



Effects of low-level inhalation exposure to carbon dioxide in indoor environments: A short review on human health and psychomotor performance



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ABSTRACT

Scientific literature and documents pertaining to the effects of inhalation exposure to carbon dioxide (CO₂) on human health and psychomotor performance were reviewed. Linear physiological changes in circulatory, cardiovascular, and autonomic systems on exposure to CO₂ at concentrations ranging from 500 to 5000 ppm were evident. Human experimental studies have suggested that short-term CO₂ exposure beginning at 1000 ppm affects cognitive performances including decision making and problem resolution. Changes in autonomic systems due to low-level exposure to CO₂ may involve these effects. Further research on the long-term effects of low-level CO₂ exposure on the autonomic system is required. Numerous epidemiological studies indicate an association between low-level exposure to CO₂ beginning at 700 ppm and building-related symptoms. Respiratory symptoms have been indicated in children exposed to indoor CO₂ concentrations higher than 1000 ppm. However, other indoor comorbid pollutants are possibly involved in such effects. In the context of significant linear increase of globally ambient CO₂ concentration caused by anthropogenic activities and sources, reducing indoor CO₂ levels by ventilation with ambient air represents an increase in energy consumption in an air-conditioned building. For the efficient energy control of CO₂ intruding a building from ambient air, the rise of atmospheric CO₂ concentration needs to be urgently suppressed.

1. Introduction

Carbon dioxide (CO₂) is a colorless, tasteless, odorless, and non-flammable gas that is heavier than air and may accumulate at lower spaces, causing a deficiency of oxygen (IPCS, 2006). It is naturally present in the earth's atmosphere as a trace gas and a product of cellular respiration or fossil fuel burning (van Groenigen et al., 2011). The typical outdoor CO₂ concentrations are approximately 380 ppm, although in urban areas these have been reported to be as high as 500 ppm because of the increased anthropogenic sources (Persily, 1997). The increasing CO₂ concentration contributes to the greenhouse effect and accelerates global warming (Bertoni et al., 2004; Cox et al., 2000). According to the World Meteorological Organization, the globally averaged CO₂ concentration in the atmosphere has reached the

symbolic and significant milestone of 400 ppm for the first time in 2015 (WMO, 2016) and has risen to 403.3 ppm in 2016 (WMO, 2017). The mean annual absolute increase during the last 10 years was 2.2 ppm per year (WMO, 2017). Simulated multi-models project the atmospheric average CO₂ concentrations to range between 794 and 1142 ppm by 2100 (IPCC, 2013).

The main source of CO₂ in the non-industrial indoor environment is human metabolism, although an increase in the ambient CO₂ concentration will also contribute to an increase in the indoor CO₂ concentration (Alberts, 1994). In addition, the need to reduce energy consumption provides an incentive for low rates of ventilation, leading to higher indoor CO₂ concentrations. The indoor CO₂ concentration represents an indicator of indoor air quality acceptability, air flow exchange suitability, and whether there is sufficient fresh air within

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indoor spaces in buildings (Emmerich and Persily, 2001). The typical average indoor CO₂ concentration ranges from 800 to 1000 ppm (NRC, 2008). National indoor air quality guidelines have established an upper limit of 1000 ppm for CO₂ concentrations in non-industrial buildings in Japan (NRC, 1981); Canada (Health Canada, 1995); Singapore (MOE, 1996); Norway (Becher et al., 1999); China (Peng et al., 2017); South Korea (Oh et al., 2012); Germany (Lahrz et al., 2008); and Taiwan (Chen et al., 2016).

Ventilation with ambient air is frequently used for reducing indoor CO₂ concentration. However, when low-level inhalation of CO₂ affects human health, the outdoor air flow rate by ventilation must be further increased to both maintain an acceptable indoor CO₂ concentration and to adapt to the increasing outdoor atmospheric CO₂ concentration, and a further step would involve the installation of an indoor CO₂ purification system within the ventilation system, leading to a tremendous increase in the energy load of buildings.

Lastly, the effects of low-level CO₂ exposure on human health should be re-examined in light of the current trend of increasing outdoor atmospheric CO₂ concentration. Herein we report a review of current literature pertaining to the association of low-level CO₂ exposure in non-industrial buildings with human health and related human responses.

