



NorthWest Occupational Health & Safety

Oxygen: Health Effects and Regulatory Limits

Part I: Physiological and Toxicological Effects of Oxygen Deficiency and Enrichment

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Introduction

Probably the biggest source of confusion and controversy involving confined spaces is the acceptable limit for atmospheres deficient or enriched in oxygen. This confusion and controversy has arisen, in part, because oxygen is essential for life, and because people can adapt in both the short-term and the long-term to oxygen levels both greater than and less than they are at sea level. Sea level, of course, is merely a convenient altitude of reference. There is no particular significance to this altitude, as people live and work quite comfortably at altitudes far below and far above this height.

Oxygen Deficiency

Complicating things further is the fact that the condition present at the legal limit for workplace exposure (19.5%) can be encountered at an altitude of 610 m (2000 feet). This altitude is readily accessible by car from sea level in many areas. One, in fact, can drive to this altitude and go considerably higher and experience no noticeable symptoms, and then be left to wonder what is the purpose for this choice and what is the concern that it reflects.

Oxygen levels are measurable in units of concentration and partial pressure. Oxygen concentration remains constant within normal habitable altitudes. This results from the relative constancy of composition of the atmosphere (Moran and Morgan 1989). Total atmospheric pressure, and by implication, the pressure of oxygen, vary according to altitude and barometric pressure. The pressure of the normal atmosphere at sea level is 760 mm Hg (millimetres of mercury). The concentration of oxygen in the normal atmosphere is 20.9% of the total of the gases (mainly nitrogen and oxygen). The pressure, but not the concentration of oxygen, decreases with altitude.

Oxygen deficiency is a major concern in the occupational setting and the subject of several standards and many regulations. Typically, the following Table 1 or a similar version which, appears in publications, summarizes the effects of acute exposure to oxygen-deficient atmospheres as commonly reported based on concentration and partial pressure (after NIOSH 1976a, Miller and Mazur 1984, after ANSI 1992, after CSA 1993). (For explanation of the acronyms, please refer to the glossary at the end of the document.)

The origins and wording of this table are not readily apparent. The table does not appear historically in the ANSI standards on confined spaces (ANSI 1977, ANSI 1989, ANSI 1995, ANSI/ASSE 2003), nor NFPA

Table 1
Effects of Acute Exposure to Oxygen Deficient Atmospheres

Effect	Atmospheric Oxygen (dry air, sea level)	
	Concentration %	Pressure mm Hg
no symptoms	16 to 20.9	122 to 159
increased heart and breathing rate, some loss of coordination, increased breathing volume, impaired attention and thinking	16	122
abnormal fatigue upon exertion, emotional upset, faulty coordination, impaired judgment	14	106
very poor judgment and coordination, impaired respiration that may cause permanent heart damage, nausea and vomiting	12	91
nausea, vomiting, lethargic movements, perhaps unconsciousness, inability to perform vigorous movement or loss of all movement, unconsciousness followed by death	< 10	< 76
convulsions, shortness of breath, cardiac standstill, spasmodic breathing, death in minutes	< 6	< 46
unconsciousness after one or two breaths	< 4	< 30

306 which is concerned with gas hazards on ships (NFPA 1988, NFPA 1993). NFPA 306 dates back to 1922.

This information is also absent from historical publications by NIOSH on confined spaces (NIOSH 1979). Articles on confined spaces, such as, Anonymous, 1967, and Allison 1976a and Allison 1976b, do provide some discussion about oxygen deficiency. The latter article by Allison (1976b) indicated that 19.5% for oxygen was the 'accepted percentage to support life'. Miller and Mazur (1984) reference Beard (1982) and Cooper (1981) as sources of their information.

The information contained in Table 1 does appear in historic standards on respiratory protection (ANSI 1980) and guides (NIOSH 1976a). (Note, that ANSI standards on respiratory protection preceded the existence of NIOSH.)

The ultimate origins of the information appear to reflect experiments performed in aerospace medicine and later adopted as the basis for discussion by the ANSI Z88.2 committee on respiratory protection. References, such as NASA (1964) and NASA (1973), contain information possibly used in later references, such as Davis (1979), and also provide historical references.

The situation highlighted in Table 1, along with comments reflected in the articles by Allison (1976a and 1976b), hint at the complexity of the questions raised. The outcome of situation apparently reflects the divergence of vision of two groups on how to manage the reality within which people work within the environmental reality in which people live. These environments present contradictions and complexities that deserve acknowledgement and recognition in order to manage the combined reality in a beneficial and unambiguous manner. In order to do this, the following background information is essential.

• Confined Space Accidents and Atmospheric Hazards

Of considerable interest to the industrial hygienist is the composition of contaminated atmospheres associated with accidents that occur in confined spaces (McManus 1999). This information provides the

key to better understanding about the hazardous nature of these workplace environments. Ultimately, this information would determine the nature and scope of the response needed to address and manage these conditions. OSHA and NIOSH reports on fatal accidents occurring in confined spaces provided the main source of information about this subject in recent times (OSHA 1985, NIOSH 1994). Both reports provided descriptive summaries of individual accidents. These made possible further speculation about the composition of the atmosphere present at the time of the accident. Sometimes the summary alluded to the presence of more than one hazardous substance. Unfortunately, these summaries provided little or no measurement data about the composition of the hazardous atmosphere involved in the accidents.

