Carbon dioxide toxicity and climate change: a serious unapprehended risk for human health.

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Abstract

As atmospheric levels of carbon dioxide continue to escalate as a driver of climate change, the issue of CO_2 toxicity is not recognised as a global risk by the science community. The toxicity of CO_2 for breathing has been well defined for high concentrations but it remains effectively unknown what level will compromise human health when individuals are exposed for their whole life. There is evidence from the few studies of long-term low-level exposure that permanent exposure, to CO_2 levels predicted by the end of the century, will have significant effects on humans. Other studies of slightly higher CO_2 levels may offer clues to effects, not yet observed, that may occur when humans experience lifelong exposure. Although humans and animals are able to deal with elevated levels of CO_2 in the short-term due to various compensation mechanisms in the body, the persistent effects of these mechanisms may have severe consequences in a perpetual environment of elevated CO_2. These include threats to life such as kidney failure, bone atrophy and loss of brain function. Existing research also indicates that as ambient CO_2 increases in the near-future, there will be an associated increase in cancers, neurological disorders and many other conditions. Research is urgently required to clearly identify the severity and proximity of this risk, associated with the primary human function of breathing, being a potential major aspect of climate change.

Introduction

Carbon dioxide is one of the most frequently overlooked of all toxic gases. Even to refer to CO_2 as a toxic gas is a surprise to many safety professionals (Henderson 2006). In indoor environments CO_2 concentration is often elevated relative to ambient outdoor levels due to the fact that the exhaled breath from humans contains high levels (about 4 %) and ventilation may not be adequate to prevent the resulting increase in CO_2 levels. Despite the possible adverse effects on the health where many people occupy buildings or vehicles, there is very low awareness of this issue in the general community.

At present the average ambient concentration of CO_2 (in fresh air) is about 400 ppm (Carbon Dioxide Information Analysis Center 2015). There is now very strong scientific evidence that carbon dioxide (CO_2) levels in our atmosphere are rapidly and consistently increasing in an uncontrolled manner due to humanity's activities, largely resulting from the burning of fossil fuels (Figure 1).

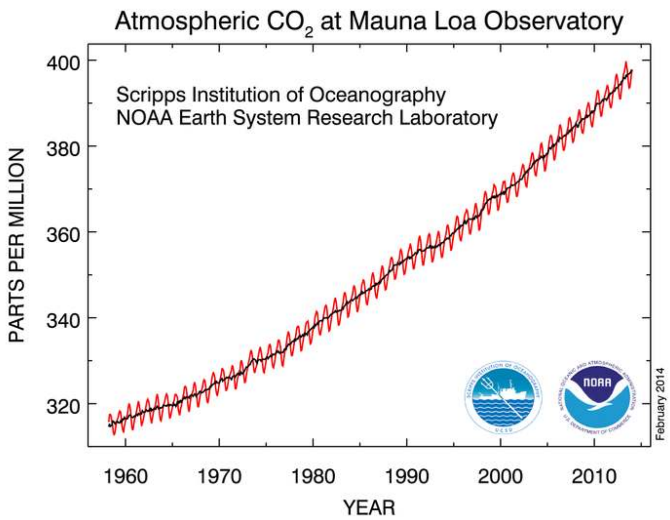

Figure 1. The rapid increase of CO_2 in the atmosphere since the start of direct measurements at Mauna Loa Observatory, Hawaii.

Early primate ancestors of humans evolved about 28 million years ago. Throughout this period of human evolution CO_2 levels in the ambient atmosphere remained relatively stable at levels below 300 parts per million (ppm) (Eggleton 2013; Beerling and Royer 2011). This is derived from a combination of studies of relict features including air trapped in ice cores, the stomata density of fossil leaves as well as the composition of fossil plankton and soils. Since about 1820, CO_2 levels have rapidly increased and are now above 400 ppm (Figure 1). This is a potentially catastrophic problem for many species of animals, including humans, for a number of reasons. The most well publicised issue is that of climate change. The mechanisms and history of global warming associated with CO_2 increase are well understood and the increase in atmospheric energy gradients will produce more extreme temperatures and weather events. Climate change itself may not appear to be catastrophic to many people – for example, it might be possible to escape the effects of even a 5 degree C increase this century by moving to a cooler and safer geographic location. However, it is possible that humans have overlooked the more direct and immediate toxicity aspect of increasing atmospheric CO_2. The earth's atmosphere has already reached CO_2 levels that are outside the range breathed by humans throughout their evolution. As well, some studies have defined the role of elevated atmospheric CO_2 in historical mass extinction events (Knoll et al. 1996)

We know that breathing CO_2 is toxic to humans when levels are high with numerous deaths reported based on occupational exposure (Scott et al. 2009). Although the CO_2 exposure limit for an 8 hour working day has been set at 5,000 ppm (OSHA 2012), this limit was decided in 1946 and based on relatively short-term observations of fit and healthy submariners (Scott et al, 2009). The safe level for lifetime exposure may be significantly lower than this and a number of researchers suggest there could be toxicity effects at CO_2 levels predicted in the near future with ongoing anthropogenic emissions (Portner et al. 2004; Robertson 2006; Ezraty et al. 2011; Antic 2012; McNeil and Sasse 2016). So the question is: how long will it take, at present and future rates of increase, to reach levels that will impact on human health, no matter where you live, over a lifetime? To answer this question, the safe level of CO_2, for continuous breathing in humans, needs to be determined. This paper is an attempt to evaluate available knowledge and to examine the likely and possible risks for the near to medium-term future.