2. Data collection

An online literature search was conducted across major electronic databases, including PubMed, Google Scholar, CiNii, and J-Dream III, between 1950 and June 11, 2018. PubMed was primarily used to identify potential articles that qualified the search criteria, and others were used as complementary databases. The following key words were used as search criteria: “carbon dioxide” AND health AND effect; “carbon dioxide” AND sick AND building; indoor AND “carbon dioxide” AND health. A total of 1475 articles were retrieved. After exclusion of duplicate publications, the retrieved articles were reviewed by a reviewer (KA) in two stages: screening of titles and abstracts, followed by full-text review. Additional articles were identified based on prior knowledge (e.g., documents or reports of international or national organizations) and by manual screening of the bibliographies of the retrieved articles. A total of 99 full-text articles were reviewed. Only peer-reviewed articles pertaining to original research or review of experimental or human studies directly associated with health and related response to exposure to CO₂, which clearly identified the air concentration of CO₂, were considered. Useful comprehensive review articles in conference proceedings were carefully considered along with the cited references. Studies focusing on poor ventilation, medical treatment, and physical exercise were excluded. The search was updated on August 19, 2018.

3. Biological effects

CO₂ is produced by intracellular metabolism in the mitochondria. The amount produced depends on the metabolism rate and the relative amounts of carbohydrates, fats, and proteins metabolized. As CO₂ accumulates in the blood, the blood pH decreases (acidity increases). Therefore, CO₂ is discharged from the human body for maintaining the acid–base balance in the blood (Geers and Gros, 2000). The CO₂ produced within the cells is transported into the blood (internal respiration) and is carried by the blood through the venous system to the lungs where CO₂ passes from the blood into the lung alveoli to be exhaled into ambient air (external respiration) (Lifson et al., 1949).

Lowering the pH or raising the partial pressure of CO₂ (pCO₂) releases of oxygen (O₂) from oxyhemoglobin (Arthurs and Sudhakar, 2005). An increase of pCO₂ delivered to the lungs, that is, hypercapnia, induces an increase of pCO₂ in the alveoli. CO₂ freely diffuses through the alveolar membrane and into the blood, resulting in an increase of CO₂ tension in arterial blood (PaCO₂). In turn, this increase in PaCO₂

(lower blood pH) results in an acute or chronic respiratory acidosis caused by the acid–base imbalance in the blood (Guais et al., 2011).

Respiratory acidosis corresponds to CO₂ accumulation. Acute or acutely worsening chronic respiratory acidosis causes headache, confusion, anxiety, drowsiness, and stupor (CO₂ narcosis). Slowly developing, stable respiratory acidosis may be well tolerated, but could result in memory loss, sleep disturbances, excessive daytime sleepiness, and personality changes. CO₂ rapidly diffuses into the brain across the blood–brain barrier. Symptoms and signs are the result of high CO₂ concentrations (low central nervous system pH) in the central nervous system and any accompanying hypoxemia (Porter et al., 2011).

Respiratory acidosis appears by definition from exposure to a CO₂ concentration of 10,000 ppm for at least 30 min in a healthy adult with a moderate physical load (DFG, 2012). An increase in the inhaled CO₂ concentration can result in increased respiratory rate, metabolic stress, increased brain blood flow, and increased minute ventilation (above 10,000 ppm); decreased exercise tolerance in workers when breathing against inspiratory and expiratory resistance (above 30,000 ppm); headache, dizziness, confusion, and dyspnea (above 50,000 ppm); sweating, dim vision, vomiting, disorientation, hypertension, and loss of consciousness (above 100,000 ppm) (ACGIH, 2017; HSDB, 2015; Rice, 2003).

4. Effects of low-level exposure to CO₂ in humans

According to traditional knowledge, although physiological studies showed that CO₂ raises the respiration rate increases above the level required for gas exchange, imposing an additional load on the respiratory system at concentrations higher than 5000 ppm, Pettenkofer and Flügge had proposed in 1881 that 700–1000 ppm should be regarded as the permissible indoor CO₂ concentration, indicating an indirect index of the contamination of air in buildings, which criteria had no physiological basis (Goromosov, 1968). A study in human subjects reported that inhalation exposure to 1000 ppm CO₂ for a short term caused marked changes in respiratory movement amplitude, peripheral blood flow increases, and the cerebral cortex functional state. While 1000 ppm CO₂ in the air reportedly has a directly harmful effect on humans, no detailed experimental methods and analyses were provided (Eliseeva, 1964). Thus, the association of CO₂ exposures at concentrations lower than 5000 ppm and human health remained very limited in the 1960s.