Anecdotal information in the accident summaries provided some indication that these atmospheres are more complex than originally described. As well, there are discrepancies between the progression of events that actually occurred versus what could be expected based on controlled studies of the toxic agents implicated in the accidents. That is, the outcomes produced by some of these substances under controlled conditions differed from what was observed during accidents attributed to them.

Considerable similarity exists in the progression of events in individual accidents involving hazardous atmospheric conditions. During a typical accident, the victim usually is affected by the atmospheric condition either at the time of entry or soon afterward. This individual collapses and may yell for help, or is discovered soon afterward by someone outside the space. The discoverer or some other individual nearby undertakes the role of would-be rescuer and enters the space without ventilation or respiratory protection. The would-be rescuer possibly succeeds in transferring the victim from the interior of the space to the access opening after expending considerable physical effort. The atmospheric condition in the space overcomes the would-be rescuer, who then collapses. The would-be rescuer often collapses more rapidly than the victim. Additional would-be rescuers may suffer the same fate as the first. These events all occur prior to response by individuals equipped appropriately for the rescue. Either the victim, a would-be rescuer or both are fatally injured during this process.

During a real-world accident, entrants often collapse either immediately or shortly after initial contact with the hazardous atmosphere. This action suggests the presence of a rapidly acting, acutely hazardous condition. The rapid onset of debilitation under real-world conditions contrasts with the slower action of many substances, including carbon monoxide and organic solvents.

The onset of unconsciousness following exposure to carbon monoxide occurs when carboxyhemoglobin saturation exceeds 50% to 60% (NIOSH 1972). Saturation to the 50% level by an atmosphere containing 1000 ppm requires approximately 180 minutes (Stewart & Peterson 1970). This time sequence is much too slow to account for the rapid onset of unconsciousness observed during actual accident situations. This discrepancy suggests that carbon monoxide alone was not the causative agent in these accidents.

Hydrogen sulphide can cause rapid collapse when inspired in high concentration. Yet, in many accidents in which hydrogen sulphide was implicated, and in which air sampling subsequently occurred, the concentration typically was in the range of 50 ppm (OSHA 1985, NIOSH 1994). Concentrations in this range are sufficiently high to cause only eye irritation, not rapid collapse (NIOSH 1977). However, the test results possibly were not reliable or loss of the source could have occurred following the accident.

In high concentration, solvent vapours can cause rapid collapse. This response is consistent with situations in which exposure to high concentrations of solvent vapours did occur. However, solvents were implicated in only a small proportion of the fatal accidents described by OSHA and NIOSH.

Oxygen deficiency can cause rapid collapse. Collapse occurs after one or two breaths of atmospheres containing less than 4% oxygen (Miller and Mazur 1984). The rate of onset of symptoms depends on many factors including breathing rate, work rate, temperature, emotional stress, age and individual susceptibility (Timar 1983). These factors can exacerbate the effects of an oxygen-deficient atmosphere and influence the onset, course and outcome of accidents that occur under these conditions.

Loss of consciousness is a key outcome in an oxygen deficient atmosphere. At a concentration of 5% oxygen at sea level, unconsciousness in inactive subjects begins after about 12 seconds, or about 2

breaths of air (Davis 1979, Miller and Mazur 1984). For a slight increase in concentration to 6.5% oxygen, the duration of consciousness for inactive subjects increases rapidly to about 30 seconds. For active or active and highly stressed subjects, loss of consciousness would occur at higher concentrations. High activity and high stress is the likely state of a would-be rescuer during an accident situation.

Atmospheres deficient in oxygen contain other gases that maintain total pressure at ambient levels. Carbon dioxide stimulates breathing at concentrations above normal levels and up to 70,000 ppm (7%) (NIOSH 1976b). The latter corresponds approximately with the legal level for oxygen deficiency (19.5%) adopted in many jurisdictions. Thus, elevated levels of carbon dioxide could stimulate inhalation of other contaminants present in the same contaminated atmosphere. At the same time under this circumstance, this atmosphere also could produce impairment because of the oxygen deficiency.

While atmospheres encountered in confined spaces likely are complex mixtures of contaminants, the preceding discussion strongly suggests that oxygen deficiency was responsible for the vast majority of accidents that involved atmospheric hazards (McManus, 1999).

• Gas Exchange

The exchange of gases between alveolar air and blood in pulmonary capillaries is the essential normal function of the lung. (The alveoli are the air sacs at the end of the respiratory tree.) The amount of exchange depends on the alveolar ventilation rate and the flow of blood through pulmonary capillaries (perfusion of the lungs), diffusivity through cellular membranes and solubility in blood. The driving forces are the differences in partial pressures, not concentration, in various environments involved in the process (Comroe et al. 1962).

