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

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Abstract

As atmospheric levels of carbon dioxide continue to escalate and drive climate change, the issue of CO₂ toxicity is not recognised as a global risk. The toxicity of CO₂ for breathing has been well defined for high concentrations but it remains effectively unknown what level will compromise human health when individuals are perpetually exposed for their lifetime. There is evidence from the few studies of long-term low-level exposure that permanent exposure, to CO₂ levels predicted by the end of the century, will have significant effects on humans. Other studies of slightly higher CO₂ levels may offer clues to effects that may occur when humans experience lifelong exposure. Unhealthy blood CO₂ concentrations causing stress on the autonomic nervous system have been measured from people in common office environments where reduced thinking ability and health symptoms have been observed at levels of CO₂ above 600 ppm for relatively short-term exposures. Although humans and animals are able to deal with elevated levels of CO₂ 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 CO₂. These include threats to life such as kidney failure, bone atrophy and loss of brain function. Human tissue calcification associated with carbonic anhydrase, the enzyme that converts CO₂ in the body, may be the greatest existential threat. Existing research also indicates that as ambient CO₂ increases in the near-future, there will also be an associated increase in cancers, neurological disorders and 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

An axiom of modern science, as quoted from TS Huxley, is “do not pretend that conclusions are certain which are not demonstrated or demonstrable”. Carbon dioxide is one of the most frequently overlooked of all toxic gases. Even to refer to CO\textsubscript{2} as a toxic gas is a surprise to many safety professionals (Henderson 2006). In indoor environments CO\textsubscript{2} concentration is often elevated relative to ambient outdoor levels due to the fact that the exhaled breath from humans contains high CO\textsubscript{2} (about 4%) and ventilation may not be adequate to prevent the resulting increase in CO\textsubscript{2}. Despite the possible adverse effects on health where many people occupy buildings or vehicles, there is very little awareness of this issue in the general community.

At present the average ambient concentration of CO\textsubscript{2} (in fresh air) is about 400 ppm (Carbon Dioxide Information Analysis Center 2015). There is now strong scientific evidence of a rapid, persistent and uncontrolled increase in atmospheric carbon dioxide (CO\textsubscript{2}) due to humanity’s activities, largely resulting from the burning of fossil fuels (Figure 1).

![Atmospheric CO\textsubscript{2} at Mauna Loa Observatory](image)

Figure 1. The rapid increase of CO\textsubscript{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\textsubscript{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 and the composition of fossil plankton (Zachos 2001). Since about 1820, CO\textsubscript{2} levels have increased rapidly 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\textsubscript{2} increase are well understood and the increase in atmospheric energy gradients will produce more extreme temperatures and weather events. To many people, climate change itself may not appear to be catastrophic – 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\textsubscript{2}. The
Earth’s atmosphere has already reached CO$_2$ levels that are outside the range breathed by humans throughout their evolution. As well, in earlier pre-primate epochs, elevated atmospheric CO$_2$ has been found to be a cause of 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 like 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 and needs to be removed from our body. CO$_2$ from respiring tissues enters the blood plasma and diffuses into the red cells, where it is rapidly hydrated to H$^+$ and bicarbonate (HCO$_3^-$) by the carbonic anhydrase enzyme (CA) (Arlot et al. 1985; Adeva-Andany et al. 2014). This enzyme enables the breakdown of CO$_2$ which returns to the plasma as bicarbonate and is then transported to the lungs (Adeva-Andany et al. 2014). When the bicarbonate reaches the lungs, CA in the alveoli catalyses the reverse reaction generating water and carbon dioxide which is exhaled as a gas. CA thus allows a large pool of otherwise slowly reacting plasma HCO$_3^-$ to be utilized in CO$_2$ excretion (Arlot et al. 1985).

