasing the concentration of HCO\(_3^-\) in the plasma which restores the pH back to normal levels.

**Anaerobic metabolism:** Without O\(_2\).

**Apnea:** Absence of breathing movements.

**Base:** Acceptor of hydrogen ions which has a pH more than 7.

**Bradycardia:** Lower than normal heart rate.

**Capillary transit time:** Time taken for blood to flow through the capillaries in a defined area or organ.

**Cardiac output:** The volume of blood ejected from the left side of the heart in one minute.

**Carboxyhaemoglobin(HbCO):** Compound formed when carbon monoxide reacts irreversibly with haemoglobin. HbCO shifts the oxyhaemoglobin dissociation curve to the left.
Chemoreceptors: A chemically sensitive structure that detects chemical changes. In the context of hypoxia the most important chemoreceptors are the central, aortic and carotid bodies which sense changes in $P_{CO_2}$, $P_{O_2}$ and $H^+$.

Chronic: Long term.

Cerebral cortex: the surface layer of grey matter in the brain that functions chiefly in coordination of higher nervous activity.

2,3-Diphosphoglyceric acid (DPG): Metabolic intermediary which is produced as part of the anaerobic (without $O_2$) metabolism of carbohydrate within the red blood cell. It decreases the affinity of haemoglobin for $O_2$.

Dyspnea: Breathlessness, difficult or laboured breathing. Uncomfortable awareness of the need for increased breathing.

Erythropoietin (EPO): A hormone formed in the kidneys that stimulates red blood cell (rbc) production.

Haemoglobin (Hb): Protein that is found in the red blood cell that combines reversibility with $O_2$ and transports it in the blood round the body.

Haematocrit: the ratio of the volume of packed (centrifuged) red blood cells to the volume of whole blood.

Hyperbaric: Pressure in excess of atmospheric pressure.

Hypercapnia: Excess of $CO_2$ in the blood usually when $P_{CO_2}$ is higher than 40 mmHg. Hypercapnia occurs when alveolar ventilation rate (hypoventilation) is too low at any given metabolic rate, when $CO_2$ is retained due to disease or other causes such as $CO_2$ poisoning.

Hyperventilation: The ventilation rate is more than required by the metabolic rate. Usually $P_{CO_2}$ decreases below 40 mmHg. It can result from increased tidal volume or frequency or a combination of the two. Hyperventilation increases arterial $P_{O_2}$ and decreases $P_{CO_2}$.

Hypobaric: Ambient pressure less than atmospheric pressure.

Hypocapnia: $CO_2$ in the blood drops significantly below normal levels of 40 mmHg. Hypocapnia occurs when alveolar ventilation rate (hyperventilation) is too high at any given metabolic rate. Hypocapnia which can cause dizziness, numbness, respiratory alkalosis and can lead to carpo-pedal spasm.

Hypoventilation: The ventilation rate is less than required by the metabolic rate. Usually $P_{CO_2}$ increases above 40 mmHg. It can result from decreased tidal volume or frequency or a combination of the two.

Hypoxaemia: Low blood $P_{O_2}$ and oxyhaemoglobin saturation.

Lactic acid: An organic acid produced in muscle and found in blood as the product of glucose and glycogen metabolism.

Isocapnic: Equal $CO_2$ partial pressures.
**Metabolic rate:** (Units: Watts or Watts/m²) Metabolic rate is usually calculated from steady state measures of oxygen consumption measured (Units: litres/min, cm³/kg/min, or ml/kg/min) and is a measure of the level of physical activity.

**Normobaric:** Atmospheric pressure at around sea-level.

**Normoxia:** Ambient P\textsubscript{O2} at sea level.

**Oedema (Edema):** An abnormal accumulation of serous fluid in a connective tissue or body cavity.

**Oxygen consumption:** The amount of O\textsubscript{2} required by the tissue or cells.

**Oxygen haemoglobin (Oxy-haemoglobin):** Reversible combination of O\textsubscript{2} with haemoglobin.

**Partial pressures (P):** (Units kPa or mmHg) A gas does not behave like a fluid but as an enormous number of discrete particles, all of which exert a pressure. The atmospheric gases at sea level have a partial pressure of 760 mmHg. Pure O\textsubscript{2} at sea level exerts a pressure of 760 mmHg, however a mixture of gases exerts a pressure in the container as if it were the only gas occupying the same space. In the lungs the gases are O\textsubscript{2}, CO\textsubscript{2}, N\textsubscript{2} and H\textsubscript{2}O (water vapour). This can be expressed in mmHg (usual physiological unit) or kPa.

**pH:** A measure of the acidity or alkalinity of an aqueous solution.

**Pre-placement medical assessments:** Baseline health assessments (HSE terminology).

**Polycythemia:** Abnormal increase in red blood cell (rbc) count.

**Pulmonary ventilation:** Tidal volume (volume of breath) x ventilation rate (frequency of breathing).

**Pulmonary ventilatory drive:** Increase or decrease in the pulmonary ventilatory response.

**Sickle cell disease:** A chronic inherited anaemia.

**Stroke volume:** The volume of blood pumped from a ventricle of the heart in one beat.

**Tidal volume:** Volume of gas that is either inspired or expired ie volume of each breath, during quiet respiration (about 500ml).

**Transcutaneously measured arterial O\textsubscript{2}:** O\textsubscript{2} concentration measured through the skin.

**Uteroplacental perfusion:** Blood flow through the uterus and placenta.

**Vasoconstriction:** Narrowing of the lumen of blood vessels reducing the blood flow.

**Vasodilation:** Widening of the lumen of blood vessels increasing the blood flow.

**Venous return:** The flow of blood from the venous system into the right atrium of the heart.

**Ventilation perfusion ratio:** The gradient between the O\textsubscript{2} in the atmosphere and the O\textsubscript{2} blood levels.

**Ventilation rate:** Frequency of breathing.
A health risk assessment of working in hypoxic atmospheres

Hypoxic atmospheres - those in which the ambient oxygen level is lower than normal – may be specifically generated in some workplaces, particularly for fire prevention. Such atmospheres potentially present a health risk to workers who are required to enter the hypoxic space. This report reviews the impact of hypoxia on human physiology, behaviour, and cognitive function, in order to provide information about the potential occupational health risks arising from working in hypoxic atmospheres.

The available evidence suggests that hypoxic environments in which the levels of oxygen are greater than 15% but below 21%, are safe for most healthy, fit individuals. However, prior to entry into such environments, risk assessments should be performed to cover: the working environment; the work and tasks undertaken; and the worker. Occupational health assessments should be in place for all workers who have a potential requirement to enter these atmospheres. Careful consideration should be given to: workers carrying out tasks that require higher levels of physical activity; and pregnant workers.

For hypoxic working environments between 12% and 15% oxygen, there is a lack of evidence-based or expert consensus-led guidance that addresses medical conditions and their severity. There is therefore an insufficient evidence-base to provide guidelines for safe working in hypoxic environments between 12-15% oxygen, other than relating to the use of supplemental oxygen.

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