Henry's Law describes the relationship at equilibrium between gas or vapour and liquids with which they are in contact (Reid et al. 1987). The quantity of a gas dissolved in a liquid at equilibrium is proportional to the partial pressure of the gas above the liquid. For each gas there is an individual Henry's constant. The value of the constant depends on a number of factors including temperature, pH and interactions between molecules of the gas and the solvent.

Two possible non-equilibrium situations also must receive consideration. The first involves contact between a solvent containing no gas or a weak solution and gas-rich atmosphere. Gas will dissolve into the solvent or weak solution until equilibrium is attained or other factor intervenes. The converse situation involves contact between a solution containing dissolved gas and an atmosphere containing no gas or a concentration less than the equilibrium value. Gas will effuse from the solution into the gas-lean atmosphere until equilibrium again is attained or other factor intervenes. Both of these processes occur in the lung and the tissues as part of gas exchange.

The relationship between atmospheric and other gases and body fluids, such as blood and extra- and intra-cellular fluids is a critical part of the process of transport and respiration. These considerations represent a direct application of Henry's Law. Oxygen diffuses into the liquid part of the blood in the lung and is transported to regions having lower concentration. This process occurs because the partial pressure of atmospheric oxygen exceeds the equilibrium partial pressure of dissolved oxygen in the fluid of the blood. Carbon dioxide diffuses into the liquid part of the blood from the tissues and effuses into airspaces in the lung. The latter process occurs because the partial pressure of dissolved gas exceeds the equilibrium partial pressure of atmospheric gas.

Gases and vapours that do not react with components of tissue or cellular fluids pass freely across the membrane barrier in both directions. Gases and vapours diffuse in response to the pressure gradient from an area of high partial pressure to an area of low partial pressure. The difference in partial pressure between alveolar air and the blood determines the net direction of flow. Gases and vapours will diffuse across the membrane barrier into or from a particular volume of blood until equilibration occurs (partial pressures become equal), or the flow has reached the end of the alveolar-capillary contact (Comroe et al. 1962, Bouhuys 1974).

Under normal conditions the partial pressure of oxygen in alveolar air is greater than that in blood entering

the pulmonary capillaries. At the same time, the partial pressure of oxygen in tissue capillaries is greater than that in tissue fluids and greater in tissue fluids than in cells of the body. Conversely, the partial pressure of carbon dioxide is higher in the cells than in the intercellular fluids, higher in the intercellular fluids than blood flowing through tissue capillaries and higher in pulmonary capillaries than in alveolar air (Bouhuys 1974).

During the breathing cycle the alveolar partial pressure of oxygen increases from a minimum of 97.9 mm Hg to a maximum of 101.5 mm Hg. The corresponding alveolar partial pressure of carbon dioxide changes from 40.8 mm Hg to 38.2 mm Hg. However, these changes in partial pressure do not correspond exactly to the inspiratory and expiratory motions of the chest. The change in alveolar partial pressure is not the same for the two gases. Metabolism consumes more oxygen than the amount of carbon dioxide produced. This means that a greater amount of oxygen is exchanged per unit time than carbon dioxide. The relative amount of carbon dioxide produced and oxygen taken up depends on metabolic activity, i.e., work (Comroe et al. 1962).

Oxygen tension of mixed venous blood entering the pulmonary capillaries is 40 mm Hg. Oxygen tension of oxygenated blood in the pulmonary veins is 100 mm Hg. This is identical to the partial pressure of oxygen in the alveolar space. The normal time spent in the pulmonary capillary bed is 0.75 s. The oxygen tension increases to almost 100 mm Hg in 0.35 s or less. This is less than half of the normal transit time. This efficiency provides redundancy for situations that are less than ideal (Comroe et al. 1962). In normal individuals only during the most strenuous of exercise when blood flow through the capillaries is extremely rapid is there insufficient time for complete equilibration. This may not be the case in individuals whose lung and circulatory function is compromised by disease, age, obesity or lack of physical conditioning. The combination of the stress induced by the situation, coupled with these factors, easily could provide the required conditions for insufficiency in gas exchange.

This process is affected by the diffusing capacity of the pulmonary capillaries and other factors. On a micro scale, this process is very complex. Ventilation of the alveoli occurs only during inspiration. On the other hand, blood flow and gas exchange occur continuously. Imbalance between the rate of ventilation and perfusion causes inefficient exchange between alveolar airspaces and the blood.

Diffusion through cellular membranes does not limit gas exchange. The rate of uptake or clearance of a gas or vapour depends on solubility in blood, the alveolar ventilation rate and the perfusion rate. The factor limiting the importance of the alveolar ventilation rate compared to the perfusion rate is solubility of the gas or vapour in the blood (Farhi 1967). Clearance of a relatively insoluble gas or vapour depends almost exclusively on the perfusion rate. The alveolar ventilation rate has little effect. For example, the rate of clearance from the blood of xenon, a relatively insoluble gas, depends mostly on the perfusion rate. Oxygen also behaves as a relatively insoluble gas. The rate of uptake of oxygen is perfusion-limited (Bouhuys 1974).