The role of carbon dioxide in breathing

Breathing is one part of physiological respiration and is required to sustain life (Raven et al. 2007). Aerobic organisms such as birds, mammals, and reptiles, require oxygen to release energy by cellular respiration, through the metabolism of molecules such as glucose. During aerobic respiration, glucose is broken down by oxygen to release energy, while carbon dioxide and water are the by-products of the reaction. Breathing delivers oxygen to where it is needed in the body and removes carbon dioxide thereby exchanging oxygen and carbon dioxide between the body and the environment. Carbon dioxide (CO_2) is essentially a waste product of the body but is important as a feedback mechanism by helping to regulate the rate of breathing (Patton and Thibodeau 2009) since the blood level of CO_2 acts directly on the respiratory centres in the brain stimulating the nerves that activate the respiratory muscles. High levels of carbon dioxide correspond with high levels of acid (low pH) in the blood and signal the need for more exchange with oxygen. The exchange of oxygen and CO_2 between the lung alveoli and the blood occurs by simple diffusion - oxygen diffusing from the lung alveoli into the blood and CO_2 from the blood into the lung alveoli depending on the concentration (or pressure) of both oxygen and CO_2 in the alveoli. We do this, of course, by breathing - continuously bringing fresh air (with a lot of oxygen and little CO_2) into the lungs and alveoli.

So there is an optimal range for the concentrations of CO_2 in the air we breathe. Too little can mean that breathing is too slow and not enough oxygen is brought into the body. But too much can compromise our ability to remove CO_2 from our bodies as a waste product. So what are the effects of too much CO_2 and what is the level that can cause health problems in humans?

Health effects from short term exposure to high levels of CO_2

Breathing too much CO_2 results in high levels of CO_2 in the blood (hypercapnia) associated with a decrease in blood pH. This results in a condition known as acidosis. The decreases in blood and tissue pH produce effects on the respiratory, cardiovascular, and central nervous systems (CNS)

(Eckenhoff and Longnecker 1995). Changes in pH act directly and indirectly on those systems producing effects such as tremor, headache, hyperventilation, visual impairment, and CNS impairment. In terms of worker safety, the US Occupational Safety and Health Administration has set a permissible exposure limit (PEL) for CO_2 of 5,000 parts per million (ppm) (or 0.5 %) over an 8-hour work day (OSHA 2012). They report that exposure to levels of CO_2 above this can cause problems with concentration, an increased heart rate, breathing issues, headaches and dizziness.

Exposures to 1-5 % CO_2 for short-term periods have been documented to produce symptoms on humans and animals such as dyspnea (shortness of breath), modified breathing, acidosis, tremor, intercostal pain, headaches, visual impairment, lung damage, increased blood pressure, bone degradation, reduced fertlity, alterations to urine and blood chemistry as well as erratic behaviour (Halperin 2007; Rice 2004; Guais et al. 2011; Schaefer et al. 1963; Yang et al. 1997). In humans, these levels of CO_2 also induce panic attacks, interrupt the processes of metabolic enzymes and disrupt normal cell division processes (Colasanti et al. 2008; Guais et al. 2011; Abolhassani et al. 2009).

Health risks to humans continue to escalate, with progressively higher CO_2 concentrations causing more severe reactions and faster responses. A value of 40,000 ppm is considered immediately dangerous to life and health given that a 30-minute exposure to 50,000 ppm produces intoxication, and concentrations around 70,000 ppm produce unconsciousness (NIOSH 1996). Additionally, acute toxicity data show the lethal concentration for CO_2 is 90,000 ppm (9%) for a 5 minute exposure.

Physiological compensation for elevated CO_2

When considering long-term effects of breathing sustained elevated CO_2, it is important to consider compensation mechanisms in the body, that regulate for increased CO_2 and acidity in the blood, and how these change over time with persistent exposure. The blood pH changes trigger various compensatory mechanisms, including pH buffering systems in the blood, increased breathing to reduce excess CO_2 in the bloodstream, increased excretion of acid by the kidneys to restore acid-base balance, and nervous system stimulation to counteract the direct effects of pH changes on heart contractility and vasodilation (widening of the blood vessels) (Burton 1978; Eckenhoff and Longnecker 1995). In respiratory acidosis, for a period the kidneys retain bicarbonate helping to normalise the pH of the blood as it passes through them. This occurs within 6 to 8 hours of exposure but achieves full effect only after a few days. With continued high levels of CO_2 in the blood, metabolic acidosis occurs and the kidneys don't respond in producing bicarbonate (Schaefer et al 1979a). After this the body uses the bones to help regulate the acid levels in the blood. Bicarbonate and a positive ion (Ca2+, K+, Na+) are exchanged for H+. Over chronic periods of acidosis, bicarbonate and elements are released from the bones resulting in bone breakdown with calcium mobilised to the kidneys. This aspect is discussed further later.

Health effects at common indoor CO_2 concentrations

There is a large recent volume of literature that has documented the occurrence and levels of CO_2 in classrooms across the world including kindergartens, day-care centres, primary schools, high schools and universities (Bako-Biro et al 2011; Widory and Javoy 2003; Kukadia et al. 2005; Dijken et al. 2005; Branco et al. 2015; Heudorf et al. 2009; Santamouris et al. 2008; Ferreira and Cardoso 2014;

Gaihre et al. 2014; Jurado, et al. 2014; Lee and Chang 2000; Muscatiello et al 2015; Carreiro-Martins et al. 2014). There is general agreement that the levels of CO_2 in classrooms commonly (20-50% of all classrooms) exceed 1,000 ppm and are often much higher, sometimes reaching levels as high as 6000 ppm for extended periods. A number of studies have identified CO_2 associated symptoms and respiratory diseases such as sneezing, rales, wheezing, rhinitis, and asthma (Carreiro-Martins et al. 2014; Ferreira and Cardoso 2014). Other symptoms, cough, headache, and irritation of mucous membranes, were also identified (Ferreira and Cardoso 2014). Lack of concentration was associated with CO_2 concentrations above 1000 ppm. Gaihre et al. (2014) found that CO_2 concentrations exceeding 1000 ppm is associated with reduced school attendance. Teachers also report neuro-physiologic (i.e., headache, fatigue, difficulty concentrating) symptoms at CO_2 levels greater than 1000 ppm (Muscatiello et al. 2015).