4.1. Building-related symptoms

Building-related symptoms (BRSs), commonly called sick building syndrome, are defined as symptoms that are experienced within the building but improve when away from the building (Redlich et al., 1997). Symptoms assessed are related to the upper and lower respiratory tract, eyes, and skin and include headache, fatigue, and difficulty concentrating (Finnegan et al., 1984). A comprehensive review of 21 studies reported that around half suggest that the risk of BRSs continues to diminish significantly with CO₂ concentrations decreasing to lower than 800 ppm (Seppänen et al., 1999). According to the Building Assessment Survey and Evaluation (BASE) study conducted in the U.S.A., significant associations of mucous membrane and lower respiratory symptoms with increasing indoor minus average outdoor CO₂ (dCO₂)(100 ppm increase) and maximum indoor 1 h moving average CO₂ minus outdoor CO₂ concentrations (250 ppm increase) were observed when workday average CO₂ concentrations remained lower than 800 ppm (1579 participants of 33 U.S. Office buildings) (Apte et al., 2000; Erdmann and Apte, 2004). In a longitudinal study conducted following the BASE study, upper respiratory symptoms were significantly associated with increased indoor CO₂ levels (98 participants of 21 Offices). However, the relationship between CO₂ concentrations and upper respiratory symptoms in this study was no longer statistically significant after adjusting for the number of people in the

office because people are the main source of CO₂ in office buildings (Chao et al., 2003).

A crossover experimental study conducted on 355 university students of four classrooms suggested that a 100 ppm increase in indoor CO₂ concentration (range, 674–1450 ppm) was significantly associated with headache and this association was independent from other related indoor environmental factors, including temperature, relative humidity, and air exchange rate (Norbäck and Nordström, 2008). Office workers exposed to indoor CO₂ concentrations higher than 800 ppm reported a significant increase in eye irritation and upper respiratory symptoms (111 participants from an office on August and November 2003) (Tsai et al., 2012). A 100 ppm increase in dCO₂ in the range from 467 to 2800 ppm in indoor CO₂ was significantly associated with dry throat, tiredness, and dizziness (417 participants from 87 offices) (Lu et al., 2015). A 100 ppm increase in CO₂ concentration (range, 549–1318 ppm) was positively correlated with non-specific symptoms including headache and dizziness (107 participants from 11 offices) although the correlation was not significant (Azuma et al., 2018).

A study in schoolchildren exposed to indoor CO₂ concentrations higher than 1000 ppm showed significantly higher risk for dry cough and rhinitis (654 children of 46 classrooms) but outdoor air flow rate per person was inversely correlated with indoor CO₂ concentrations (Simoni et al., 2010). A 200 ppm increase in indoor CO₂ concentration (range, 1000–2000 ppm) in 45 day care centers (DCCs) was significantly associated with reported wheezing in the 3186 attending children, and a positive trend was observed between CO₂ concentration and the prevalence of asthma. However, a positive association was found between indoor CO₂ concentration and the increasing number of children per room. In addition, indoor CO₂ concentration was negatively associated with increased outdoor wind velocity and open window practice. Therefore, poor ventilation in DCCs appears to enhance respiratory symptoms in children (Carreiro-Martins et al., 2014). The following phase II study conducted in DCCs confirmed that a 200 ppm increase in CO₂ concentration is significantly associated with asthma diagnoses (1191 children from 19 centers) (Carreiro-Martins et al., 2016).