The rate of clearance of a relatively soluble gas or vapour depends almost exclusively on the alveolar ventilation rate. The perfusion rate has little effect. Clearance of the relatively soluble vapour, diethyl ether, increases dramatically with increasing alveolar ventilation at constant perfusion rate. The rate of clearance is little affected by the perfusion rate at constant alveolar ventilation rate (Farhi 1967). The rate at which carbon dioxide leaves the blood is largely determined by the rate of alveolar ventilation. Carbon dioxide behaves as a soluble gas.

The ratio of partition coefficients of oxygen and carbon dioxide is about 1:10. Carbon dioxide diffuses 20 times more readily than oxygen through the pulmonary membranes (Bouhuys 1974).

Blood leaving the alveoli contains nitrogen in direct proportion to the alveolar partial pressure of nitrogen. No net exchange between gas and blood normally occurs because nitrogen from atmospheric air saturates the tissues of the body (Moran Campbell et al. 1984).

The critical agent that sets apart oxygen from almost other gases that exchange between alveolar spaces and the capillaries is haemoglobin. Haemoglobin reacts in the lung capillaries to form oxyhaemoglobin and

releases the oxygen in the tissues. Reaction between oxygen and haemoglobin is quantified through the haemoglobin saturation curve. The haemoglobin saturation curve is an important component in understanding oxygen deficiency.

• High Altitude

People live and work through a range of altitudes. Sea level is an arbitrary elevation in consideration of overall living conditions.

Travel by large numbers of unacclimatized individuals to high altitudes has increased considerably over the last three decades. (Hultgren 1992) The transient population at ski resorts in the U.S. is estimated at one million. Most of these individuals reside near sea level. This phenomenon adds another dimension to the study of hypoxia (oxygen deficiency). Travel characteristically entails rapid ascent, often within several hours, a brief stay at altitude and rapid descent. Travel activities can include skiing, backpacking, trekking and hiking. All of these involve strenuous exercise.

Table 2 summarizes characteristics of the atmosphere at different altitudes encountered during travel (Hultgren 1992).

Moderate altitude includes many commonly visited and well-inhabited regions of the world. Mild discomfort may occur in susceptible individuals.

The atmosphere of habitable areas above sea level contains the same relative concentration of gases. The total pressure, and hence the partial pressures of individual components, including oxygen, decreases with increasing altitude (de Treville 1988, Lahiri et al. 1972, Davis 1979). Acclimatization from sea level to high level can require weeks or even months. This discussion will consider acute effects of transition to high altitude, as these are more likely to be comparable to events that occur in confined spaces.

The zone of high altitude begins at 8000 ft (2440 m). The latter is generally regarded as the threshold above which altitude-related illness occurs. At this altitude, the arterial partial pressure of oxygen is 60 mm Hg. Corresponding haemoglobin saturation relative to sea level is 92%. At higher altitudes, haemoglobin saturation decreases rapidly. At 14,000 ft (4270 m), arterial partial pressure is 46 mm Hg; arterial haemoglobin saturation is 82%.

The first response of a person acclimatized to sea level upon arrival at high altitude is increased ventilation at rest and during work. Ventilation increases to compensate for acute hypoxia. Hyperventilation increases the partial pressure of O_2 and decreases the partial pressure of CO_2 . The increase in alveolar partial pressure of O_2 continues during the period of acclimatization. Acclimatization requires weeks or even months to accomplish. Thus, acclimatization results in increased alveolar partial pressure of O_2 at the cost of increased ventilation and decreased alveolar partial pressure of CO_2 . Decrease in alveolar and arterial partial pressure of carbon dioxide initially increases pH in blood and cerebrospinal fluid (Bouhuys 1974, Lahiri 1972, Lahiri et al. 1972, Davis 1979). The increase in pH modifies the oxygen-haemoglobin binding relationship. This results in increased haemoglobin saturation beyond what would be predicted, based solely on consideration of partial pressure. As well, haemoglobin binds oxygen more tightly at higher pH and releases less to the tissues for a given decrease in arterial partial pressure (Bellingham et al. 1970).

Despite the increase in pH, the haemoglobin dissociation curve for healthy humans shifts to the right within 24 to 36 hours after arrival at high altitudes (3 000 m or more). This shift promotes unloading of oxygen from haemoglobin, thus increasing its availability to body tissues. This increase reverts to normal upon return to sea level. Associated with this effect is an increase in the level of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells. When long-term residents of high altitude travel to sea level, the reverse occurs. That is, the level of 2,3-DPG decreases and oxygen affinity of haemoglobin increases. Increased 2,3-DPG formation appears to be part of an adaptive response to high altitudes (Lenfant et al. 1968, Lenfant & Sullivan 1971).

Table 2
Altitudes Encountered During Travel

Altitude		Atmospheric Pressure		Equivalent Oxygen Level %	Comments
ft	m	Total mm Hg	Oxygen mm Hg		
0	0	760	159	20.9	sea level, dry reference atmosphere
5000 to 8000	1525 to 2440	636 to 570	133 to 120	17.5 to 15.8	moderate altitude
8000 to 14,000	2440 to 4270	570 to 456	120 to 95	15.8 to 12.5	high altitude
14,000 to 18,000	4270 to 5490	456 to 390	95 to 82	12.5 to 10	very high altitude
18,000 to 29,028	5490 to 8850	390 to 249	82 to 52	10.8 to 6.8	extreme altitude

Altitude illness and high altitude pulmonary edema are extremely rare at ski lodges below 7000 ft (2135 m), yet occur with low frequency at lodges located at 9000 ft (2745 m). Ski areas are located at higher levels. The important factor seems to be related to sleep.

