Environmental Science Advances

CRITICAL REVIEW

Cite this: *Environ. Sci.: Adv.*, 2025, **4**, 1364

Carbon dioxide as a pollutant: the risks on human health and the stability of the biosphere

Ugo Bardi, *[a] Phil Bierwirth,[b] Kuo-Wei Huang [c] and John McIntyre[d]

Received 22nd January 2025
Accepted 30th June 2025

DOI: 10.1039/d5va00017c

rsc.li/esadvances

The consequences of the human-caused increase in carbon dioxide concentration in the atmosphere are normally discussed mainly in terms of its radiative forcing effect and the consequent global warming and climate change. However, CO_2 is a chemically active molecule in aqueous environments, and it has multiple effects on the biosphere. Increasing CO_2 concentrations in the atmosphere increase the acidity of seawater and harm marine organisms. High CO_2 concentrations can make the photosynthetic reaction faster in some plants but also negatively affect the metabolism of aerobic metazoans, with harmful effects on human health. These effects are already important for people living in closed spaces and can only become stronger with the projected future increases in CO_2 atmospheric concentration. The present paper is a critical review of a field that is important for the future of humankind. We find that the chemical and biochemical pollution associated with CO_2 is a serious problem that may turn out to be no less important than that of radiative forcing in terms of damage to human health and to the whole biosphere. These results also indicate that geoengineering techniques based on Solar Radiation Management (SRM) alone cannot be sufficient to counter the ecosystem disruption caused by anthropogenic CO_2 emissions.

Environmental significance

We are submitting a paper assessing the chemical and biochemical effects of CO_2 on the biosphere and human health. Warming is just one of the several effects of the human perturbation of Earth's ecosystem, which also include seawater acidification ("the ugly sister of global warming"), unbalance of the metabolic activity of plants, and all sorts of harmful effects on human health, mainly resulting from the combined effects of acidification and reduced oxygen supply to tissues. These harmful effects are not compensated for by the minor (if any) advantages in agriculture generated by the fertilization effect of higher CO_2 levels. Our study highlights an extremely important subject, unfortunately much neglected and ignored so far. It provides a new perspective on the urgent need to reduce CO_2 emissions, independent of their climatic effects. In the long run, it may be necessary to find ways to restore the CO_2 concentrations to levels compatible to those at which the human species evolved, no more than *ca.* 300 ppm. Our study also shows that geoengineering technologies involving solar radiation management are not sufficient to solve the ecosystemic problems generated by anthropogenic carbon emissions.

Introduction

The impact of increasing CO_2 concentrations in the atmosphere was discussed for the first time in 1896 by Svante Arrhenius in terms of its radiative forcing effects,[1] an interpretation that has remained standard up to our times.[2] The non-radiative chemical and biochemical effects of atmospheric CO_2 started to be identified only about half a century later, first in terms of marine water acidity, as discussed in the IPPC's Special Report on the Ocean and Cryosphere in a Changing Climate (srocc).[3]

[a]Club of Rome, Consorzio Interuniversitario per la Scienza e la Tecnologa Dei Materiali (INSTM), Italy. E-mail: ugo.bardi@unifi.it
[b]Emeritus Faculty, Australian National University, Australia. E-mail: Philip.Bierwirth@anu.edu.au
[c]Club of Rome, Center for Renewable Energy and Storage Technologies, Division of Physical Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal 23955-6900, Saudi Arabia. E-mail: hkw@kaust.edu.sa
[d]Independent Researcher, Ullapool, Scotland, UK. E-mail: johndmcintyre@gmail.com

Non-radiative CO_2 climatic effects were also identified; for instance, the feedback of acidity and atmospheric radiation transfer.[4] Increasing CO_2 in the atmosphere also affects Earth's radiation balance in terms of albedo changes resulting from its fertilization effect on land plants.[5] Furthermore, CO_2 enhances the effects of other atmospheric pollutants, particularly in urban CO_2 domes.[6]

The biochemical effects of CO_2 are potentially its most important non-radiative effects on the ecosystem since they directly affect the metabolic system of living beings. This is the main subject of the present paper, which explores an area where, so far, no comprehensive review had been published.

CO_2 is a component of the two main reactions that create and maintain Earth's biosphere: photosynthesis and respiration. Increased CO_2 atmospheric concentrations can make the photosynthetic reaction faster, leading, at least in part, to the "global greening" effect observed in recent years.[7,8] Up to some limits, CO_2 also increases agricultural yields in greenhouses but it does not generate an increase in the nutritional content of the food produced.[9–11]

In the case of respiration, the present review highlights how CO_2 may negatively affect the metabolism of metazoans[12] and human health in particular by altering the acidity of the blood, the oxygen transfer rate, and the body's main metabolic processes, including human cognitive performance. These effects are already detectable at CO_2 atmospheric concentrations not much higher than the current ones.[13] The projected increase in CO_2 concentrations in the coming decades can only worsen the problem, especially considering the human habit of living in closed spaces where the CO_2 concentration is higher than in open air.

Our results highlight the need to rapidly reduce CO_2 emissions and bring them to zero as soon as possible. This exploration is also relevant to the current debate on geoengineering, in particular, Solar Radiation Management (SRM), which is based on placing mirrors in orbit or injecting particles into the upper atmosphere to increase Earth's albedo.[14] This technology can only affect atmospheric temperature, but it cannot avoid the biochemical and chemical damage caused by increasing CO_2 levels, as discussed in this paper. Carbon removal by geological or biological sequestration, instead, goes in the right direction to relieve the problem, even though it remains expensive and involves considerable uncertainties.[15,16] Phasing out fossil fuels and replacing them with low-carbon energy sources remains the most urgent and the most effective option to avoid further increases in atmospheric CO_2 concentration.