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 (Patton and Thibodeau 2009). 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 (increased acidity) resulting in a condition known as acidosis. The decreases in blood and tissue pH produce effects on the respiratory, cardiovascular, and central nervous systems.
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 fertility, 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). 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 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 do not 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+. The kidneys are involved in a wider array of physiological compensation responses to CO$_2$ induced pH imbalance (acidosis). The kidney tubule recovers filtered bicarbonate or secretes bicarbonate into the urine to help maintain acid-base balance in the blood and this again involves the CA enzyme (Adeva-Andany 2014). The kidney compensatory response can begin within minutes and takes effect over a period of hours to days.

Health effects at common indoor CO$_2$ concentrations

There is a large volume of recent 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 20-50% of classrooms commonly 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; i.e. cough, headache, and irritation of mucous membranes, were also identified (Ferreira and Cardoso 2014). Lack of concentration was associated with CO$_2$ levels 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 symptoms (i.e., headache, fatigue, difficulty concentrating) at CO$_2$ levels greater than 1000 ppm (Muscatiello et al. 2015).

Offices have levels of CO$_2$ similar 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; Vehviläinen et al. 2016; MacNaughton et al. 2016). 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).

More recently a number of studies have demonstrated that CO$_2$ has direct impacts on human physiology at levels commonly found in indoor environments (Azuma et al. 2018). Symptoms such as fatigue and drowsiness caused directly by CO$_2$ have been demonstrated by the use of electroencephalogram (EEG) techniques (Snow et al. 2018). In a study of office workers, a 20% increase in blood CO$_2$, to significantly above normal levels, was measured along with sleepiness, headaches, heart rate variation and poor concentration in air that averaged 2,800 ppm CO$_2$ (Vehviläinen et al. 2016). Heart rate variation at 2700pm is confirmed by Snow et al. (2019) for 10 minute exposure. Increases in blood CO$_2$ were found to be a result of restricted lung function at levels between 2,000 and 3000 ppm CO$_2$ (Shriram et al. 2019). MacNaughton et al. (2016) found that a 1,000 ppm increase in CO$_2$ from background levels was associated with a 2.3 bpm increase in heart rate after adjusting for potential confounders. Another older study (Goromosov 1968) reported harmful physiological effects on humans at only 1,000 ppm CO$_2$ with changes in respiration, circulation, and cerebral electrical activity. These physiological effects are being observed at much lower levels of CO$_2$ than previously anticipated (Azuma et al. 2018).

Although rarely 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). With five people in a car with recirculated air levels of CO₂ can exceed 10,000 ppm (1%) after only 28 minutes, this being a level that is known to result in respiratory acidosis (Constantin et al. 2016). Buses with high numbers of passengers consistently reach average CO₂ 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 CO₂ after 2 hours of being submerged (Ferrari et al. 2005). Extremely high CO₂ 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 CO₂ on learning and cognitive abilities in schools and offices. Testing of students has found that CO₂ can negatively affect attention, memory, concentration and learning ability impacting on academic performance (Bako-Biro et al. 2011; Coley et al. 2007). Several recent university studies of cognitive effects of CO₂ were notable in their strong research design (Satish et al 2012; Allen et al 2016; Allen et al 2018) with the testing environments injected with pure CO₂ meaning that the analysis of CO₂ effects was not confounded by the presence of other substances. These studies showed that low level CO₂ (between 950 ppm and 2500 ppm CO₂) affected the cognitive abilities of students, information professionals and pilots in the indoor environment. Satish et al. (2012) tested only variations in CO₂ 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 CO₂ levels. For example, compared with mean raw scores at 600 ppm CO₂, mean raw scores at 1,000 ppm CO₂ were 11–23% lower, and at 2,500 ppm CO₂ were 44–94% lower. As part of a larger study that included volatile organic compounds (VOCs), Allen et al. (2016) found that, after CO₂ 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 CO₂, even focussed activity was found to have declined (Allen et al 2016). In a study of pilots’ performance, Allen et al. (2018) found that negative impacts on cognitive function were observed between 700 ppm and 1500 ppm CO₂. Another 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 CO₂ 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.