High altitude pulmonary edema (HAPE) results from leakage of fluid from pulmonary capillaries (Bhattacharjya 1964). This can occur in unacclimatized persons who undertake very strenuous physical exercise at altitude, as well as the native-born, following return after prolonged stay at lower altitude. Four to eight weeks are required to de-acclimatize during which time these individuals experience a decrease in haemoglobin and red blood cells. Upon return to altitude, the hypertrophied hearts in these individuals receive insufficient oxygenation due to the decrease in haemoglobin. These changes again comment about differences between those native to low versus high altitude.

Very high altitudes are easily accessible to trekkers and climbers. Rapid ascent to these levels is accompanied by high incidence of severe medical problems, including death. The upper level, 18,000 ft (5490 m) is the limit for prolonged stay. Prolonged stay above this altitude results in deterioration, not acclimatization. This, coincidentally, also is the limit for permanent habitation.

Most people who ascend rapidly to altitudes above 10,000 feet (3050 m) experience some form of altitude effect. At this altitude, total atmospheric pressure is 530 mm Hg and the partial pressure of oxygen is 111 mm Hg. Symptoms include breathlessness, heart palpitations, headache, nausea, fatigue and impairment of mental processes (Vander et al. 1990). These symptoms are similar to those quoted for similar pressures in Table 1 describing oxygen deficiency. These effects disappear during the course of several days, although maximum physical capacity remains reduced.

Residents of high altitudes ventilate less than newly acclimatized lowlanders during exercise or in hypoxic conditions (Lahiri et al. 1972). This indicates greater efficiency of pulmonary gas exchange. Dilation of the pulmonary capillaries may account for the increase in diffusion of alveolar oxygen (Hurtado 1956). Highlanders native to 2900 m or higher tolerate hypoxia better than acclimatized lowlanders and apparently can work harder (Lahiri et al. 1972). People living at altitude are on the steep slope of the oxygen-haemoglobin dissociation curve. This means that a slight change in the oxygen tension delivers more oxygen to the tissues (Hurtado 1956).

There are many genetic variants of haemoglobin in humans. Some lead to disease, whereas others represent

adaptation to environmental conditions, such as high altitude (Bouhuys 1974). Many variants have higher or lower affinity for oxygen than "normal" haemoglobin (Stamatoyannopoulos et al. 1971). In general, the higher the affinity for oxygen, the higher the capacity.

An important effect demonstrated by travel to high altitude is a progressive decrease in maximum exercise capacity and maximum oxygen consumption and decrease in maximum heart rate (West et al. 1983). This decrement occurs even at moderate altitudes and led to increases in times of 5% to 10% for distance races in the Mexico Olympics. The altitude of Mexico City is 7350 ft (2240 m) (Grover et al. 1986).

Decreased performance capacity could have important significance in accidents that occur in confined spaces. This could be especially significant in oxygen-deficient atmospheres during rescue attempts. The rescuer operates under extreme physical and emotional duress. Decreased performance capacity considerably increases the risk of exceeding one's limits under such circumstances.

Adaptation or acclimatization from lower to higher altitudes certainly is possible and occurs all the time. The ability to climb to the top of Mount Everest by people born into low altitude environments without supplemental oxygen is the supreme testimony to that achievement. Adaptation or acclimatization differs from being native-born to the altitude. Altitude-born people and animals have greater number of capillaries in muscle. This enables performance of work at a rate not possible in newcomers even after prolonged residence at altitude (Hurtado 1956). Hence, adaptation or acclimatization is never complete in newcomers.

Davis (1979) summarized the literature on acclimatization as follows:

- people vary in their ability to acclimatize
- the limiting altitude for acclimatization for dwellers at sea level is about 5500 m (18,000 ft), subject to individual differences
- mountaineers can achieve partial acclimatization to about 7000 m (23,000 ft), subject to individual differences
- deterioration in acclimatization begins around 6100 m (20,000 ft)
- drug therapy produces limited benefit
- recommended acclimatization schedule : spend 10 days at each of 6000 to 7000 ft, 9000 to 10,000 ft, 12,000 to 13,000 ft before proceeding to the next higher altitude (Bhattacharjya 1964)

• **Hypoxia (Oxygen Deficiency)**

A condition that mimics the effects of hypoventilation in normal individuals is exposure to an atmosphere containing less than the normal partial pressure of oxygen. In the occupational setting, this condition is produced by asphyxiants. Asphyxiants interfere with the supply or use of oxygen in the body. Asphyxiants include both simple asphyxiants and chemical asphyxiants. Simple asphyxiants include acetylene, argon, ethylene, hydrogen, helium, neon, nitrogen, propylene and water vapour, mist or steam (ACGIH 1994).