Results

CO_2 in the atmosphere

CO_2 in the atmosphere originates in part from outgassing from the mantle and the crust and in part from the combustion or the metabolic processing of organic carbon compounds at or near the Earth's surface. Conversely, CO_2 is removed from the atmosphere by dissolution in the oceans, being turned into biomass by photosynthesis, being turned into solid carbonates by calcifying organisms, and by the inorganic silicate weathering reaction, or the "silicate reaction," which turns mineral silicates into carbonates.[17] If there was no outgassing, these processes would completely eliminate carbon dioxide from the atmosphere in less than a million years.[18]

Some of these processes involve stabilizing feedback. For instance, an inflow of CO_2 in the atmosphere generated by intense volcanism will cause temperatures to rise. But higher temperatures will accelerate the silicate weathering reaction, hence drawing down CO_2, and restoring the previous conditions. Conversely, some reactions involve enhancing feedback. For instance, higher CO_2 concentrations cause an increase in temperature, which may lead the oceans to release some of the dissolved CO_2 they contain, causing more warming.[19]

The early Earth's atmosphere is believed to have been composed mainly of CO_2 and CH_4. With the evolution of oxygenic photosynthesis, 3.2–3.8 billion years ago, carbon dioxide started to be turned into organic carbon compounds while molecular oxygen was produced from the splitting of water molecules. The "Great Oxygenation Event" (GOE), around 2.3–2.4 billion years ago, marked the start of a phase of Earth's history in which free molecular oxygen was present in the atmosphere. About 55 million years ago, during the Cenozoic Era, a robust trend of decline in atmospheric CO_2 started.[20] During the last *ca.* 12 million years, the second half of the Miocene, the decline has been especially rapid.[21,22]

During the ice ages of the Pleistocene, the epoch that precedes the current Holocene Epoch, CO_2 concentrations fell to values as low as 180 ppm, possibly the lowest ever during Earth's history.[23] The pre-industrial concentration was higher, *ca.* 280 ppm, but still very low in comparison with the average levels during the Phanerozoic.[24]

The first to discuss the biochemical consequences of the declining CO_2 concentration during the Miocene were Lovelock and Whitfield in a 1982 paper.[25] They proposed that it was the result of the ecosystem compensating for the temperature increase caused by the sun becoming brighter, a phenomenon known to occur at a rate of *ca.* 9% per billion years.[26] They estimated that, if the trend were to continue, the biosphere would go extinct in approximately 100 million years because CO_2 concentrations would have to go below 150 ppm and, at such low concentrations, photosynthesis would become impossible. It was a remarkable insight, recently supported by calculations based on GCM climate models.[27] However, Lovelock and Whitfield were wrong in their time scale estimates. The decline in solar radiation is much too slow to explain the CO_2 decline of the past few million years. In addition, they didn't take into account the "C_4" photosynthetic mechanism that allows the plants that adopt it to survive at CO_2 concentrations well below 100 ppm. Other authors found that, in principle, the biosphere will be able to survive for several hundred million years in the future.[28,29]

On a much shorter time scale, the decline in CO_2 concentration has been interrupted during the Holocene by human activities which likely prevented the re-glaciation of the planet expected to occur as a continuation of the Pleistocene temperature oscillations.[30] Nowadays, the combustion of fossil fuels and other factors are pushing CO_2 concentrations to levels over 400 ppm, comparable to those existing at least 12 million years ago. The trend is continuing at a rate of nearly 3 ppm per year.

CO_2 and photosynthesis

Carbon dioxide is one of the reactants of the oxygenic photosynthesis reaction that can be written in a simplified form as,

$$h\nu + CO_2 + H_2O \rightarrow O_2 + CH_2O$$

Here, the photon's energy is written as $h\nu$, and CH_2O is the empirical formula for the glucose molecule ($C_6H_{12}O_6$). The reaction occurs in two stages inside specific cells called "chloroplasts". The first is the photocatalytic reaction, which splits water into atomic hydrogen and oxygen. The second, the "Calvin–Benson Cycle", makes CO_2 react with hydrogen atoms to create organic compounds. It uses as a catalyst, an enzyme called "ribulose bisphosphate carboxylase/oxygenase", or "Rubisco".

In vascular plants, the exchange of oxygen and carbon dioxide occurs through pores called "stomata" that directly connect the chloroplast cells to the atmosphere. The stomata can open and close, controlling the exchange of CO_2 and water and preventing the leaf from drying out. This connection is direct in the case of the "C_3" photosynthesis mechanism, the ecosystem's oldest and most common one. The mechanism's efficiency is negatively affected by "dark respiration" or "photorespiration", especially at low CO_2 concentrations. Rubisco has an affinity with oxygen, and in the absence of solar light, it may run the reaction in reverse, producing CO_2 by oxidizing organic compounds.

The C_4 photosynthesis pathway[31] became an important element of the biosphere around the start of the rapid fall in the CO_2 concentrations in the mid-Miocene, about 10 million years ago. Today, it accounts for only about 3% of plant species but contributes around 25% of global terrestrial photosynthesis. It uses the same molecular machinery as the older C_3 mechanism, but the reaction centers are no longer directly connected to the atmosphere. Instead, CO_2 is transformed into malic acid by the phosphoenolpyruvate (PEP) carboxylase enzyme and then accumulated in "bundle sheath" cells. It is later converted again into CO_2 by specific enzymes and then transferred to the Rubisco reaction centers. Succulent plants (Crassulaceae and cacti) use a third photosynthetic pathway: CAM (crassulacean acid metabolism), which also uses PEP but makes plants even more resistant to arid conditions. For low CO_2 concentrations, the C_4 reaction path is faster and more efficient than the C_3 one. In addition, since the stomata remain closed for longer, C_4 plants do not transpire large amounts of water and are more resistant to arid conditions.