There are indoor situations where exhaled human breath and restricted air flow can produce extreme and dangerous levels of CO₂. For example infant deaths have been associated with levels of up to 8% (80,000 ppm) CO₂ for an infant covered by blankets (Campbell et al. 1996).

**Health effects from long term exposure to lower elevated levels (< 1%) of CO₂**

Where indoor levels of CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 CO₂ levels, it seems reasonable to examine the research available for medium-term studies on levels of CO₂ 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 CO₂ at levels at or below 1%.

Table 1. Documented health effects from breathing CO₂ at concentrations below 1%.

<table>
<thead>
<tr>
<th>CO₂ Level</th>
<th>Health effect</th>
<th>Exposure</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,000 ppm (1%)</td>
<td>kidney calcification, decreased bone formation and increased bone resorption in guinea pigs</td>
<td>6 weeks</td>
<td>Schaefer et al., 1979a</td>
</tr>
<tr>
<td>8500 ppm</td>
<td>Increased lung dead space volume</td>
<td>20 days</td>
<td>Rice 2004</td>
</tr>
<tr>
<td>7000 ppm (0.7%)</td>
<td>35% increase in cerebral blood flow (implications for cognitive effects seen in other studies)</td>
<td>23 days</td>
<td>Sliwka et al. 1998</td>
</tr>
<tr>
<td>5000-6600 ppm</td>
<td>Headaches, lethargy, moodiness, mental slowness, emotional irritation, sleep disruption</td>
<td>Short-term</td>
<td>Chronin et al. 2012; Law et al. 2010</td>
</tr>
<tr>
<td>5000 ppm</td>
<td>Kidney calcification, bone degradation in guinea pigs</td>
<td>8 weeks</td>
<td>Schaefer et al 1979b</td>
</tr>
<tr>
<td>5000 ppm</td>
<td>Current allowable levels for continuous exposure in submarines and spacecraft</td>
<td>Operational continuous</td>
<td>Halperin et al. 2007; Chronin et al 2012</td>
</tr>
<tr>
<td>5000 ppm</td>
<td>Permissible exposure limit (PEL) for a work day</td>
<td>8 hours</td>
<td>OSHA 2012</td>
</tr>
<tr>
<td>2700 ppm</td>
<td>Drowsiness measured by EEG</td>
<td>10 min</td>
<td>Snow et al. 2018</td>
</tr>
<tr>
<td>2700 ppm</td>
<td>Increase in heart rate</td>
<td>10 min</td>
<td>Snow et al. 2019</td>
</tr>
<tr>
<td>2000-4000 ppm</td>
<td>Unhealthy blood CO₂ levels - 15% above normal range, sleepiness, headaches and heart rate variations</td>
<td>4 hours</td>
<td>Vehviläinen et al. 2016</td>
</tr>
<tr>
<td>2000-3000 ppm</td>
<td>Restrictive lung behaviour and elevated blood CO₂</td>
<td>3 hours</td>
<td>Shriram et al. 2019</td>
</tr>
<tr>
<td>2000 ppm</td>
<td>Kidney effects in animals (likely calcification) - incomplete study</td>
<td>Chronic studies</td>
<td>Schaefer 1982</td>
</tr>
<tr>
<td>1400-3000 ppm</td>
<td>Significant impairment of cognitive function including fatigue</td>
<td>2.5 to 8 hours</td>
<td>Satish et al 2012; Allen et al 2016; Kajtar &amp; Herczeg 2012</td>
</tr>
<tr>
<td>1000 ppm</td>
<td>Harmful changes in respiration, circulation, and the cerebral cortex</td>
<td>A short time</td>
<td>Goromosov 1968</td>
</tr>
</tbody>
</table>
### Table 1: Effects of CO₂ Concentrations on Humans