Simple asphyxiants are physiologically inert; that is, they do not affect biochemical processes. Chemical asphyxiants interfere with cellular respiration. Simple asphyxiants dilute or displace the normal atmosphere, so that the resultant partial pressure of oxygen is insufficient to maintain oxygen tensions at levels needed for normal tissue respiration. The areas of the body considered most sensitive to oxygen deprivation are the brain and myocardium (heart muscle). Cerebral hypoxia occurs when the partial pressure of inspired oxygen is lowered to 60 to 70 mm Hg (Comroe et al. 1962). Brain cells perish in three to five minutes under conditions of complete hypoxia. Damage sustained by these oxygen-sensitive tissues is not reversible upon restoration of the atmosphere (Ayers et al. 1969, Davis 1979).

Table 3 summarizes physiological effects of brief exposure (8 to 10 min) to oxygen-deficient atmospheres on resting subjects (Comroe et al. 1962). (Minute volume is the amount of air expired per minute. Alveolar ventilation rate is the amount of air expired that equilibrates (exchanges) with alveolar gas per minute.

The characteristic response to hypoxemia (low oxygen in the blood) induced by breathing an oxygen-deficient atmosphere is an increase in depth (tidal volume) and frequency of breathing. This is a direct response to triggering of oxygen chemoreceptors in the carotid and aortic bodies by the decrease in arterial partial pressure. These receptors are somewhat insensitive and not immediate in their response. Atmospheric

Table 3
Effect of Brief Exposure to Oxygen-Deficient Atmospheres

Oxygen		Breathing Frequency (breaths/min)	Minute Volume L/min	Alveolar Ventilation Rate L/min
Concentration %	Volume mL			
20.9	500	14	7	4.9
18	500	14	7	4.9
16	536	14	7.5	5.4
12	536	14	7.5	5.4
10	593	14	8.3	6.2
8	812	16	13	10.4
6	-	-	18	-
5.2	-	-	22	-
4.2	933	30	28	23.2

oxygen concentration must decrease to 16% (sea level) prior to the initiation of response. Said another way, the delay in increasing the depth and frequency of breathing in these situations appears to correlate with decrease in haemoglobin saturation to the steep part of the curve.

The apparent delay in response could be construed as an emergency response when hypoxemia becomes severe. This may not be the case, since there is a similar delay in the onset of more rapid and deeper breathing following the start of vigorous exercise, such as running, from resting status. Hypoxemia is capable of causing increased respiration in normal individuals. However, hypoxemia greater than that seen in most patients with chronic pulmonary disease is required before breathing in normal individuals is stimulated conspicuously (Comroe et al. 1962).

The extent of saturation of haemoglobin reflects partial pressure of oxygen in the blood. Many normally occurring situations, including changing metabolic status from rest to vigorous exercise, rapid ascent to high altitude, and cardiac or pulmonary insufficiency are characterized by reduced alveolar and therefore arterial partial pressure of oxygen.

Decrease of arterial partial pressure from 100 to 60 mm Hg causes only a 10 % decrease in haemoglobin saturation. Hyperventilation by a normal person at sea level produces little change in haemoglobin saturation for this reason (Vander et al. 1990). At arterial partial pressures less than 50 mm Hg, saturation of haemoglobin decreases rapidly. Oxygen tension in tissue capillaries is 40 mm Hg. Oxygen dissociates from the haemoglobin molecule and enters into physical solution in the plasma whenever the oxygen tension in the plasma decreases. Thus, as fast as oxygen diffuses from the plasma into tissues through the capillaries, it is replenished by oxygen dissociating from the haemoglobin (Bouhuys 1974). Oxygenated haemoglobin gives up large quantities of oxygen under these conditions.

Another aspect in exposure to reduced levels of oxygen (normal resting subjects) is transfer from alveolar spaces into blood (Table 4) (Comroe et al. 1962).

As mentioned previously, the normal time spent in the pulmonary capillary bed is 0.75 s. Under normal conditions, the oxygen tension increases to almost 100 mm Hg in 0.35 s or less. This results from the steepness of the pressure gradient across the capillary membranes. The change in pressure gradient with

Table 4
Effect of Oxygen Partial Pressure on Alveolar Gas Exchange

Atmospheric Oxygen %	Alveolar Partial Pressure mm Hg	Capillary Partial Pressure		Partial Pressure Gradient		Haemoglobin Saturation	
		Start mm Hg	End mm Hg	Start mm Hg	End mm Hg	Start %	End %
20.9	101	40	100	61	1	75	97
14	57	32	51	25	4	58	84
12	44	27.5	40	16.5	6	53	75

time as blood perfuses through the capillary is hyperbolic and reaches equilibrium asymptotically. Under normal conditions, the alveolar-capillary pressure gradient is approximately 60 mm Hg. This causes rapid transfer of oxygen from the alveolar airspace into the fluid of the capillary. The partial pressure of O₂ in blood and that in the alveolar airspaces equilibrate before the end of travel through the pulmonary capillary.