Offices have similar levels of CO_2 to classrooms depending on the number or density of workers and the types of ventilation systems (Lu et al. 2015; Tsai et al. 2012, Seppanen et al. 1999). These studies have found strong evidence of the relationship between CO_2 levels in offices and Sick Building Syndrome (SBS) health effects such as headaches, dizziness, fatigue, respiratory tract symptoms, eye symptoms, nasal and mucous membrane symptoms (Seppanen et al. 1999; Lu et al. 2015; Tsai et al. 2012). Seppanen et al. 1999 conducted a review of available literature and were careful to eliminate other confounding airborne building contaminants. The reviewed studies included over 30,000 human subjects, and they concluded that the risk of SBS symptoms decreased significantly with carbon dioxide concentrations below 800 ppm. Whether CO_2 itself is responsible for the health symptoms is still a subject of debate since historically it has been assumed, despite lack of direct evidence, that other airborne contaminants are the cause (Zhang et al. 2016).

Although not studied for health effects, vehicles can often contain even higher levels of CO_2 particularly where there are multiple passengers for relatively long journey times. CO_2 levels can build up to 5,000 ppm after less than an hour of driving with two people in a car with only internal air (Gładyszewska-Fiedoruk 2011). Buses with high numbers of passengers consistently reach average CO_2 concentrations of > 2500 ppm (Chiu et al 2015). Airliners can contain levels of around 2000 ppm for the duration of the flight (Gładyszewska-Fiedoruk 2012). Measurements on an Italian submarine showed a steady increase to 5000 ppm CO_2 after 2 hours of being submerged (Ferrari et al. 2005). Extremely high CO_2 concentrations (10,000-20,000 ppm) are commonly found inside motorcycle helmets in both stationary and moving situations (Bruhwiler et al. 2005).

There is increasing concern about the effect of CO_2 on learning and cognitive abilities relating to schools and offices. Testing of students has found that CO_2 can negatively affect attention, memory, concentration and learning ability affecting academic performance (Bako-Biro et al. 2011; Coley et al. 2007). Two recent university studies of cognitive effects of CO_2 were notable in their strong research design (Satish et al 2012; Allen et al 2015). They showed that low level CO_2 (between 950 ppm and 2500 ppm CO_2) affected the cognitive abilities of students and information professionals in the indoor environment. Satish el al. (2012) tested only variations in CO_2 over periods of 2.5 hours of exposure. For seven of nine scales of decision-making performance (basic activity, applied activity, task orientation, initiative, information usage, breadth of approach, and basic strategy), performance was significantly impaired in a dose-response manner with higher CO_2 levels. For example, compared with mean raw scores at 600 ppm CO_2, mean raw scores at 1,000 ppm CO_2 were 11–23% lower, and at 2,500 ppm CO_2 were 44–94% lower. As part of a larger study that included volatile organic compounds (VOCs), Allen et al. (2015) found that, after $CO_2$was independently modified (from a baseline of 480-600 ppm) for individual 8 hour exposures, cognitive function scores were 15% lower at 950 ppm and 50% lower at 1400 ppm. This study used similar methodology to score cognitive function and the results largely repeated the findings of the earlier work (Satish et al 2012). However one difference was that, at 1500 ppm CO_2, even focussed activity was found to have declined (Allen et al 2015). A third study found similar negative effects on human cognitive abilities, in experiments involving 140 minute sessions, as well as increased fatigue at levels of 3000 ppm CO_2 compared with 600 ppm (Kajtar and Herczeg 2012). This study also measured some physiological parameters with heart rate analysis suggesting significantly increased mental effort at 3000-4000 ppm. A more recent study (Zhang et al. 2016) has suggested that none of these effects are due to CO_2 and that human bioeffluents are the likely cause. This was based on experiments that showed no cognitive impairment in humans when high CO_2 levels were artificially supplied but significant effects when the CO_2 was due to human respiration with the latter case assumed to allow the associated build-up of human bioeffluents. Zhang et al (2016) appear to recognise that their results contradict those of the previous three studies which found cognitive impairment using artificially supplied CO_2.They argue that the studies of Satich et al (2012) and Allen et al (2015) involved cognitive testing was too complex for the type of thinking that would be required in a normal indoor environment. However, this criticism of previous work appears to be irrelevant to the issue. Given that Zhang et al. (2016) used fairly simple cognitive tests, and that their conclusions disagree with previous relevant studies and generally support earlier untested theories about the causes of sick building syndrome, the paper might be flawed. Nevertheless, further studies of the effect of CO_2 on cognitive impairment and human well-being are needed.

There are also indoor situations where exhaled human breath and restricted air flow can produce extreme and dangerous levels of CO_2. For example infant deaths have been associated with level of up to 8% (80,000 ppm) CO_2 based on modelling for an infant covered by blankets (Campbell et al. 1996).

Health effects from continuous long term exposure to lower elevated levels of CO_2

Where indoor levels of CO_2 are relatively high and affecting health, it is generally possible to obtain relief by going outdoors. However this may not be the case in a climate change future where ambient CO_2 is persistently high and effects of continuous long-term exposure must be considered. There have been very few studies related to long-term exposure at lower CO_2 levels, elevated above ambient, perhaps for logistical reasons since it is difficult to arrange an experiment for the duration of a human life-span. We are looking for information on the effect on humans of CO_2 levels at 1,000 ppm or less – noting that this is the level that some feasible models predict could be reached in the ambient atmosphere in less than 100 years (Smith and Woodward 2014). Given the lack of research at these CO_2 levels, it seems reasonable to examine the research available for medium-term studies on levels of CO_2 less than 10,000 ppm (1%). Table 1 provides a summary of health effects, found in the published literature and discussed in this paper, resulting from breathing CO_2at levels at or below 1%.