<table>
<thead>
<tr>
<th>CO₂ Concentration</th>
<th>Effects</th>
<th>Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 ppm</td>
<td>Oxidative stress and damage to DNA in bacteria (implications for cancer diseases in humans)</td>
<td>3 hours</td>
<td>Ezraty et al. 2011</td>
</tr>
<tr>
<td>1000 ppm</td>
<td>Level associated with respiratory diseases, headache, fatigue, difficulty concentrating in classrooms</td>
<td>Short-term</td>
<td>Carreiro-Martins et al. 2014; Ferreira and Cardoso 2014; Seppanen et al. 1999</td>
</tr>
<tr>
<td>950-1400 ppm</td>
<td>Health symptoms (respiratory, skin, eyes, headaches, cognitive, dizziness, sensory), increase in heart rate</td>
<td>30 min</td>
<td>MacNaughton et al. 2016</td>
</tr>
<tr>
<td>950-1000 ppm</td>
<td>Moderate impairment of cognitive function</td>
<td>2.5 to 8 hours</td>
<td>Satish et al. 2012; Allen et al 2016; Allen et al. 2018</td>
</tr>
<tr>
<td>800 ppm</td>
<td>Level associated with Sick Building Syndrome - headaches, dizziness, fatigue, respiratory tract, eye, nasal and mucous membrane symptoms</td>
<td>Short-term</td>
<td>Seppanen et al. 1999; Lu et al. 2015; Tsai et al. 2012</td>
</tr>
<tr>
<td>400 ppm</td>
<td>Current average outdoor air concentration - no known effect</td>
<td>Lifetime</td>
<td>Carbon Dioxide Information Analysis Center 2015</td>
</tr>
<tr>
<td>280-300 ppm</td>
<td>Pre-industrial outdoor level from about 1820 to at least 25 million years ago - no effect</td>
<td>Lifetime</td>
<td>Beerling and Royer 2011; Zachos 2001.</td>
</tr>
</tbody>
</table>

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 CO₂, but found little research focused on levels below 10,000 ppm CO₂; as such, there was no definitive study available to guide standards (Cronyn et al. 2012). They set the maximum allowable CO₂ 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 CO₂ exposure at levels of 5,000 to 6,600 ppm CO₂. The most commonly reported symptom was headache; 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 CO₂: 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 on human subjects of various low-to-moderate CO₂ concentrations (from ambient levels up to 1%). Consequently flight rules have been employed to reduce CO₂ limits in the ISS to about 3 mm Hg (4,000 ppm) (Ryder et al. 2017).

Studies of CO₂ effects on humans in enclosed submarines have been reviewed by the US government (Halperin 2007) although most of these studies are for high (> 1%) CO₂ 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 CO₂. 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.

The relationship between CO$_2$ and calcium carbonate deposits in the body

Carbonic anhydrase (CA) enzymes participate in metabolic reactions that result in the precipitation of calcium carbonate (Adeva-Andany 2015; Kim et al. 2012; Tan et al. 2018). CA is implicated in calcification of human tissues, including bone and soft-tissue calcification (Adeva-Andany 2015). The enzyme may be also involved in bile and kidney stone formation and carcinoma-associated microcalcifications. The molecular mechanisms regulating the development of calcification in human tissues and arteries are similar to those that regulate physiological mineralization in bone tissue, being poorly understood (Adeva-Andany 2015). Carbon dioxide conversion by the CA enzyme provides bicarbonate and hydrogen ions that fuel the uptake of ionized calcium which is then deposited in the body tissues.

Although the causes of calcification in human tissues are unclear, one theory is that it may be an adaptation to change or damage (Adeva-Andany 2015). Vascular calcification is believed to be a process initiated by primary damage to the artery wall although the original causes have not been identified (Adeva-Andany 2015). One possible causative process is the effect of pH on CA enzyme activity. In blood plasma, where most of the carbon dioxide is transported in the form of bicarbonate (Adeva-Andany 2014), increased acidity (lower pH) can significantly increase the activity of the CA enzyme (Tan 2018). Increased CO$_2$ in the blood caused by breathing higher levels of the gas could lower the pH enough to increase the activity of CA thereby potentially increasing calcium carbonate deposits. This would occur by CA activity where tissues connect with plasma, e.g. arteries, kidneys. Significant tissue calcification has been observed in animals after 12 weeks exposure with only slight reductions in pH (Schaefer 1979b).