The C_4 mechanism was never adopted by trees, likely because it is incompatible with the mechanism that pulls water and dissolved minerals from the roots to the leaves through the xylem.[32] Because of this factor, forests are poorly adapted to low-CO_2 environments. Indeed, during the last glacial maximum, about 20 000 years ago, with a CO_2 concentration as low as 180 ppm, Earth's forests were reduced to sparse patches surrounded by steppes or savannas.[33]

At present, the rise in atmospheric CO_2 caused by human activity is affecting the biosphere in various ways. Transpiration from C_3 trees has substantial effects on the hydrological cycle[34] because changes in column water vapor have a non-linear effect on rainfall, amplifying the effects of a reduction in transpiration. On one hand, a reduction in transpiration reduces low cloud cover, causing warming and reducing the strength of the horizontal water transport by means of the biotic pump mechanism.[35] It also increases runoff and hence flooding. Retallack and Conde[22] reported a 29% reduction in the transpiration of Ginkgo trees since 1829 and showed a direct connection to increased flooding in Southern USA. On the other hand, increasing temperatures (which is an effect of increasing CO_2 concentration) causes an increased leaf-to-air vapor pressure deficit and hence increases transpiration across all biomes and most (though not all) species. The results are reduced photosynthesis, carbon starvation, and cavitation, which stop the flow of water and causes hydraulic stress. These effects are likely more significant than commonly believed. They may cause the range of Northern hemisphere conifers to contract and at the same time increase mortality in Amazonian trees.[36] However, it is not yet clear which of these effects will have the biggest ecological and climate impact.[36–40]

The increasing CO_2 concentrations during the industrial age has been going in parallel with a global increase in forest cover, called "global greening".[41,42] The data show that while the forest area decreased globally (by around 4.7 million hectares per year from 2010 to 2020), the biomass per unit area has generally increased, particularly in Europe and North America.[43] This greening is generally attributed to the increase in the photosynthesis rate of trees (C_3 plants), generated by higher levels of CO_2. However, the effect of agricultural fertilizers spreading in the biosphere cannot be ruled out as the primary cause of this phenomenon.[44]

The response of crop plants to increased atmospheric CO_2 concentration has been extensively studied, finding that it may vary considerably with light, temperature, and humidity. Species also differ, with some responding to a doubling of CO_2 by reducing mean midday conductance (water flow rates) by less than 15%, and in some cases by more than 50%. Simulations and measurements of carbon dioxide enrichment effects in open-air systems indicate that the relatively large reductions in stomatal conductance in crops translate into reductions of <10% in evapotranspiration, partly because of increases in temperature and decreases in humidity in the air around crop leaves. Acker *et al.*[45] reported that transpiration in wheat and tall fescue was unchanged due to CO_2-stimulated leaf growth, but increased in rye grass. Bunce[46] reported reductions in leaf stomatal conductance with increasing atmospheric carbon dioxide concentrations reducing water use by crops.

The effect of increasing CO_2 concentration on food production is a more complex matter, also considering how crop yield has been increasing during the past few decades due to the extensive use of fertilizers, the so-called "green revolution". One source attributes all the increases to CO_2 fertilization,[47] which is improbable, to say the least. Other studies are, correctly, more cautious, but they indicate an effect on crop yields. The results of the "Free Air CO_2 Enrichment (FACE)" experiments[48] found that, apart from fertilizers, the main factors affecting crop yield are irrigation and temperature. Zheng[49] found that the increase in productivity tends to taper off and then decline for CO_2 concentrations over around 1000 ppm. This is what one should expect considering the well-established "Liebig principle", which states that plant growth is determined not by the total resources available, but by the scarcest resource. C_4 plants (maize, millet, and sugarcane) show little or no increase in productivity for increasing CO_2 concentration.[50] For all cases, the increased total biomass produced is not accompanied by a corresponding increase in its nutritional content.[9,10]

CO_2 and respiration

The respiration reaction in aerobic organisms takes place in specialized organelles called "mitochondria". It can be schematically written as follows:

$$O_2 + CH_2O \rightarrow CO_2 + H_2O + ATP$$

"ATP" stands for adenosine triphosphate, the "fuel" for most metabolic reactions in living beings. Unicellular organisms can exchange oxygen and carbon dioxide by diffusion through the cell's lipid bilayer membrane. Large multicellular organisms, instead, use a liquid-based transport system to move gases in and out of their bodies. CO_2 is soluble in water as bicarbonate ions (HCO_3^-), and hence it can be directly dissolved in blood. The reaction is helped by a specific enzyme, carbonic anhydrase.[51] O_2, instead, is a non-polar molecule, not easily dissolved in polar liquids such as water. Hence, it is transported in blood by special molecules contained in cells called "red blood cells" or "erythrocytes". In mammals and other vertebrates, haemoglobin is the transporting molecule; hemocyanin plays the same role in arthropods. Haemoglobin can bind up to four oxygen molecules and transports approximately 97% of the oxygen in the body. Haemoglobin can also transport carbon dioxide bound to it to form a compound called "carbaminohaemoglobin". About 10% of the transported CO_2 in mammalian blood moves in this form.

For the O_2/CO_2 exchange mechanism to work, haemoglobin must act as a "truck". It must load oxygen at the alveoli in the lungs and unload it near the cells that need it. This mechanism is called the "Bohr effect" when referring to oxygen binding/unbinding and the "Haldane effect" when referring to the parallel and opposite binding/unbinding of CO_2.[52] The regulation mechanism is based on a conformational change of the haemoglobin molecule, which can assume two different "allosteric" states: the "R-state" (relaxed state), which makes it release O_2, and the "T-state" (tense state), which causes it to bind O_2. The CO_2 molecule acts as the allosteric regulator. When it is dissolved in blood as bicarbonate, the resulting acidic environment stabilizes the T-state of haemoglobin, promoting the release of oxygen. It results from the N-terminal amino groups of haemoglobin's α-subunits and the C-terminal histidine of the β-subunits becoming protonated under acidic conditions. This protonation enhances ionic interactions that stabilize the T state, facilitating oxygen unloading. Finally, CO_2 can also react with the N-terminal amino groups to form carbamates, further stabilizing the T state and contributing to oxygen release. This reaction generates additional protons, reinforcing the acidic environment and promoting the Bohr effect.