CO_2 Level	Health effect	Exposure duration	Source
10,000 ppm (1%)	kidney calcification, decreased bone formation and increased bone resorption in guinea pigs	6 weeks	Schaefer et al., 1979
8500 ppm	Increased lung dead space volume	20 days	Rice 2004
7000 ppm	35% increase in cerebral blood flow (implications for cognitive effects seen in other studies)	23 days	Sliwka et al. 1998
5000-6600 ppm	Headaches, lethargy, moodiness, mental slowness, emotional irritation, sleep disruption	Short-term	Chronin et al. 2012; Law et al. 2010
5000 ppm (0.5%)	kidney calcification and bone degradation in guinea pigs	8 weeks	Schaefer 1979
5000 ppm	Current allowable levels for continuous exposure in submarines and spacecraft	Operational continuous	Halperin et al. 2007; Chronin et al 2012
5000 ppm	Permissible exposure limit (PEL) for a work day	8 hours	OSHA 2012
2000 ppm	Kidney effects in animals (likely calcification) - incomplete study	Chronic studies	Schaefer 1982
1400-3000 ppm	Significant impairment of cognitive function including fatigue	2.5 to 8 hours	Satish et al 2012; Allen et al 2015; Kajtar & Herczeg 2012
1000 ppm	Harmful changes in respiration, circulation, and the cerebral cortex	A short time	Goromosov 1968
1000 ppm	Oxidative stress and damage to DNA in bacteria (implications for cancer diseases)	3 hours	Ezraty et al 2011
1000 ppm	Level associated with respiratory diseases, headache, fatigue, difficulty concentrating in classrooms	Short-term	Carreiro-Martins et al. 2014; Ferreira and Cardoso 2014;Seppanen et al. 1999
950-1000 ppm	Moderate impairment of cognitive function	2.5 to 8 hours	Satish et al 2012; Allen et al 2015
800 ppm	Level associated with sick building syndrome - headaches, dizziness, fatigue, respiratory tract, eye, nasal and mucous membrane symptoms	Short-term	Seppanen et al. 1999; Lu et al. 2015; Tsai et al. 2012
400 ppm	Current average outdoor air concentration - no known effect	Lifetime	Carbon Dioxide Information Analysis Center 2015
280-300 ppm	Pre-industrial outdoor level from about 1820 to at least 25 million years ago - no effect	Lifetime	Beerling and Royer 2011

A good information source may be the safety guideline documents for activities where humans are required to remain in enclosed spaces for long periods such as spacecraft and submarines. NASA sought to determine the safe levels for long-term exposure to CO_2, in spacecraft and submarines, but found little research focused on levels below 10,000 ppm CO_2; as such, there was no definitive study available to guide standards (Cronyn et al. 2012). They set the maximum allowable CO_2 concentration limits, for long term (1,000 day) habitation of submarines and spacecraft, at 5000 ppm (James and Macatangay 2009). International Space Station (ISS) crew members have repeatedly reported symptoms associated with acute CO_2 exposure at levels of 5,000 to 6,600 ppm CO_2. Headache was the most commonly reported symptom; other symptoms reported included lethargy, mental slowness, emotional irritation, and sleep disruption (Law et al. 2010). For space flight, Cronyn et al. (2012) identified three potential areas of operational impact of low level CO_2: renal calculi (kidney calcification) and bone reabsorption; cerebral blood flow; and mission performance. With no definitive research to provide insight into these areas, further evaluation was recommended to examine the effects of various low-to-moderate CO_2 concentrations (from ambient levels up to 1%) on human subjects.

Studies of CO_2 effects on humans in enclosed submarines have been reviewed by the US government (Halperin 2007) although again most of these studies are for high (> 1%) CO_2 levels at relatively short exposure durations. At these levels (>1%), many of the debilitating and acute symptoms described above were noted. Current safe levels for continuous exposure in submarines were deemed to be around 5,000 ppm CO_2 – this level is set arbitrarily at one third of the level where there were obvious signs of health problems (James and Macatangay 2009). It was also noted that if problems are observed, a submarine can surface so that its occupants can be exposed to the ambient atmosphere. Halperin (2007) reports that exposures to CO_2 levels as low as 7,000 ppm can lower blood pH by up to 0.05 units and induce renal (kidney) compensation in healthy subjects. This compensation occurs over a variable period of time, but effects of lowered pH on clinical status or performance have not been reported either experimentally or operationally. Given that kidney compensation cannot occur indefinitely, there is some doubt about whether submariners could sustain the "safe" level of 5,000 ppm CO_2 if they spent years exposed to it.

Other serious effects related to the body's compensation activities under persistent exposure have been observed at or less than 10,000 ppm CO_2 including lung dead space volume, kidney calcification, decreased bone formation and increased bone resorption (Rice 2004; Schaefer et al., 1979). As part of a US Navy experimental program in the 1960's and 1970's investigating impacts of long-term CO_2 exposure, Schaefer (1979) found that, in a study of Guinea pigs in an enclosed environment breathing 5.000 ppm CO_2 for 8 weeks, under these conditions the kidneys started to calcify with the calcium having been released from bone. Schaefer (1982) also indicated that preliminary experiments have found kidney effects in animal studies for CO_2 concentration as low as 2.000 ppm.

Other important physiological CO_2 effects on health

Cerebral blood flow (CBF) effects from breathing CO_2 is a significant issue for humans. As CO_2 in the blood increases, CBF increases to effectively wash out CO_2 from brain tissue and helps regulate central pH (Ainslie and Duffin, 2009). In a 23 day experiment on humans, Sliwka et al. (1998) found that cerebral blood flow is increased in the presence of 7,000 ppm (0.7%) CO_2 by as much as 35% and that CBF remained elevated until the end of the evaluation period, 2 weeks after the exposure. The impacts of persistent increase in CBF are unclear although there may be a risk of raised intracranial pressure (ICP) which can compress and damage delicate brain tissue. There is also evidence that the CBF response to increased CO_2 is impaired in Alzheimer's patients and that this is linked to the decline in cognitive abilities (Glodzik et al 2013) which will worsen as CO_2 in the atmosphere increases.

In humans, carbon dioxide is also known to play a role in oxidative stress caused by reactive oxygen species (ROS) (Ezraty et al. 2011). ROS are produced by aerobic metabolism of molecular oxygen and play a major role in various clinical conditions such as malignant diseases, diabetes, atherosclerosis, chronic inflammation and neurological disorders such as Parkinson's and Alzheimer's diseases (Waris and Ahsan 2006). In particular, oxidative damage to cellular DNA can lead to mutations resulting in the initiation and progression of cancer. Ezraty et al (2011) demonstrated that current atmospheric CO_2 levels play a role in oxidative stress and that increasing CO_2 levels between 400 and 1,000 ppm increasingly exacerbated oxidative stress and damage to DNA in bacteria. Increased CO_2 increases the production of ROS leading to increased incidence of cancers and other diseases including the promotion of virus activity. Ezraty et et al (2012) concluded that with increasing atmospheric CO_2 concentrations, this exacerbation might be of great ecological concern with important implications for life on Earth.

