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 safe levels for breathing remain unclear. The toxicity of CO_2 for breathing has been well defined for high concentrations but it is unknown what levels will compromise human health when individuals are perpetually exposed for their lifetime. There is now substantial evidence that permanent exposure, to CO_2 levels predicted by the end of the century, will have significant effects on humans. Unhealthy blood CO_2 concentrations have been measured from people in common indoor environments where reduced thinking ability and health symptoms have been observed at levels of CO_2 above 600 ppm for relatively short-term exposures. 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 chronic inflammation, kidney failure, bone atrophy and loss of brain function. Human tissue calcification associated with carbonic anhydrase, the enzyme that converts CO_2 in the body, could be the greatest existential threat. Existing research also indicates that as ambient CO_2 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_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 CO_2 (about 4%) and ventilation may not be adequate to prevent the resulting increase in CO_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.

The average ambient concentration of CO_2 (in fresh air) has been rapidly increasing and is currently around 410 ppm (Scripps Institution of Oceanography 2020; Schmidt 2020) (Figure 1). This increase is due to humanity's activities, largely resulting from the burning of fossil fuels (Eggleton 2013).

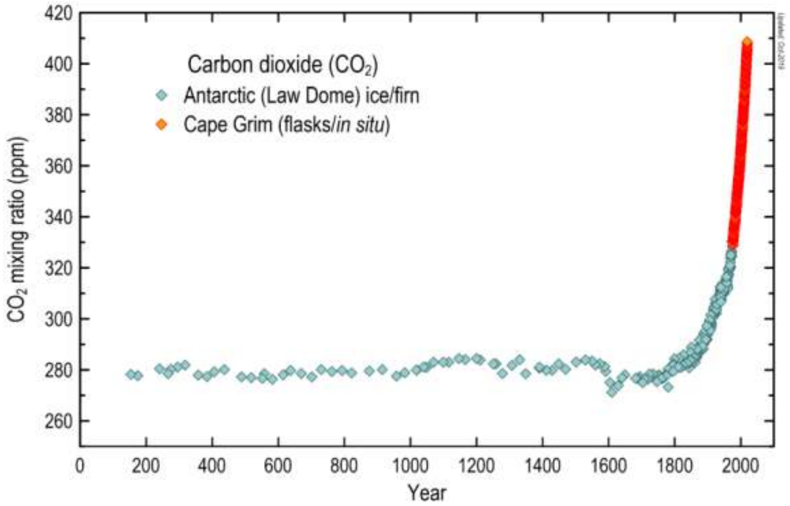

Figure 1. The atmospheric carbon dioxide concentrations (in ppm) over the last 2000 years, based on measurements of air trapped in Antarctic ice, shown in blue-grey diamonds, and the modern Cape Grim, Tasmania direct air measurements, shown in orange. (From Schmidt 2020).

Very early primate ancestors of humans were evolving around 23 million years ago. Throughout all of the ensuing period of human evolution it is clear that levels of CO_2 in the ambient atmosphere remained relatively stable at below or close to 300 parts per million (ppm), this being derived from a combination of studies of relict features including air trapped in ice cores (Schmidt 2020), the composition of fossil plankton (Zachos et al. 2001) and Carbon-13 (^{13}C) content in fossil plant material (Cui et al. 2020). Since about 1820, CO_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_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_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; Karnauskas et al. 2020). 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 C02 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 (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). 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. 2017).

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) while lowered arousal level (fatigue) is clear at 4000 ppm (Xia et al. 2020). Measurements of end-tidal Pco_2 show a significant increase in human blood CO_2 levels during tests conducted on astronauts after 4 months continually exposed to about 5,000 ppm (Hughson et al. 2016). 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). Zheutlin et al. 2014 used statistical data to determine an increasing trend in the average levels of CO_2 in the blood for a national sample of 5,000 people from 1999 to 2012. Heart rate variation at 2700 ppm is confirmed by Snow et al. (2019) for 10 minute exposure. 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 CO_2 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 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 now a significant body of research studies involving the detrimental effect of CO_2 on learning and cognitive abilities in humans at common indoor concentrations (Du et al. 2020). Testing of students has found that CO_2 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 CO_2 have been notable in their strong research design (Satish et al 2012; Allen et al 2016; Allen et al 2018; Scully et al 2019) 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 CO_2 (between 950 ppm and 2500 ppm CO_2) affected the cognitive abilities of students, information professionals and pilots 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. (2016) 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 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 CO_2. 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 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.