The consequence of this mechanism is that the oxygen transport in blood is not independent of the parallel mechanism of CO_2 removal. More CO_2 dissolved in blood means that less oxygen is transported and that has harmful consequences on the metabolism of aerobic creatures. This effect may start at the alveoli, where the partial pressure of oxygen can be calculated using the alveolar gas equation:[53]

$$p_aO_2 = (p_{atm} - pH_2O)\, F_iO_2 - p_aCO_2/RQ$$

Here p_aO_2 is the partial pressure of oxygen in the alveoli, and P_{atm} is the atmospheric pressure at sea level. pH_2O is the partial pressure of water equal to approximately 45 mmHg. F_iO_2 is the fraction of inspired oxygen. p_aCO_2 is the partial pressure of carbon dioxide in the arteries and RQ is the ratio between the metabolic production of carbon dioxide and the uptake of oxygen. This equation is approximate and the values of the parameters are too uncertain to make it usable as a predictive tool. But it shows that CO_2 may reduce the supply of oxygen to the body tissues. As atmospheric CO_2 increases, levels of CO_2 in the blood are already known to be increasing in the general human population.[54]

The adverse effects of high CO_2 concentrations on human health have been known since the 19th century under the name of "hypercapnia" (from the Greek *hyper*, "above" and *kapnos*, "smoke"). It is known that exposure to CO_2 concentrations over *ca.* 50 000 ppm (5% of the atmospheric pressure) can be immediately lethal. Until recently, values up to 5000 ppm were considered acceptable for limited times, *i.e.*, an 8-hour working day. However, recent studies have shown that short-term exposures to values in the range of 1000–2000 ppm and even lower have measurable negative effects on human cognitive performance.[13,55–59]

In this range, there are further physiological effects on humans and animals in the biosphere, including marine animals. In the 1960s, Eliseeva[60] reported marked changes in the properties of respiration, cardiovascular system, and cerebral cortex for short-term exposures at just 1000 ppm CO_2. More recent studies have shown harmful effects such as increased blood pressure, changes in the heart rate, kidney calcification, oxidative stress, neural damage, and inflammation.[61–65]

High concentrations of CO_2 appear to directly affect the oxygen transport into the brain. Studies of the brain activity using electroencephalogram (EEG) techniques and functional magnetic resonance imaging (fMRI)[66] detected a reduction in brain metabolic activity, interestingly coupled with increased oxygen content in the plasma, probably as the result of hyperventilation, but not sufficient to compensate for the reduction in metabolic activity due to increased CO_2 concentration. A recent review of the EEG results identified changes in brain activity even at concentrations below 1000 ppm, as found inside buildings.[67]

There are only a few animal studies in this field; the existing ones show evidence of physiological harm from CO_2 including increased stress hormones, reduced growth, and impaired lung function. The most relevant studies have been conducted for the entire life cycle of mammals (including gestation) at relatively long-term (4 months) durations and moderate levels of CO_2 (890 ppm).[68–71] These studies demonstrate impaired lung function and muscle structure, reduced growth, hyperactivity, and reduced attention, together with increased stress hormones associated with anxiety and cognitive impairment.

Excess CO_2 in the atmosphere also tends to reduce the blood's pH.[72] The body compensates for this effect by excreting acid *via* the kidneys, as well as mobilizing Ca^{2+} ions from bone tissue to replace H^+ ions. The long-term effect may be the calcification of organs such as kidneys and arterial walls causing cardiovascular disease and affecting neuron activity in the brain. The body's compensation mechanism, however, will eventually fail under chronic elevated CO_2 conditions resulting in acidosis,[72] although it's unclear how long this would take, possibly many months. Compensation for low pH, however, doesn't prevent CO_2 retention in the body which contributes to cellular malfunctions.[73]

Tissue calcification has been observed at concentrations as low as 2000 ppm CO_2 after a number of weeks[63] and the effect may be driven by the over-expression of the carbonic anhydrase enzyme caused by having more CO_2 to catalyze.[58,73] This is a protein malfunction that appears possible at projected future CO_2 levels given lifetime exposure, an example of how increased CO_2 might affect the proteome. Protein malfunctions linked to oxidative stress can potentially cause diseases like cancers and neurological disorders.[74] Other malfunctions may cause respiratory failure, cardiac diseases, cognitive impairment, and more. There exists, however, evidence that pathologies involving hypoxia can benefit from the vasodilatation effect of CO_2, as reviewed by Stepanek *et al.*[75]

Despite the several studies indicating harmful effects of CO_2 on human health, the field is still developing and we are far from having a definitive assessment of the problem. The existing studies have been criticized for internal inconsistencies and reproducibility problems.[76] We also note how some studies could not detect any effects of relatively large CO_2 concentrations on cognitive performance[77] although these data are for young and healthy submarine crew members.

Clearly, we need more and better studies, but the available data are consistent in reporting that CO_2 can harm human health in various ways even at concentrations often experienced today in indoor environments and that human beings could continuously experience in the future.

Discussion

Increasing CO_2 concentrations in the atmosphere have been shown to affect several vital elements of the biosphere even at the current levels of *ca.* 420 ppm. The effect of CO_2 on photosynthesis is relatively straightforward. As in all chemical reactions, an increase in the concentration of a reactant leads to the equilibrium of the reaction being shifted forward. So, more CO_2 leads to higher photosynthesis rates, also as a result of inhibiting the "dark photosynthesis" reaction. However, CO_2 is not the only reactant involved, and the efficiency of photosynthesis is also determined by the availability of water and other nutrients. Furthermore, the enhancing effect works only for plants that directly collect CO_2 from the atmosphere (the C_3 photosynthesis pathway) and are therefore sensitive to its concentration.

The other main photosynthesis pathway, the C_4 one, uses an intermediate step to concentrate CO_2 before it reaches the reaction centers. In this case, it is not surprising that more CO_2 in air does not significantly affect the process rate. In contrast, it is known that perturbations of climate created by the radiative forcing effects of CO_2 have negative effects on agriculture.[76]

The effects of high CO_2 concentration on respiration are more complex. There is no evidence that the current atmospheric concentration of CO_2 of *ca.* 420 ppm causes serious health problems for humans. However, the comparison with the case of photosynthesis shows how sensitive the regulation of the biochemical mechanisms of the biosphere is to the reactant concentrations. Up to now, no human being, and none of our hominin ancestors, ever lived a whole life at CO_2 concentrations higher than 300 ppm. But we will now be forced to do exactly that, while our descendants will experience even higher concentrations. The situation is especially worrisome given the modern tendency for humans to live indoors in scarcely ventilated spaces where CO_2 concentrations may be at least double that in open air and sometimes 3–4 times higher. Even higher concentrations are breathed when face masks are worn Table 1.[78,79]