As mentioned earlier kidney calcification is known to occur with longer term exposure to elevated CO$_2$ levels (Rice 2004; Schaefer et al., 1979a). A similar causal link between the activity of CA enzyme, which is mainly responsible for the reversible breakdown of CO$_2$, and calcium deposits has also been established for arteries (Adeva-Andany 2014). As part of a US Navy experimental program in the 1960’s and 1970’s investigating impacts of long-term CO$_2$ exposure, Schaefer et al (1979b) found that, in a study of guinea pigs in an enclosed environment breathing 5,000 ppm CO$_2$ for 8 weeks, the kidneys started to calcify with the calcium having been released from bone. Schaefer (1982) also indicated that preliminary experiments had found kidney effects in animal studies for CO$_2$ concentration as low as 2.000 ppm. Although these studies did not identify a mechanism, they established the casual link between CO$_2$ and kidney calcification. It is possible that, as suggested above, the CA enzyme activity is enhanced by low pH (caused by breathing elevated CO$_2$ levels) thereby causing calcium carbonate precipitation.
Other important physiological CO₂ effects on health

Cerebral blood flow (CBF) effects from breathing CO₂ is a significant issue for humans. As CO₂ in the blood increases, CBF increases to effectively wash out CO₂ 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%) CO₂ 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 CO₂ 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 CO₂ 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 including 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 CO₂ levels play a role in oxidative stress and that increasing CO₂ levels between 400 and 1,000 ppm exacerbated oxidative stress and damage to DNA in bacteria. Increased CO₂ promotes the production of ROS leading to greater incidence of cancers and other diseases including the promotion of virus activity. Ezraty et al (2011) concluded that with higher atmospheric CO₂ concentrations, this exacerbation might be of great ecological concern with important implications for life on Earth.

In addition to cancer there are a number of conditions where some individuals are currently impacted by the effects of CO₂ 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 CO₂ 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 CO₂ levels in the atmosphere increase it is logical that the level of impact and the number of individuals will increase.

Discussion

The main question here is: what is the direct risk to the human species posed by the breathing of ambient atmospheric CO₂ concentrations that are rapidly increasing? More specifically, what is the effect on physiology and what is the level of ambient atmospheric CO₂ 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 CO₂ 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 experienced levels below and up to the current level of 400 ppm.

As observed in this paper, there are no 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 and physiological effects at levels around 1000 ppm CO$_2$ as well as reduced cognitive ability in humans at around 800 ppm CO$_2$; these are CO$_2$ levels that are typically present in offices, classrooms and apartments (Gall et al. 2016). It appears that many of the physiological effects of CO$_2$ are due to the stimulation of the autonomic nervous system resulting in elevated blood pressure, respiration, and heart rate (MacNaughton et al. 2016) and this is also associated with a decline in cognitive ability 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). Autonomic dysfunction through CO$_2$ stress also has a wide array of health impacts to cognitive, urinary, sexual, and digestive systems (MacNaughton et al. 2016). Given these results showing short-term physiological effects, it is logical that chronic effects of autonomic dysfunction, through long-term exposure to elevated concentrations of CO$_2$ (as in a climate changed future), could cause significant health problems.