Cognitive and neurological effects are also observed in animal studies. Mice exposed from birth to 1,000 ppm CO_2 for 38 days had decreased Insulin-like Growth Factor-1 (IGF-1) which resulted in greater anxiety and reduced cognitive function (Kiray 2014). Neurons were reduced in number and were malformed at this CO_2 level for several areas of the brain, with the largest effect for those areas associated with learning and memory.

There are 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 levels of up to 8% (80,000 ppm) CO_2 for an infant covered by blankets (Campbell et al. 1996).

Health effects from long term exposure to lower elevated levels (< 1%) 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_2 at levels at or below 1%.

Table1. Documented health effects from breathing CO_2 at concentrations below 1%.

CO_2 Level	**Health effect**	**Exposure**	**Source**
10,000 ppm (1%)	Kidney calcification, decreased bone formation and increased bone resorption in guinea pigs	6 weeks	Schaefer et al., 1979a
8500 ppm	Increased lung dead space volume	20 days	Rice 2004
7000 ppm (0.7%)	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	Kidney calcification, bone degradation in guinea pigs	8 weeks	Schaefer et al 1979b
5000 ppm	Elevated blood CO_2 levels in astronauts	4 months	Hughson et al. 2016
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

4000 ppm	Increase in heart rate, lowered arousal level/ increased fatigue and sleepiness	17 minutes	Xia et al. 2020
3000 ppm	Cognitive impairment, anxiety, neural damage, oxidative stress in mice	38 days	Kiray et al. 2014
3000 ppm	Systemic inflammation and physiological stress in rodents	9-13 days	Beheshti et al. 2018
2700 ppm	Drowsiness measured by EEG	10 min	Snow et al. 2018
2700 ppm	Increase in heart rate	10 min	Snow et al. 2019
2000-4000 ppm	Unhealthy blood CO_2 levels - 15% above normal range, sleepiness, headaches and heart rate variations	4 hours	Vehviläinen et al. 2016
2000-4000 ppm	Inflammation and vascular damage in mice	2 hours	Thom et al.2017
2000-3000 ppm	Restrictive lung behaviour and elevated blood CO_2	3 hours	Shriram et al. 2019
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 2016; Kajtar & Herczeg 2012
1200 ppm	Reduced cognitive function	2.5 hours	Scully et al. 2019
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 in humans)	3 hours	Ezraty et al. 2011
1000 ppm	Cognitive impairment, anxiety, neural damage, oxidative stress in mice	38 days	Kiray et al. 2014
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
950-1400 ppm	Health symptoms (respiratory, skin, eyes, headaches, cognitive, dizziness, sensory), increase in heart rate	30 min	MacNaughton et al. 2016
950-1000 ppm	Moderate impairment of cognitive function	2.5 to 8 hours	Satish et al 2012; Allen et al 2016; Allen et al 2018

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; Zachos 2001.

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, 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. 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 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 on human subjects of various low-to-moderate CO_2 concentrations (from ambient levels up to 1%). Consequently flight rules have been employed to reduce CO_2 limits in the ISS to about 3 mm Hg (4,000 ppm) (Ryder et al. 2017).

Studies of CO_2 effects on humans in enclosed submarines have been reviewed by the US government (Halperin 2007) although 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.

The relationship between CO2 and calcium carbonate deposits in the body

Carbonic anhydrase (CA) enzymes participate in metabolic reactions that convert CO_2 and result in the precipitation of calcium carbonate (Adeva-Andany et al. 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 et al. 2015). The enzyme may be also involved in bile and kidney stone formation and carcinoma-associated micro-calcifications. 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 et al. 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 as calcium carbonate.

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 et al. 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 along with bone degradation. Schaefer (1982) also indicated that preliminary experiments had found kidney calcification 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.

Although the mechanism of calcification in human tissues is unclear, one theory is that it may be an adaptation to change or damage (Adeva-Andany et al. 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 et al. 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 et al. 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). Increased CA activity caused by increased CO_2 in the blood is also linked to cancer where the enzyme helps create a hostile, low pH environment suitable for cancers to flourish in (Hulikova et al. 2014; Logozzi et al. 2019; Di Fiore et al. 2020).

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; Kiray et al. 2014). 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 CO_2 levels play a role in oxidative stress and that increasing CO_2 levels between 400 and 1,000 ppm exacerbated oxidative stress and damage to DNA in bacteria. Kiray et al. (2014) concluded that oxidative stress and oxidative damage to brain tissue in mice is associated with low IGF-1 levels in mice. Increased CO_2 promotes the production of ROS leading to greater incidence of cancers and other diseases including the promotion of virus activity (Waris and Ahsan 2006). Ezraty et et al (2011) concluded that with higher atmospheric CO_2 concentrations, this exacerbation might be of great ecological concern with important implications for life on Earth.