In an oxygen-deficient atmosphere containing, for example, 14% oxygen, the initial pressure gradient may be only 25 mm Hg. Because of the shallower pressure gradient, oxygen transfer occurs at a slower rate. A measurable pressure gradient exists between oxygen in the alveolar airspace and blood at the end of the capillary. Under this condition, equilibration fails to occur. Hence, a decrease in the partial pressure of O₂ in inspired air leads to a decrease in arterial partial pressure and a decrease in saturation of haemoglobin (Comroe et al. 1962).

At low levels of oxygen, for example, 12%, oxygen tension in incoming blood decreases to 27.5 mm Hg. The pressure gradient is linear and less steep than that at higher concentrations. The rapid increase in saturation early in the passage through the capillary no longer occurs. Instead, saturation increases proportionate to distance along the capillary. As well, there is a net difference in partial pressure between alveolar air and blood at the end of the capillary due to lack of equilibration.

As the oxygen concentration or atmospheric partial pressure is reduced, haemoglobin saturation decreases. At alveolar oxygen partial pressure of 60 mm Hg, haemoglobin saturation reduces to 90%. The atmospheric partial pressure of oxygen corresponding to this alveolar partial pressure is about 120 mm Hg. At this point, most physiologists agree that symptoms of oxygen deficiency become evident (NIOSH 1976a)

Altitude introduces an additional complicating factor. The body responds to partial pressure of oxygen, rather than concentration. Total atmospheric pressure, and hence the partial pressure of oxygen, both decrease with increasing altitude. Alveolar oxygen partial pressure of 60 mm Hg corresponds to atmospheric oxygen partial pressure at 3000 m (10,000 ft). Altitudes exceeding this height are normally considered to be oxygen-deficient for individuals acclimatized to sea level (Davis 1985). At these altitudes, less oxygen depression in a workspace atmosphere is required to produce an oxygen-deficient condition. As well, a greater percentage of oxygen is required in supplied breathing air to prevent oxygen deficiency. For example, at 10,000 m (33,000 ft), an atmosphere containing 100% oxygen is needed (NIOSH 1976a).

Complicating this situation is the impact of exercise and work. Exercise decreases the time spent by blood in the pulmonary capillaries. This would further reduce saturation in an individual breathing a reduced level of oxygen. To a first approximation (this could be influenced by change in pH), the remaining pressure gradient could be estimated using reduced transit time as a fraction of normal and the linear increase of saturation with time in the capillary. For example, in 14% oxygen and 0.30 s for transit time in place of 0.75 s, partial pressure in blood would increase from 32 to 40 mm Hg. Saturation of haemoglobin would increase from 58% to 75%. Reducing the level of exercise so that the transit time increases to 0.45 s would provide

only marginal increase in partial pressure in blood from 40 to 45 mm Hg. Partial pressure of 45 mm Hg corresponds to saturation of 80%. Saturation would increase during passage through the pulmonary capillaries from 58% to 80% (an increase from 75% to 80%).

A number of stressors that reflect the metabolic demand for gas exchange can modify the breathing pattern. Feedback about arterial partial pressures of oxygen and carbon dioxide and pH provides the information. Under most conditions, ventilation rate regulates arterial oxygen and carbon dioxide tensions within narrow limits. Oxygen deprivation also can become regulating. This occurs when the oxygen content of the inspired gases is reduced to nearly half that in air at sea level (approximately 11%). Hence, under normal circumstances regulation of breathing occurs by bodily requirements to control carbon dioxide tension. However, the concentration of oxygen in an oxygen-deficient atmosphere may become the regulator of breathing. Elevated levels of carbon dioxide (30,000 to 70,000 ppm) increase tidal volume, breathing rate, and minute ventilation (Bouhuys 1974).

Healthy people live long and active lives at high altitudes where arterial saturation ranges from 85% to 95%. Few patients with cardiopulmonary disease have arterial oxygen saturation less than 85%. The lower limit of arterial oxygen saturation compatible with moderately active existence depends on the abruptness with which hypoxemia develops, compensatory mechanisms and other limiting factors in the disease process. Haemoglobin saturation in persons with congenital heart disease may be less than 80% without causing disability. On the other hand, an asthmatic may sustain adequate alveolar gas exchange and arterial saturation only by extreme effort. Persons with emphysema may experience disability despite the fact that arterial saturation is 90% to 95% (Comroe 1962).

• Oxygen Enrichment (Hyperoxia)

Oxygen enrichment is the condition resulting when the partial pressure of oxygen exceeds that found under normal ambient conditions. Normal ambient conditions can include workspaces, such as deep mines, whose workings occur at depths considerably below sea level. At partial pressures considerably greater than those found in normal atmospheres, oxygen exerts both acute and chronic toxic effects.

Hyperoxia has little impact on haemoglobin saturation. Increasing alveolar partial pressure beyond normal values increases haemoglobin saturation insignificantly. This outcome results from the dynamics of the saturation process as reflected in the saturation/partial pressure curve (Bouhuys 1974).

Table 5 indicates the toxic activity of oxygen at elevated partial pressures (Yarborough 1947, Donald 1947, after Dukes-Dobos and Badger 1977, after Behnke 1978).