Human health is not the only entity being affected by increasing CO_2 concentrations. Pushing the parameters of the current biosphere back to the conditions that existed before the Pleistocene, and perhaps before the Miocene, may have unexpected consequences on the metabolic processes of an ecosystem that had adapted to the current conditions over

Table 1 Levels of CO_2 in the atmosphere

CO_2 concentration ppm	Biochemical effects	Notes
180–280	Evolution of large brains during the Pleistocene	Lowest values ever in Earth's history
280	Normal value for the current ecosystem	Stable during the Holocene
420	Marine acidification, global greening, and metabolic disruption	Current value
600–1200	Limits to CO_2 plant fertilization	Above these levels the fertilization effect becomes negative
1000	Safe indoor limit	Measurable brain slowdown observed above 600 ppm for short-term exposure
2000	Upper limit for continuous indoor exposure	Short-term exposure symptoms such as headaches, slight cardiac alterations, and higher blood pressure
5000	Upper limit for exposure in workplaces and under special conditions	Inflammation, bone decalcification, headaches, high blood pressure, and others
10 000	Acceptable for occasional short exposures	Unknown safe limits for long-term exposure. Poses an immediate risk
50 000	Life endangering limit	Lethal for human beings

several million years. Remarkably, the evolution of large brains with a high neuron density in humans and other species[80,81] occurred during the late Miocene Period, under conditions of CO_2 concentrations of the order of 180 ppm. This observation raises the question of whether the metabolic requirements of large brains with densely packed neurons can be maintained at the high CO_2 atmospheric concentrations expected to develop in the future. It is not unreasonable to propose that some recent trends in declining human cognitive abilities may be attributed to the current increase in CO_2 atmospheric concentrations,[13] including the "reverse Flynn effect" (aka "global dumbing"),[82] attributed to environmental factors,[83] and the increasing incidence of senile dementia in the United States.[84]

Conclusion

When dealing with a substance known to have harmful effects on human health, producers have an obligation to show that these effects can be controlled by setting exposure limits. In the case of CO_2, limits have been established for high concentrations and short exposure times, but not for lifetime exposure at the current levels in the atmosphere and at the higher levels experienced indoors, and expected for the coming decades if human emissions continue to pump CO_2 into the atmosphere. Yet, these are the highest levels ever experienced in human history and far exceeding the atmospheric conditions (180–280 ppm) that early humans and their hominin ancestors experienced. Unfortunately, this problem is neglected or ignored in the public discussion. CO_2 is often defined as an "inert gas", and as "food for plants", and, hence, it is not only harmless, but the more of it, the better.

The results reported in the present paper show that even slightly higher CO_2 concentrations than the current ones may have harmful consequences on human health, including on the performance of human brains. Consider that, at present, CO_2 emissions continue to increase, causing its atmospheric concentration to increase at nearly 3 ppm per year. Hence, the potential future damage to the ecosystem and human beings is potentially large and highly worrisome. It is not even remotely compensated by the "greening" effect on some plants, which generates only minor advantages (if any) in terms of food production.

These considerations highlight the urgent need to understand that the current ecosystemic crisis is not just a problem of rising temperatures, but also, and perhaps primarily, of controlling emissions and eventually reducing the CO_2 concentration in the atmosphere to avoid biochemical damage to the human metabolic processes and other parts of the biosphere. Accordingly, solar radiation management technologies can only be useful as a last-ditch effort to buy time to avoid a catastrophically rapid warming trend. Technologies to remove CO_2 from the atmosphere exist, *e.g.*, CCS and BECCS, but at present, they are too expensive.[15,16] Natural methods based on forest[34,85] and marine[86] productivity management could be a better approach but, in any case, the effort must prioritize reducing emissions by phasing out major fossil sources and transitioning to low-carbon ones.

Data availability

All the data reported in the present paper are publicly available in the scientific literature.

Author contributions

Ugo Bardi: conceptualization, supervision, writing the initial draft. Bierwirth, Huang, and Mcintyre: resources, methodology, revision, data provision.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors are grateful to the Club of Rome and the Consorzio Interuniversitario di Scienza e Tecnologia dei Materiali (INSTM) for partially supporting this research.

References

1 S. Arrhenius, On the Influence of Carbonic Acid in the Air upon the Temperature of the Ground, *Phil. Mag. J. Sci.*, 1896, **41**, 237–275.
2 T. R. Anderson, E. Hawkins and P. D. Jones, CO_2, the greenhouse effect and global warming: from the pioneering work of Arrhenius and Callendar to today's Earth System Models, *Endeavour*, 2016, **40**(3), 178–187.
3 H. Lee and J. Romero, *Sixth Assessment Report — IPCC*, [Internet], IPCC, 2024, [cited 2024 Jul 23], available from: https://www.ipcc.ch/assessment-report/ar6/.
4 M. Z. Jacobson, Studying ocean acidification with conservative, stable numerical schemes for nonequilibrium air-ocean exchange and ocean equilibrium chemistry, *J. Geophys. Res. Atmos.*, 2005, **110**(D7), DOI: 10.1029/2004JD005220.
5 R. M. Bright, K. Zhao, R. B. Jackson and F. Cherubini, Quantifying surface albedo and other direct biogeophysical climate forcings of forestry activities, *Glob. Change Biol.*, 2015, **21**(9), 3246–3266.
6 M. Z. Jacobson, Enhancement of Local Air Pollution by Urban CO_2 Domes, *Environ. Sci. Technol.*, 2010, **44**(7), 2497–2502.
7 S. Piao, X. Wang, T. Park, C. Chen, X. Lian, Y. He, *et al.*, Characteristics, drivers and feedbacks of global greening, *Nat. Rev. Earth Environ.*, 2020, **1**(1), 14–27.
8 X. Zhang, J. P. Evans and A. L. Burrell, Less than 4% of dryland areas are projected to desertify despite increased aridity under climate change, *Commun. Earth Environ.*, 2024, **5**(1), 1–9.
9 E. Lemon, The Land's response to more carbon dioxide, in *The Fate of Fossil Fuel CO_2 in the Oceans*, Plenum Press, New York, 1977.
10 L. H. Ziska, Rising Carbon Dioxide and Global Nutrition: Evidence and Action Needed, *Plants*, 2022, **11**(7), 1000.