Inflammation is a serious illness that is known to be caused by low-level CO_2 exposure in humans and animals (Thom et al. 2018; Beheshti et al. 2018; Zappulla 2008; Jacobson et al. 2019). CO_2 increases result in higher levels of Interleukin, a protein involved in regulating immune responses, which causes inflammation and vascular damage in mice (Thom et al. 2017). Rodents exposed to 3,000 ppm CO_2 in spacecraft experiments for 9-13 days showed evidence of inflammation and physiological stress (Beheshti et al. 2018).

Another study has shown that increased CO_2 in the blood of patients can increase the severity of Subarachnoid haemorrhage; a life threatening form of stroke, due to the dilatation of arterial cerebral vessels (Reiff et al 2020).

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 experienced levels below and up to the current level of 400 ppm.

As observed in this paper, there are few long term physiological studies of exposure to 1,000 -2,000 ppm CO2 or less. However, there are short-term exposure studies describing disease symptoms and physiological effects at these levels 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). Long-term exposure to environmentally relevant levels of CO_2 leads to increases in the levels of CO_2 in human blood (Zheutlin et al. 2014; Hughson et al. 2016; Vehviläinen et al. 2016). This is retention of CO_2 in the human body at greater than normal levels. Increased CO_2 in the blood also affects protein behaviour causing both inflammation (Thom et al. 2018) and calcification (Schaefer 1982) of body tissue, both with potentially serious outcomes. Given these results showing short-term physiological effects, it is logical that 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.

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. 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 CO_2, where blood plasma with slightly lower pH connects with tissues, thereby producing calcification of the kidneys and arteries.

Carbonic anhydrase (CA), a group of isoenzymes that catalyse the reversible hydration of carbon dioxide, participate in calcification processes in a variety of biological systems, including shell formation in shell-forming animals (Adeva-Andany et al. 2015; Lotlikar et al. 2019). It is logical that an increase in atmospheric CO_2 might result in excessive calcification in humans and animals (Bierwirth 2020). This also fits with observations from animal experiments where kidney calcification effects in guinea pigs were documented at 5,000 ppm (Schaefer et al. 1979b) after 8 week exposures and also observed at 2,000 ppm in animals under long-term exposure (Schaefer 1982). There are still few, if any, studies at lower values and longer timeframes although it is likely that the calcification effect would be observed for the CO_2 levels and durations (i.e. lifetime) relevant for climate change. Furthermore, the incidence and prevalence of human kidney calcification (i.e. stones) is increasing globally (Romero et al. 2010; Turney et al. 2011; Kittanamongkolchai et al. 2018) and it is possible that rising office CO_2 levels (boosted by increasing ambient CO_2) is the contributing cause.

So what level of permanent CO_2 will cause significant calcification effects? It has been suggested 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 ongoing compensation would occur at this level. Ambient conditions may already be dangerously close to CO_2 levels that cause human tissue calcification, particularly when considering the additive effect of increased ambient levels on indoor CO_2 concentrations. In the final paper of the US Navy CO_2 research program in the 1960's and 1970's, 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. Calcification of kidneys and arteries can be fatal through renal and cardiovascular failure. 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 CO_2 contribute to increased indoor concentrations (Azuma et al. 2018). The growing prevalence of human kidney calcification (Romero et al. 2010) could be due to rising office CO_2 levels. As well there is evidence that CO_2 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 CO_2 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 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 (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).

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.

The issue of direct impacts of CO_2 on health, related to near-future ambient atmosphere concentrations, is yet to be seriously addressed? Despite significant documentation of health issues due to CO_2 in indoor environments, there is minimal awareness in the community. It seems that there has been little concern 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 most recent IPCC report on the health impacts of climate change, which is now well out of date, 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). Since then there have been many more studies of cognitive decline (Du et al. 2020) and other potentially more physically damaging effects (this paper). CO_2 toxicity is a discipline of environmental medicine which has not focussed on the potential problem because chronic impacts of increasing environmental CO_2 have not yet been recognised. This may be a reason why there are very few researchers involved at this stage.

Conclusions

From the evidence presented here, there appears to be current health impacts of rising CO2 levels and a serious health risk for humans 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 inflammation, 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 CO_2 and 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 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 physiological effects resulting in serious health problems.

The risk from rising CO_2 levels for human and animal population health in the near-future is extremely high. The level of CO_2 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 CO_2 emissions. New research on the health effects of long term exposure to realistic future atmospheric CO_2 levels is urgently needed to quantify this risk.

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