Similar to cancer there are a number of conditions where some individuals are currently impacted by the effects of CO_2 toxicity. One example is people affected by sleep disordered breathing (SDB). Brillante et al (2012) found that the development of nocturnal hypercapnia in normal indoor CO_2 air concentration, quantitated by a large difference in carbon dioxide in the blood between morning and evening, predicted increased mortality in SDB patients. This is a result of the lack of efficacy of an individual's respiratory regulatory system in sleep for maintaining normal blood gas tensions (Brillante et al. 2012). As CO_2 levels in the atmosphere increase into the future, the impacts on and number of affected individuals will logically increase.

Another study (Goromosov 1968) reported harmful physiological effects on humans at only 1,000 ppm CO_2 reporting changes in respiration, circulation, and cerebral electrical activity.

Discussion

The main question here is: what is the direct risk to the human species posed by the breathing of ambient atmospheric CO_2 concentrations that are rapidly increasing? More specifically, what is the effect on physiology and what is the level of ambient atmospheric CO_2 that provides unacceptable risk? If this level is reached in the near future, the global human society should be concerned. Some climate models suggest that atmospheric CO_2 levels could be as high as 1,000 ppm in this century – this is completely unknown for the whole primate evolutionary lineage which has only ever experienced levels below and up to the current level of 400 ppm.

As observed in this paper, there is no documentation of long term physiological studies of exposure to 1,000 -2,000 ppm CO_2 or less. However, there are short-term exposure studies describing disease symptoms at levels around 1000 ppm CO_2 and reduced cognitive ability in humans at around 800 ppm CO_2. The studies of cognitive effects were conducted at CO_2 levels that represent typical conditions currently present in offices, classrooms and apartments. Although the modest reductions in multiple aspects of decision making, seen as low as 950 ppm (Allen et al. 2015), may not be critical to individuals, at a societal level, or for employers, an exposure that reduces performance even slightly could be economically significant. Surprisingly it is possible that such effects occur without recognition in daily life (Satish et al. 2012). It appears that the CO_2 induced decline in cognitive ability is due to increased Cerebral Blood Flow (CBF) and the resulting effects on central nervous system and brain cortical function (Satish et al 2012; Glodzik et al 2013). The effect on cortical function is supported by a study of infants that showed an inverse relationship between blood CO_2 and electrocortical activity (Wikstrom et al. 2011).

The impacts on students including sickness, reduced attendance and reduced learning abilities should be a concern for society. Moreover, the relatively high levels of CO_2 in vehicles associated with declining concentration and fatigue has serious implications for the safety of drivers and their passengers. This is an issue that does not appear to have been raised in research on driver fatigue illustrating the general lack of awareness about CO_2 effects.

Most of the problems associated with elevated indoor CO_2 levels greater than about 800 ppm, can be alleviated by spending time in fresh air. The indoor environments can be restored to acceptable CO_2 levels with effective ventilation although this is often not being achieved. The available resource of fresh air may be the underlying misguided reason why there is a lack of concern for pollution and its effects. Significantly this resource may not available in the future as rising atmospheric CO_2 associated with climate change may exceed the 800 ppm level in the current century (Smith and Woodward, 2014). At that stage, there will be no outdoor escape from the described symptoms. It seems possible, even likely, that under such a condition of permanent exposure, there may be health impacts at levels below that where obvious effects are observed, i.e. less than 800 ppm.

As mentioned previously the body compensates for high levels of CO_2, through a combination of increased breathing, blood pH buffering, kidney and bone adaptations depending on the length of continuous exposure, until we can resume breathing lower levels of CO_2. There are very few studies that indicate what level of CO_2 in the air will induce the longer-term compensation activities. Kidney involvement has been documented to occur in animals at 2,000 ppm (Schaefer 1979) and 7,000 ppm in humans (Halperin 2007) although no lower limits were defined. One author suggests that blood pH would be reduced to dangerous levels, if there were no physiological compensation, at CO_2 levels as low as about 430 ppm (Robertson 2006) implying that compensation would occur at this level. Ambient conditions may already be dangerously close to CO_2 levels that will induce continuous body compensation. Moreover, there is strong evidence that, with chronic activity, compensation mechanisms can produce serious health issues such as kidney calcification and bone loss. There are known health problems associated with persistent body compensation for blood acidity at CO_2 levels that are about 10 times the current ambient air concentration, but these are for a relatively short duration studies. Although studies are lacking, it is conceivable that these problems might appear at much lower levels of CO_2 if compensation persisted for a much longer periods, for example living a whole lifetime in an elevated CO_2 atmosphere of a climate changed future. In the final paper of the US Navy CO_2 research program, Schaefer (1982) indicated that this issue had "become the concern of the Department of Energy and other US government agencies" although it appears to have been largely forgotten since. If allowed to persist, problems such as kidney calcification could lead to renal failure. In the extreme case lifespans could become shorter than the time required to reach reproductive age. This would result in extinction of the species without interventions such as the creation of artificial living environments.

While this sounds alarmist, the fact remains that the level of CO_2 in the ambient atmosphere, beyond which the health or survival of the species could be threatened, remains unknown. This is surely an unacceptable risk. The current evidence that the human species is already impaired in indoor environments this is likely to get worse as rising outdoor levels of CO_2 contribute to increased indoor concentrations. Furthermore, the incidence and prevalence of human kidney calcification (i.e. stones) is increasing globally with the rate highest for males (Romero et al. 2010). Although this may not be related, it is possible that rising office levels of CO_2 is a contributing cause. As well there is evidence that CO_2 toxicity contributes to a range of serious health issues including cancer, neurological diseases and sleep disorders, is being experienced by individuals at the current ambient levels which are now 40% higher that pre-industrial levels. It seems likely that CO_2 toxicity related to human-induced climate change is already having an impact on population health but not yet recognised.