11 S. Wang, Y. Zhang, W. Ju, J. M. Chen, P. Ciais, A. Cescatti, *et al.*, Recent global decline of CO_2 fertilization effects on vegetation photosynthesis, *Science*, 2020, **370**(6522), 1295–1300.
12 T. A. Jacobson, J. S. Kler, M. T. Hernke, R. K. Braun, K. C. Meyer and W. E. Funk, Direct human health risks of increased atmospheric carbon dioxide, *Nat. Sustain.*, 2019, **2**(8), 691–701.
13 P. Bierwirth, *Are increasing atmospheric carbon dioxide levels lowering our intelligence and making us anxious? ResearchGate*, 2023, available from: **https://www.researchgate.net/publication/328781907_Are_increasing_atmospheric_carbon_dioxide_levels_lowering_our_intelligence_and_making_us_anxious**.
14 K. Brent, M. Simon and J. McDonald, From informal to formal governance of solar radiation management, *Clim. Policy*, 2025, 1–18.
15 S. Chatterjee and K. W. Huang, Unrealistic energy and materials requirement for direct air capture in deep mitigation pathways, *Nat. Commun.*, 2020, **11**(1), 3287.
16 S. Sgouridis, M. Carbajales-Dale, D. Csala, M. Chiesa and U. Bardi, Comparative net energy analysis of renewable electricity and carbon capture and storage, *Nat. Energy*, 2019, **4**(6), 456–465.
17 A. J. West, A. Galy and M. Bickle, Tectonic and climate control on silicate weathering, *Earth Planet. Sci. Lett.*, 2005, **235**, 211–228.
18 R. A. Berner and R. A. Berner, *The Phanerozoic Carbon Cycle: CO_2 and O_2*, Oxford University Press, USA, 2004, p. 159.
19 J. E. Hansen and M. Sato, Paleoclimate Implications for Human-Made Climate Change, in *Climate Change*, ed.A. Berger, F. Mesinger and D. Sijacki, Springer Vienna, Vienna, 2012 pp. 21–47, DOI: **10.1007/978-3-7091-0973-1_2**.
20 CenCO_2PIP Consortium. Toward a Cenozoic history of atmospheric CO_2, *Science*, 2023;**382**(6675):eadi5177.
21 A. E. Holbourn, W. Kuhnt, S. C. Clemens, K. G. D. Kochhann, J. Jöhnck, J. Lübbers, *et al.*, Late Miocene climate cooling and intensification of southeast Asian winter monsoon, *Nat. Commun.*, 2018, **9**(1), 1584.
22 G. Retallack and G. Conde, Deep time perspective on rising atmospheric CO_2, *Global Planet. Change*, 2020, **189**, 103177.
23 D. Rapp, *Ice Ages and Interglacials: Measurements, Interpretation and Models*, Environmental Sciences, Springer-Verlag, Berlin Heidelberg, 2009, [cited 2019 Dec 4], available from, **https://www.springer.com/gp/book/9783642100512**.
24 E. J. Judd, J. E. Tierney, D. J. Lunt, I. P. Montañez, B. T. Huber, S. L. Wing, *et al.*, A 485-million-year history of Earth's surface temperature, *Science*, 2024, **385**(6715), eadk3705.
25 J. E. Lovelock and M. Whitfield, Life span of the biosphere, *Nature*, 1982, **296**(5857), 561–563.
26 B. Charnay, E. T. Wolf, B. Marty and F. Forget, Is the Faint Young Sun Problem for Earth Solved?, *Space Sci. Rev.*, 2020, **216**(5), 90.
27 K. Ozaki and C. T. Reinhard, The future lifespan of Earth's oxygenated atmosphere, *Nat. Geosci.*, 2021, **14**(3), 138–142.
28 K. Caldeira and J. F. Kasting, The life span of the biosphere revisited, *Nature*, 1992, **360**(6406), 721–723.
29 S. Franck, C. Bounama and W. von Bloh, Causes and timing of future biosphere extinctions, *Biogeosciences*, 2006, **3**(1), 85–92.
30 W. Ruddiman, Geographic evidence of the early anthropogenic hypothesis, *Anthropocene*, 2017, **20**, 4–14.
31 J. A. Langdale, C4 Cycles: Past, Present, and Future Research on C4 Photosynthesis|The Plant Cell|Oxford Academic, *Plant Cell*, 2011, **23**(11), 3879–3892.
32 M. Urli, A. J. Porté, H. Cochard, Y. Guengant, R. Burlett and S. Delzon, Xylem embolism threshold for catastrophic hydraulic failure in angiosperm trees, *Tree Physiol.*, 2013, **33**(7), 672–683.
33 C. Carcaillet, J. L. Latil, S. Abou, A. Ali, B. Ghaleb, F. Magnin, et al., Keep your feet warm? A cryptic refugium of trees linked to a geothermal spring in an ocean of glaciers, *Glob. Change Biol.*, 2018, **24**(6), 2476–2487.
34 A. M. Makarieva, A. V. Nefiodov, A. Rammig and A. D. Nobre, Re-appraisal of the global climatic role of natural forests for improved climate projections and policies, *Front. For. Glob. Change.*, 2023, DOI: **10.3389/ffgc.2023.1150191/full**.
35 A. M. Makarieva and V. G. Gorshkov, Biotic pump of atmospheric moisture as driver of the hydrological cycle on land, *Hydrol. Earth Syst. Sci.*, 2007, **21**, 1013–1033.
36 M. Baudena, O. Tuinenburg, P. Ferdinand and A. Staal, Effects of land-use change in the Amazon on precipitation are likely underestimated, *Glob. Change Biol.*, 2021, **27**, 5580–5587.
37 M. Gattmann, S. A. M. McAdam, B. Birami, R. Link, D. Nadal-Sala, B. Schuldt, *et al.*, Anatomical adjustments of the tree hydraulic pathway decrease canopy conductance under long-term elevated CO2, *Plant Physiol.*, 2023, **191**(1), 252–264.
38 S. M. Vicente-Serrano, D. G. Miralles, N. McDowell, T. Brodribb, F. Domínguez-Castro, R. Leung, *et al.*, The uncertain role of rising atmospheric CO_2 on global plant transpiration, *Earth-Sci. Rev.*, 2022, **230**, 104055.
39 S. D. Wullschleger and R. J. Norby, Sap velocity and canopy transpiration in a sweetgum stand exposed to free-air CO_2 enrichment (FACE), *New Phytol.*, 2001, **150**(2), 489–498.
40 Y. Malhi, L. E. O. C. Aragão, D. Galbraith, C. Huntingford, R. Fisher, P. Zelazowski, *et al.*, Exploring the likelihood and mechanism of a climate-change-induced dieback of the Amazon rainforest, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**(49), 20610–20615.
41 X. Chen, T. Chen, B. He, S. Liu, S. Zhou and T. Shi, The global greening continues despite increased drought stress since 2000, *Glob. Ecol. Conserv.*, 2024, **49**, e02791.
42 E. C. Davis, B. Sohngen and D. J. Lewis, The effect of carbon fertilization on naturally regenerated and planted US forests, *Nat. Commun.*, 2022, **13**(1), 5490.
43 Forest Research, *Forestry Statistics*, 2024, **https://www.forestresearch.gov.uk/tools-and-resources/statistics/forestry-statistics/forestry-statistics-2024/**.