At partial pressures exceeding 400 mm Hg, oxygen produces respiratory irritation. In hyperbaric atmospheres exceeding 2280 mm Hg, oxygen produces nervous signs and symptoms that culminate in convulsive seizures. Oxygen toxicity is exerted in the lungs, central nervous system and the eyes, although it is probably toxic to all organs at sufficient concentration (Piantadosi 1991). Generally, the rate of onset is a hyperbolic function of the inspired partial pressure (Clark & Lambertson 1971a, Clark & Lambertson 1971b). Sensitivity of the central nervous system to the toxic effects of oxygen is considerably greater than that of the pulmonary system. Tolerance to elevated partial pressures of pure oxygen atmospheres ranges from several minutes to two hours. Toxic action of hyperbaric oxygen atmospheres is greatly enhanced by exercise and elevated levels of carbon dioxide (Yarborough 1947). This translates into reduced tolerance time. Individual tolerance varies widely (Donald 1947).

Oxygen toxicity is expressed through production of reactive intermediates, such as the superoxide anion O_2^- and the hydroxyl radical (OH) (Freeman & Crapo 1982). The superoxide anion is highly reactive toward biological molecules. Normally, enzymic action and reaction by free radical scavengers, such as reduced glutathione, remove these species. During hyperoxia, production of reactive oxygen metabolites greatly increases and may exceed the capacity of scavengers to remove them. Tissue injury and subsequent effects in both brain and lungs appear to be related to increased metabolism (Mayevsky 1984).

Another extremely important consideration about oxygen enrichment is the increased ignitability of clothing and other combustible materials, including the skin (OSHA 1985). OSHA documented a number of fatal

**Table 5
Toxic Action of Oxygen**

Atmospheric Pressure		
Total mm Hg	Oxygen mm Hg	Comments
760	159	sea level
	400	respiratory irritation
	760	throat irritation; no systemic effects provided that exposure is brief
	1520	tracheal irritation, slight burning on inhalation; tolerance increased when periods of oxygen interspersed with air; reduced vital capacity develops
	>1520	signs and symptoms of oxygen poisoning: tingling of fingers and toes, visual disturbances, acoustic hallucinations, confusion, muscle twitch, nausea, vertigo, possible convulsions
	>2280	nervous signs and symptoms twitching, vertigo, anxiety, paresthesia in toes and fingers, nausea, convulsive seizures

accidents in which oxygen enrichment occurred through inadvertent or deliberate release of pressurized oxygen gas from tanks in oxy-fuel systems. The resulting fires indicate the considerably enhanced risk of ignitability, even at normal atmospheric pressure.

The enhanced ignitability hazard in an oxygen-enriched atmosphere is due in part to the reduction in minimum energy needed for ignition and the greater rate of flame spread (Frankel 1991). That is, combustible materials ignite more easily and burn more rapidly in an oxygen-enriched atmosphere. Generally, ignition energy decreases with increasing oxygen concentration and rate of flame spread increases with increasing atmospheric pressure. Almost all materials will burn in pure oxygen. This situation can seriously challenge presumptions about safety in selection of materials for use in oxygen service.

Table 6 summarizes the effects of exposure of substances, fabrics and polymers to an oxygen-enriched atmosphere on ignitability (Hugget et al. 1965, Johnson and Woods 1966, after Kuchta et al. 1967, after Kuchta and Cato 1968, after Frankel 1991).

Lubricants and hydraulic fluids are the most sensitive of the types of substances for which information is available. In the case of lubricants, this sensitivity changes from oxygen-deficiency through normal concentrations through oxygen-enrichment. The lowest of the tested partial pressures corresponded to a concentration of 31% oxygen relative to the sea level dry atmosphere.

Table 6
Effect of Oxygen-Enrichment on Combustibility/Flammability

Atmospheric Pressure		
Oxygen mm Hg	Total mm Hg	Comments
159	760	normal atmosphere, sea level, dry air
range	760	decrease in autoignition temperature of hydraulic fluids with increase in partial pressure of oxygen
range	760	decrease in autoignition temperature of lubricants with increase in partial pressure of oxygen from less than normal through 760 mm Hg
236	760	increase in ignitability in oxygen/nitrogen mixture of materials (fabrics, paper, polymers) that did not burn in normal atmosphere
258	760	considerable increase in flame spread rate in combustible materials (fabrics and polymers)
319	760	decrease in ignition temperature of combustible fabrics and sheeting
760	760	slight decrease in autoignition temperature of most hydrocarbon fuels, solvents and anaesthetic gases; broadening of flammable range by increase in upper flammable limit

Glossary of Terms

ACGIH = American Conference of Governmental Industrial Hygienists

ANSI = American National Standards Institute

ASSE = American Society of Safety Engineers

CSA = Canadian Standards Association

mm Hg = millimetres of mercury (Hydrargium = Hg); the normal height of a mercury barometer at sea level is 760 mm

NASA = National Aeronautics and Space Administration

NFPA = National Fire Protection Association

NIOSH = National Institute for Occupational Safety and Health

OSHA = Occupational Safety and Health Administration

ppm = parts per million, a unit of concentration in air

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