Of course it is not only humans that are at risk. It has been demonstrated that animals have varying degrees of susceptibility to carbon dioxide (Schaefer et al. 1971). The impacts of elevated CO_2 are even greater for water breathing animals than air breathing animals. In general, land animals have much higher blood CO_2 than aquatic animals and can compensate for hypercapnia by increasing ventilation. In aquatic animals, compensation by increased ventilation is rare and a small increase in ambient CO_2 causes hypercapnic acidosis (Portner et al. 2004; Knoll et al. 1996; McNeil and Sasse 2016). Studies have shown that hypercapnia in fish produces substantial neurological, behavioural and physiological effects for even short term exposures at a CO_2 concentration predicted to be persistent in the ocean before the year 2100; this level corresponding with an atmospheric concentration of 650 ppm CO_2 (McNeil and Sasse 2016).

So why is the issue of CO_2 respiration toxicity related to near-future ambient atmosphere concentrations not being addressed? Despite significant documentation of health issues due to CO_2 in indoor environments, there is very low awareness in the community. For spacecraft and submarines there are practical considerations that influence the recommended safe levels. Initial safe limits for the International Space Station were partly decided by engineering requirements (Cronyn et al. 2012) and submarine limits were balanced by the ability to surface and renew air quality. It seems that there has been little concern about low-level toxicity of CO_2 because we have always had the back-up of an ambient atmosphere with low levels of CO_2. It is also possible that climate change has become the main focus of rising CO_2 levels and there is a lack of perception amongst scientists about the potential dangers of CO_2 toxicity. The latest IPCC report on climate change states that CO_2 is not considered a health damaging air pollutant at lower levels of concentration (Smith and Woodward 2014) although these levels are not defined. The IPCC report did however describe the findings of Satich et al. (2012) as a reported "reduction in mental performance at 1,000 ppm CO_2 and above, within the range that all of humanity would experience in some extreme climate scenarios by 2100" (Smith and Woodward 2014). Moreover, CO_2 toxicity is very much a discipline of environmental medicine which has not focussed on the potential problem because chronic toxicity cases have not yet been recognised; this may be a reason why there are very few researchers involved at this stage.

Conclusions

The main aim of this paper was to explore the question of toxicity for human breathing at levels of CO_2 that could be attained with the continued unabated rise in atmospheric CO_2 associated with climate change. For humans, breathing is paramount before finding water, food and shelter. From the evidence presented here, there appears to be current health impacts of rising CO2 levels and a significant risk of serious health issues arising in the human population at some time in this century.

Current impacts of elevated and increasing ambient CO_2 in indoor environments include respiratory diseases, headaches, fatigue and other symptoms at levels above 800 ppm. This finding together with the impairment of cognitive abilities at CO_2 levels just above ambient (between 600 and 1,000 ppm) is significant in that it has implications at a societal level for human function particularly for jobs with critical responsibility (e.g. surgery, air-traffic controllers, drivers etc.) together with the impact on learning, human development and economies. These impairing CO_2 effects will be increased and more permanent in a future with elevated outdoor ambient CO_2 concentrations. Other ongoing impacts may include the exacerbation by CO_2 of cellular oxidative stress resulting in an increase in cancers, neurological diseases, viruses and many other conditions. Studies of health effects at higher levels of CO_2 at around 2,000-5,000 ppm demonstrate the impact of persistent attempts by the body to compensate for increased acidity in the blood. These effects include kidney calcification, bone degradation and cerebral blood flow disorders. The latter can be related to a decrease in cognitive abilities and potential brain damage. While there is a lack of studies in humans at lower CO_2 levels, demonstrated effects in animals and symptoms experienced by humans indicate that longer-term mechanisms compensating for increased blood CO_2 might be active when breathing at around 800-1000 ppm CO_2. This is a level predicted for the ambient atmosphere by the end of the century in a "business as usual" world. This means that most humans could at this time be experiencing persistent body compensation for acidosis effects resulting in serious health problems that may threaten species viability. The risk for near-future human and animal population health is extremely high and should be communicated since global awareness of this issue may enable a change practice on CO_2 emission activities. Also, new research on the health effects of long term exposure to realistic future atmospheric CO_2 levels is urgently needed.

References

Abolhassani M, Guais A, Chaumet-Riffaud P, Sasco A, Schwartz L. 2009. Carbon dioxide inhalation causes pulmonary inflammation. Am J Physiol Lung Cell Mol Physiol 296: L657–L665.

Ainslie PN, Duffin J. 2009. Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. Am J Physiol Regul Integr Comp Physiol 296: R1473–1495.

Allen JG, MacNaughton P, Satish U, Santanam S, Vallarino J, Spengler JG. 2015. Associatios of Cognitive Function Scores with Carbon Dioxide, Ventilation, and Volatite Organic Compound Exposures in Office Workers: A Controlled Exposure Study of Green and Conventional Office Environments. Environmental Health Perspectives DOI:10.1289/ehp.1510037.

Antic NA. 2012. Global warming and increased sleep disordered breathing mortality, rising carbon dioxide levels are a serial pest. Respirology 17: 885–886.

Beerling DJ, Royer DL. 2011. Convergent Cenozoic CO_2 history. Nature Geoscience 4: 418-420.

Bakó-Biró Z, Clements-Croome DJ, Kochhar N, Awbi HB, Williams MJ. 2011. Ventilation rates in schools and pupils' performance. Building and Environment 48: 1-9.

Branco PTBS, Alvim-Ferraz MCM, Martins FG, Sousa SIV. 2015. Children's exposure to indoor air in urban nurseries-part I: CO2 and comfort assessment. Environmental Research 140: 1–9.

Brillante R, Laks L, Cossa G, Peters M, Liu P. 2012. An overnight increase in CO_2 predicts mortality in sleep disordered breathing. Respirology 17: 933-939.

Bruhwiler PA, Stämpfli R, Huber R, Camenzind M. 2005. CO2 and O2 concentrations in integral motorcycle helmets. Appl Ergon 36(5): 625-633.