44 J. W. Erisman, M. A. Sutton, J. Galloway, Z. Klimont and W. Winiwarter, How a century of ammonia synthesis changed the world, *Nat. Geosci.*, 2008, **1**(10), 636–639.

45 V. Acker, J. L. Durand, C. Perrot, E. Roy, E. Frak and R. Barillot, Effects of atmospheric CO_2 concentration on transpiration and leaf elongation responses to drought in wheat, perennial ryegrass and tall fescue, *bioRxiv*, 2023, preprint, 2023.12.06.570419, DOI: 10.1101/2023.12.06.570419v1.

46 J. A. Bunce, Carbon dioxide effects on stomatal responses to the environment and water use by crops under field conditions, *Oecologia*, 2004, **140**(1), 1–10.

47 C. A. Taylor and W. Schlenker, *Environmental Drivers of Agricultural Productivity Growth: CO_2 Fertilization of US Field Crops*, National Bureau of Economic Research, 2021, https://www.nber.org/papers/w29320.

48 E. A. Ainsworth and S. P. Long, 30 years of free-air carbon dioxide enrichment (FACE): What have we learned about future crop productivity and its potential for adaptation?, *Glob. Change Biol.*, 2021, **27**(1), 27–49.

49 Y. Zheng, F. Li, L. Hao, A. A. Shedayi, L. Guo, C. Ma, *et al.*, The optimal CO_2 concentrations for the growth of three perennial grass species, *BMC Plant Biol.*, 2018, DOI: 10.1186/s12870-018-1243-3, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5799915/.

50 A. D. B. Leakey, M. Uribelarrea, E. A. Ainsworth, S. L. Naidu, A. Rogers, D. R. Ort, *et al.*, Photosynthesis, Productivity, and Yield of Maize Are Not Affected by Open-Air Elevation of CO_2 Concentration in the Absence of Drought, *Plant Physiol.*, 2006, **140**(2), 779–790.

51 C. Supuran, A. Garcia-Llorca, F. Carta and T. Eysteinsson, Frontiers | Carbonic anhydrase, its inhibitors and vascular function, *Front. Mol. Biosci.*, 2024, **11**, DOI: 10.3389/fmolb.2024.1338528/full.

52 M. F. Perutz, Mechanisms Regulating the Reactions of Human Hemoglobin With Oxygen and Carbon Monoxide, *Annu. Rev. Physiol.*, 1990, **52**(1), 1–26.

53 S. Sharma and M. F. Hashmi, Partial Pressure Of Oxygen, in *StatPearls*, StatPearls Publishing, Treasure Island, 2024, http://www.ncbi.nlm.nih.gov/books/NBK493219/.

54 A. R. Zheutlin, S. D. Adar and S. K. Park, Carbon dioxide emissions and change in prevalence of obesity and diabetes in the United States: an ecological study, *Environ. Int.*, 2014, **73**, 111–116.

55 U. Satish, M. J. Mendell, K. Shekhar, T. Hotchi, D. Sullivan, S. Streufert, *et al.*, Is CO_2 an Indoor Pollutant? Direct Effects of Low-to-Moderate CO_2 Concentrations on Human Decision-Making Performance, *Environ. Health Perspect.*, 2012, **120**(12), 1671–1677.

56 J. G. Allen, P. MacNaughton, U. Satish, S. Santanam, J. Vallarino and J. D. Spengler, Associations of Cognitive Function Scores with Carbon Dioxide, Ventilation, and Volatile Organic Compound Exposures in Office Workers: A Controlled Exposure Study of Green and Conventional Office Environments, *Environ. Health Perspect.*, 2016, **124**(6), 805–812.

57 P. Eichholtz and N. Kok, in *Indoor Environmental Quality and Human Performance : Evidence from a Large-Scale Field Study*, 2018, https://www.semanticscholar.org/paper/Indoor-Environmental-Quality-and-Human-Performance-Eichholtz-Kok/04e77b6f3c65f898a1dff6b9e33f15be06de2d88.

58 P. Bierwirth, *Long-term carbon dioxide toxicity and climate change: a critical unapprehended risk for human health*, 2024.

59 K. B. Karnauskas, S. L. Miller and A. C. Schapiro, Fossil Fuel Combustion Is Driving Indoor CO_2 Toward Levels Harmful to Human Cognition, *Geohealth*, 2020, **4**(5), e2019GH000237.

60 O. V. Eliseeva, [On The Determination Of Maximum Permissible Carbon Dioxide Concentrations In The Air Of Apartment Buildings And Public Buildings], *Gig. Sanit.*, 1964, **29**, 10–15.

61 T. Vehviläinen, H. Lindholm, H. Rintamäki, R. Pääkkönen, A. Hirvonen, O. Niemi, *et al.*, High indoor CO_2 concentrations in an office environment increases the transcutaneous CO_2 level and sleepiness during cognitive work, *J. Occup. Environ. Hyg.*, 2016, **13**(1), 19–29.