Cognitive decline due to CO$_2$, evidenced by definitive studies (Satish et al 2012; Allen et al 2016; Allen et al 2018) of indoor environments, would logically produce lower intelligence scores in IQ tests. In fact this phenomenon of declining intelligence is now being measured around the world (Bratsberg and Rogeberg 2018) with the data suggesting an unidentified environmental cause. It is feasible that rising outdoor CO2 levels are the cause of the measured decline in human intelligence (Bierwirth 2018). It is possible that such effects occur without recognition in daily life (Satish et al. 2012). The modest reductions in multiple aspects of decision making, seen as low as 950 ppm (Allen et al. 2016), may not be critical to individuals, but at a societal level or for employers an exposure that reduces performance even slightly could be economically significant.

The impacts on students including sickness, reduced attendance and reduced learning abilities should also 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 be available in the future as rising atmospheric CO$_2$ associated with climate change could exceed the 800 ppm level in the current century (Smith and Woodward, 2014). At that stage, there would be no outdoor escape from the described symptoms. Under such a condition of permanent exposure, there could be health impacts at levels less than 800 ppm.
As mentioned previously the body compensates for high levels of CO₂, 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 CO₂. There are very few studies that indicate what level of CO₂ in the air will induce the longer-term compensation activities. Vehviläinen et al. (2016) appear to demonstrate rapid bicarbonate compensation in the blood that dissipates after 2 hours, well before longer term compensation takes effect. Kidney calcification due to longer-term compensation has been documented to occur in animals at 2,000 ppm (Schaefer 1982) and 7,000 ppm in humans (Halperin 2007) although no lower limits were defined. This process of calcium carbonate precipitation appears to be caused by the increased activity of the CA enzyme, responsible for the conversion of CO₂, where blood plasma with slightly lower pH connects with tissues, thereby producing calcification of the kidneys and arteries.

It has been suggested that blood pH would be reduced to dangerous levels, if there were no physiological compensation, at CO₂ 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 CO₂ levels that will induce continuous body compensation associated with serious health issues such as human tissue calcification and bone loss. These health problems are associated with CO₂ levels that are about 10 times the current ambient air concentration, but these are for relatively short duration studies. It is conceivable that these problems might appear at much lower levels of CO₂ than this when living a whole lifetime in an elevated CO₂ atmosphere of a climate changed future. In the final paper of the US Navy CO₂ 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 and artery calcification could lead to cardiovascular failure. In the extreme case lifespans could become shorter than the time required to reach reproductive age. This could threaten the viability of human and animal species without interventions such as the creation of artificial living environments.

The human species is already impaired in indoor environments and this is likely to get worse as rising outdoor levels of CO₂ contribute to increased indoor concentrations (Azuma et al. 2018). 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 CO₂ is a contributing cause. As well there is evidence that CO₂ toxicity contributes to a range of serious health issues including cancer, neurological diseases and sleep disorders, and is being experienced by individuals at the current ambient levels which are now 40% higher than pre-industrial levels. It seems likely that CO₂ toxicity related to human-induced climate change is already having an unrecognised impact on population health.

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 CO₂ are even greater for water breathing animals than air breathing animals. In general, land animals have much higher blood CO₂ 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 CO₂ 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 (Ishimatsu et al. 2005; Heuer and Grosell 2014) 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).

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 minimal 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). CO$_2$ toxicity is 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 is 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. From the evidence presented here, there appears to be current health impacts of rising CO$_2$ 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, mostly due to activation of the autonomic nervous system, include respiratory diseases, headaches, fatigue, increased heart rate, increased blood pressure, and other symptoms at levels above about 800 ppm. This finding together with the associated 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 physiological 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 human tissue calcification and bone degradation; the former may represent the greatest existential threat for many animals. 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 CO₂ might be active when breathing at around 800-1000 ppm CO₂. 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 physiological effects resulting in serious health problems.

The risk from rising CO₂ levels for human and animal population health in the near-future is extremely high. The level of CO₂ in the ambient atmosphere, beyond which the health or survival of species could be threatened, remains unknown. Communication and global awareness of this issue alongside climate change would further strengthen the need to drastically reduce CO₂ emissions. New research on the health effects of long term exposure to realistic future atmospheric CO₂ levels is urgently needed to quantify this risk.

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