Burton RF. 1978. Intracellular buffering. Respiration Physiology 33: 51-58.

Campbell AJ, Bolton DPG, Williams SM, Taylor BJ. 1996. A potential danger of bedclothes covering the face. Acta Paediatr 85(3): 281-284.

Carbon Dioxide Information Analysis Center. 2014. U.S. Department of Energy. Available: http://cdiac.esd.ornl.gov [accessed 23 December 2014].

Carreiro-Martins P, Viegas J, Papoila AL, Aelenei D, Caires I, Araújo-Martins J, Gaspar-Marques J, Cano MM, Mendes AS, Virella D, Rosado-Pinto J, Leiria-Pinto P, Annesi-Maesano I, Neuparth N. 2014. CO(2) concentration in day care centres is related to wheezing in attending children. Eur J Pediatr 173: 1041-1049.

Chiu CF, Chen MH, Chang FH. 2015. Carbon Dioxide Concentrations and Temperatures within Tour Buses under Real-Time Traffic Conditions. PLoS One 10(4): e0125117.

Colasanti A, Salamon E, Schruers K, van Diest R, van Duinen M, Griez E, 2008. Carbon Dioxide-Induced Emotion and Respiratory Symptoms in Healthy Volunteers. Neuropsychopharmacology 33: 3103-3110.

Coley DA, Greeves R, Saxby BK. 2007. The effect of low ventilation rates on the cognitive function of a primary school class. International Journal of Ventilation 6: 107-112.

Cronyn PD, Watkins S, Alexander DJ. 2012. Chronic Exposure to Moderately Elevated CO_2 during Long-Duration Space Flight. NASA Technical Report NASA/TP-2012-217358. Available: http://ston.jsc.nasa.gov/collections/trs/_techrep/TP-2012-217358.pdf [accessed 23 December 2014].

Dijken FV, Bronswijk JV, Sundell J. 2005. Indoor environment in Dutch primary schools and health of the pupils. Proceedings of Indoor Air, Beijing, Vol 1: 623-627.

Eckenhoff RG, Longnecker DE. 1995. The therapeutic gases. Effects of carbon dioxide. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Ed (Hardman JG,ed). McGraw Hill, 355-356.

Eggleton T. 2013. A short introduction to climate change. Cambridge University Press.

Ezraty B, Chabalier M, Ducret A, Maisonneuve E, Dukan S. 2011. CO_2 exacerbates oxygen toxicity. EMBO Reports 12: 321–326.

Ferrari M, Lodola L, Dellavalle C, Rotondo P, Ricciardi L, Menghini A. 2005. Indoor air quality in an Italian military submarine. G Ital Med Lav Ergon 27(3): 308-311.

Ferreira AM, Cardoso M. 2014. Indoor air quality and health in schools. J Bras Pneumol 40(3): 259-268.

Gaihre S, Semple S, Miller J, Fielding S, Turner S. 2014. Classroom carbon dioxide concentration, school attendance, and educational attainment. J Sch Health 84(9): 569-574.

Gładyszewska-Fiedoruk K.2011. Concentrations of carbon dioxide in the cabin of a small passenger car. Transportation Research Part D 16: 327–331.

Gładyszewska-Fiedoruk K.2012. Indoor air quality in the cabin of an airliner. Journal of Air Transport Management 20: 28-30.

Glodzik L, Randall C, Rusinek H, de Leon MJ. 2013. Cerebrovascular reactivity to carbon dioxide in Alzheimer's disease. A review. J Alzheimers Dis. 35(3):427-440

Goromosov MS. 1968. The Physiological Basis of Health Standards for Dwellings. World Health Organization Geneva. Available: http://apps.who.int/iris/handle/10665/39749 [accessed 26 August 2014].

Guais A, Brand G, Jacquot L, Karrer M, Dukan S, Grevillot G, Jo Molina T, Bonte J, Regnier M, Schwartz L. 2011 Toxicity of Carbon Dioxide: A Review. Chem Res Toxicol 24 2061-2070.

Halperin WE. 2007. National Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants. Vol. 1. National Research Council of the National academies. National Academies Press. Available: http://www.nap.edu [accessed 9 April 2015].

Henderson R. 2006. Carbon dioxide measures up as a real hazard. Occupational Health & Safety 75.7 : 64,68-69.

Heudorf U, Neitzert V, Spark J. 2009. Particulate matter and carbon dioxide in classrooms – The impact of cleaning and ventilation. Int. J. Hyg. Environ. Health 212: 45–55.

Kajtar L, Herczeg, L. 2012. Influence of carbon-dioxide concentration on human well-being and intensity of mental work. Q. J. Hung. Meteorol. Serv 116: 145–169.

Kukadia V, Ajiboye P, White M. 2005. Ventilation and indoor air quality in schools, BRE Information paper IP06/05. Watford: BRE publication.

James JT, Macatangay A. 2009. Carbon Dioxide – Our Common "Enemy" . NASA Technical report JSC-CN-18669. SAMAP Submarine Air Monitoring Air Purification Conference, 19-22 October 2009, San Diego, CA. Available: http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20090029352.pdf [accessed 9 April 2015].

Jurado SR, Bankoff ADP, Sanchez A. 2014. Indoor air quality in Brazilian universities. International journal of environmental research and public health 11(7): 7081-7093.

Knoll AH, Bambach RK, Canfield DE, Grotzinger JP. 1996. Comparative Earth History and Late Permian Mass Extinction. Science 273: 452-457.

Law J, Watkins S, Alexander, D. 2010. In-Flight Carbon Dioxide Exposures and Related Symptoms: Associations, Susceptibility and Operational Implications. NASA Report TP–2010–216126. Available: http://ston.jsc.nasa.gov/collections/trs/_techrep/TP-2010-216126.pdf [accessed 26 August 2014].

Lee SC, Chang M. 2000. Indoor and outdoor air quality investigation at schools in Hong Kong. Chemosphere 41(1-2): 109-113.