62 M. Kiray, A. R. Sisman, U. M. Camsari, M. Evren, A. Dayi, B. Baykara, *et al.*, Effects of carbon dioxide exposure on early brain development in rats, *Biotech. Histochem.*, 2014, **89**(5), 371–383.

63 K. E. Schaefer, Effects of increased ambient CO_2 levels on human and animal health, *Experientia*, 1982, **38**(10), 1163–1168.

64 S. R. Thom, V. M. Bhopale, J. Hu and M. Yang, Inflammatory responses to acute elevations of carbon dioxide in mice, *J. Appl. Physiol.*, 2017, **123**(2), 297–302.

65 D. Zappulla, Environmental stress, erythrocyte dysfunctions, inflammation, and the metabolic syndrome: adaptations to CO_2 increases?, *J. CardioMetab. Syndr.*, 2008, **3**(1), 30–34.

66 F. Xu, J. Uh, M. R. Brier, J. Hart, U. S. Yezhuvath, H. Gu, *et al.*, The influence of carbon dioxide on brain activity and metabolism in conscious humans, *J. Cereb. Blood Flow Metab.*, 2011, **31**(1), 58–67.

67 N. Zhang, C. Liu, C. Hou, W. Wang, Q. Yuan and W. Gao, The impact of indoor carbon dioxide exposure on human brain activity: A systematic review and meta-analysis based on studies utilizing electroencephalogram signals, *Build. Environ.*, 2024, **259**, 111687.

68 A. N. Larcombe, M. G. Papini, E. K. Chivers, L. J. Berry, R. M. Lucas and C. S. Wyrwoll, Mouse Lung Structure and Function after Long-Term Exposure to an Atmospheric Carbon Dioxide Level Predicted by Climate Change Modeling, *Environ. Health Perspect.*, 2021, **129**(1), 17001.

69 C. S. Wyrwoll, M. G. Papini, E. K. Chivers, J. Yuan, N. J. Pavlos, R. M. Lucas, *et al.*, Long-term exposure of mice to 890 ppm atmospheric CO_2 alters growth trajectories and elicits hyperactive behaviours in young adulthood, *J. Physiol.*, 2022, **600**(6), 1439–1453.

70 J. M. Martrette, C. Egloff, C. Clément, K. Yasukawa, S. N. Thornton and M. Trabalon, Effects of prolonged exposure to CO_2 on behaviour, hormone secretion and respiratory muscles in young female rats, *Physiol. Behav.*, 2017, **177**, 257–262.

71 H. Stolp, Developing in a polluted atmosphere: A link between long-term exposure to elevated atmospheric CO_2 and hyperactivity, *J. Physiol.*, 2022, **600**, 1275–1276.
72 D. Robertson, Health effects of increase in concentration of carbon dioxide in the atmosphere, *Curr. Sci.*, 2006, **90**(12), 1607–1609, https://www.jstor.org/stable/i24091841.
73 D. E. Phelan, C. Mota, C. Lai, S. J. Kierans and E. P. Cummins, Carbon dioxide-dependent signal transduction in mammalian systems, *Interface Focus*, 2021, **11**(2), 20200033.
74 B. Ezraty, A. Gennaris, F. Barras and J. F. Collet, Oxidative stress, protein damage and repair in bacteria, *Nat. Rev. Microbiol.*, 2017, **15**(7), 385–396.
75 J. Stepanek, R. Dunn, G. Pradhav and M. Cevette, Supplemental CO_2 improves oxygen saturation, oxygen tension, and cerebral oxygenation in acutely hypoxic healthy subjects - Stepanek - 2020 - Physiological Reports - Wiley Online Library, *Physiol. Rep.*, 2020, **8**(14), e14513.
76 B. Du, M. C. Tandoc, M. L. Mack and J. A. Siegel, Indoor CO_2 concentrations and cognitive function: A critical review, *Indoor Air*, 2020, **30**(6), 1067–1082.
77 C. D. Rodeheffer, S. Chabal, J. M. Clarke and D. M. Fothergill, Acute Exposure to Low-to-Moderate Carbon Dioxide Levels and Submariner Decision Making, *Aerosp Med Hum Perform.*, 2018, **89**(6), 520–525.
78 M. C. Acuti, M. E. Flacco, M. Martellucci, F. S. Violante and L. Manzoli, Inhaled CO_2 Concentration While Wearing Face Masks: A Pilot Study Using Capnography, *Environ. Health Insights.*, 2022, **16**, DOI: 10.1177/11786302221123573.
79 H. Walach, H. Traindl, J. Prentice, R. Weikl, A. Diemer, A. Kappes, *et al.*, Carbon dioxide rises beyond acceptable safety levels in children under nose and mouth covering: Results of an experimental measurement study in healthy children, *Environ. Res.*, 2022, **212**, 113564.
80 S. Herculano-Houzel, The human brain in numbers: a linearly scaled-up primate brain, *Front. Hum. Neurosci.*, 2009, DOI: 10.3389/neuro.09.031.2009/full.
81 D. M. Bailey and D. C. Poole, Battle of the gases in the race for survival: Atmospheric CO_2 *versus* O_2, *Exp. Physiol.*, 2022, **107**(12), 1383–1387.
82 E. Dutton, D. van der Linden and R. Lynn, The negative Flynn Effect: A systematic literature review, *Intelligence*, 2016, **59**, 163–169.
83 B. Bratsberg and O. Rogeberg, Flynn effect and its reversal are both environmentally caused, *Proc. Natl. Acad. Sci. USA*, 2018, **115**(26), 6674–6678.
84 M. Fang, J. Hu, J. Weiss, D. S. Knopman, M. Albert, B. G. Windham, *et al.*, Lifetime risk and projected burden of dementia, *Nat. Med.*, 2025, **13**, 1–5.
85 K. Psistaki, G. Tsantopoulos and A. K. Paschalidou, An Overview of the Role of Forests in Climate Change Mitigation, *Sustainability*, 2024, **16**(14), 6089.
86 K. O. Buesseler, D. Bianchi, F. Chai, J. T. Cullen, M. Estapa, N. Hawco, *et al.*, Next steps for assessing ocean iron fertilization for marine carbon dioxide removal, *Front. Clim.*, 2024, DOI: 10.3389/fclim.2024.1430957/full.