Lu CY, Lin JM, Chen YY, Chen YC. 2015. Building-related symptoms among office employees associated with indoor carbon dioxide and total volatile organic compounds. International journal of environmental research and public health 12(6): 5833-5845.

McNeil B, Sasse T. 2016. Future ocean hypercapnia driven by anthropogenic amplification of the natural CO2 cycle. Nature 529: 383-386.

Muscatiello N, McCarthy, A, Kielb C, Hsu WH, Hwang SA, Lin S. 2015. Classroom conditions and CO_2 concentrations and teacher health symptom reporting in 10 New York State Schools. Indoor Air 25(2): 157-167.

National Institute for Occupational Safety and Health (NIOSH). 1996. Criteria for a Recommended Standard, Occupational Exposure to Carbon Dioxide. August 1976. In: Documentation for

Immediately Dangerous to Life or Health Concentrations (IDLHs) for carbon dioxide. Available: www.cdc.gov/niosh/docs/1970/76-194.html [accessed 23 December 2014].

OSHA (Occupational Safety and Health Administration). 2012. Sampling and Analytical Methods: Carbon Dioxide in Workplace Atmospheres. Available: http://www.osha.gov/dts/sltc/methods/inorganic/id172/id172.html [accessed 23 December 2014].

Patton KT, Thibodeau GA. 2009. Anatomy & Physiology. 7th ed. St Louis. Mosby.

Portner HO, Langenbuch M, Reipschlager A. 2004. Biological Impact of Elevated Ocean CO_2 Concentrations: Lessons from Animal Physiology and Earth History. Journal of Oceanography 60:705-718.

Raven P, Johnson G, Mason K, Losos J, Singer S. 2007. Biology. 8th ed. New York. McGraw-Hill.

Rice SA. 2004. Human health risk assessment of CO_2: Survivors of acute high-level exposure and populations sensitive to prolonged low-level exposure. Third Annual Conference on Carbon Sequestration. 3-6 May 2004, Alexandria, Virginia, USA. Available: http://www.netl.doe.gov/publications/proceedings/04/carbon-seq/169.pdf [accessed 13 April 2015].

Robertson DS. 2006. Health effects of increase in concentration of carbon dioxide in the atmosphere. Current Science 90:1607-1609.

Romero V, Akpinar P, Assimos DG. 2010. Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors. Reviews in Urolology 12: e86–e96.

Santamouris M, Synnefa A, Asssimakopoulos M, Livada I, Pavlou K, Papaglastra M, Gaitani N, Kolokotsa D, Assimakopoulos V. 2008. Experimental investigation of the air flow and indoor carbon dioxide concentration in classrooms with intermittent natural ventilation. Energy and Buildings 40; 1833–1843.

Satish U, Mendell MJ, Shekhar K, Hotchi T, Sullivan D, Streufert S, Fisk WJ. 2012. Is CO_2 an Indoor Pollutant? Direct Effects of Low-to-Moderate CO_2 Concentrations on Human Decision-Making Performance. Environmental Health Perspectives 120:1671-1677.

Schaefer KE, Hastings BJ, Carey CR, Nichols JR. 1963. Respiratory acclimatization to carbon dioxide. Journal of Applied Physiology 18:1071-1078.

Schaefer KE, Niemoller H, Messier A, Heyder E, Spencer J. 1971. Chronic CO_2 Toxicity: Species Difference in Physiological and Histopathological Effects. Report No 656, pp 1_26, US Navy Dept, Bureau of Medicine and Surgery, Naval Submarine Medical Center, Submarine Medical Research Laboratory, Groton, CT.

Schaefer KE, Pasquale SM, Messier AA, Niemoeller H. 1979. CO_2-Induced Kidney

Calcification. Undersea Biomed Res. Suppl 6:S143-S153.

Schaefer KE. 1979. Effect of Prolonged Exposure to 0.5% CO_2 on Kidney Calcification and Ultrastructure of Lungs. Undersea Biomed Res. Suppl 6:S155-S161.

Schaefer K E. 1982. Effects of increased ambient CO_2 levels on human and animal health. Experientia 38:1163-1168.

Scott JL, Kraemer DG, Keller RJ. 2009. Occupational hazards of carbon dioxide exposure. Journal of Chem Health and Safety 16:18-22.

Seppänen OA, Fisk WJ, Mendell MJ. 1999. Association of Ventilation Rates and CO2-Concentrations with Health and other Responses in Commercial and Institutional Buildings. Indoor Air 9: 226-252.

Sliwka U, Krasney JA, Simon SG, Schmidt P, Noth J. 1998. Effects of sustained low-level elevations of carbon dioxide on cerebral blood flow and autoregulation of the intracerebral arteries in humans. Aviat Space Environ Med 69:299-306.

Smith KR, Woodward A. 2014. Chapter 11. Human health: impacts, adaptation, and co-benefits. In: **IPCC**, 2014: Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. New York, 709-754. Available: http://ipcc-wg2.gov/AR5/report/full-report/ [accessed 26 August 2014].

Tsai DH, Lin JS, Chan CC. 2012. Office workers' sick building syndrome and indoor carbon dioxide concentrations. J Occup Environ Hyg 9(5): 345-351.

Waris G, Ahsan H. 2006 Reactive oxygen species: role in the development of cancer and various chronic conditions. Journal of Carcinogenesis 5: 14.

Widory D, Javoy M. 2003. The carbon isotope composition of atmospheric CO_2 in Paris. Earth and Planetary Science Letters 215: 289-298.

Wikstrom S, Lundin F, Ley D, Pupp IH, Fellman V, Rosén I, Hellström-Westaset L. 2011. Carbon dioxide and glucose affect electrocortical background in extremely preterm infants. Pediatrics 127(4): e1028-1034.

Yang Y, Sun C, Sun M. 1997. The effect of moderately increased CO_2 concentration on perception of coherent motion. Aviat Space Environ Med 68: 187-91.

Zhang X, Wargocki P, Lian Z, Thyregod C. 2016. Effects of exposure to carbon dioxide and bioeffluents on perceivedair quality, self-assessed acute health symptoms, and cognitive performance. Indoor Air, doi:10.1111/ina.12284.