Several epidemiological studies indicate a relationship between low-level exposure to CO₂ and BRSSs. However, BRSS is possibly influenced by other comorbid indoor pollutants, including artificial volatile organic compounds (VOCs) brought into buildings or occupant-generated pollutants (Apte et al., 2000; Chao et al., 2003; Engvall et al., 2005; Erdmann and Apte, 2004). In usual indoor environments, indoor CO₂ concentration is used as an approximate surrogate for the concentrations of occupant-generated pollutants, particularly bioeffluents, and for estimating a proper ventilation rate per occupant (Apte et al., 2000). Bioeffluent is an organic contaminant, especially an atmospheric pollutant, that emanates from the bodies of humans or animals. Occupants of a room contribute to air bioeffluent emissions including VOCs, water vapor, particulate matter, CO₂ and bioaerosols. Bioeffluent sometimes causes unpleasant odors in an enclosed space (Engvall et al., 2005). In addition, there are many artificial hazardous pollutants brought into buildings and their concentration ranges depend on the indoor environment of buildings and building characteristics (Azuma et al., 2016; Azuma et al., 2018). However, those pollutants were not sufficiently taken into account in the above-described studies because indoor CO₂ concentration is often correlated with other indoor pollutants that may cause BRSSs (Apte et al., 2000; Azuma et al., 2018; Erdmann and Apte, 2004). One human experimental study indicated an independent effect of CO₂ from air exchange rate between low-level exposure to CO₂ and headache (Norbäck and Nordström, 2008). However, numerous indoor environmental factors including indoor air quality, work environment, and especially psychosocial factors (Marmot et al., 2006) contribute to BRSSs including headache (Azuma et al., 2015). As described in the following section, in recent human experimental studies primarily conducted for evaluating the psychomotor performance under controlled ventilation conditions, the

relationship between low-level exposure to CO₂ and the reported symptoms remain inconsistent between studies (MacNaughton et al., 2016; Zhang et al., 2016; Zhang et al., 2017a). A relationship between low-level exposure to CO₂ and BRSSs is therefore very complicated to prove and strength of the evidence is very limited.

4.2. Autonomic function or psychomotor performance

Historically, CO₂ exposures at concentrations lower than 5000 ppm were not anticipated to affect blood CO₂ levels. However, recent studies have reported linear increases of pCO₂ in the blood at CO₂ exposures in the range from 500 to 4000 ppm. These studies report other physiological responses consistent with increased sympathetic stimulation, including changes in heart rate variability and peripheral blood circulation increases at CO₂ exposures in the range from 500 to 4000 ppm (MacNaughton et al., 2016; Vehviläinen et al., 2016). These effects were previously observed at CO₂ exposures at concentrations from 600 to 5000 ppm (Kajtar and Herczeg, 2012). Groups exposed for a couple of hours to levels higher than 1500 ppm CO₂ showed an increase in their blood pressure and heart rate compared with that of the 600 ppm exposure group. Autonomic dysfunction impacts a wide array of human functions including cognitive, urinary, sexual, and digestive systems. The activation of the autonomic system through stress reduces strategic ability and working memory (Starcke and Brand, 2012), which supports a recent finding that showed a decrease in decision-making performance between 600 and 2500 ppm CO₂.

Twenty-two participants were exposed to CO₂ at 600, 1000, and 2500 ppm (three 2.5-h sessions, one day; artificially elevated CO₂ concentrations) in an office-like chamber. Statistically significant decrements occurred in cognitive performance (decision making, problem resolution) starting at 1000 ppm (Satish et al., 2012). Twenty-four participants spent six full work days (from 9 AM to 5 PM) during two weeks in an environmentally controlled office space, blinded to different test conditions: concentrations of VOCs, outdoor air ventilation rate, and artificially elevated CO₂ concentrations independent of ventilation. VOCs and CO₂ were independently associated with decreased cognitive scores (basic activity level, applied activity level, focused activity level, crisis response, information usage, breadth of approach, strategy) in the groups exposed to CO₂ at 945 and 1410 ppm compared with controls (537 ppm) (Allen et al., 2016). The same research group reported additional results from the above experimental study, in which a 1000 ppm increase in CO₂ was associated with an increase in heart rate and in the number of symptoms (respiratory, eyes and skin, headache, cognitive, and sensory) per participant per day (MacNaughton et al., 2016). Furthermore, this group reported a study of the in-flight performance of airplane pilots during advanced maneuvers in a flight simulator under varying concentrations of CO₂. Thirty male active commercial airline pilots performed three 3-h flight simulations on the flight deck at 700, 1500, 2500 ppm CO₂. The concentration of CO₂ was modified by introducing ultra-pure CO₂ into the simulator, and the ventilation rates remained the same for each test. The in-flight performance at 2500 ppm CO₂ was significantly lower than that at 1500 ppm and 700 ppm. The difference in flight performance at 700 ppm and 1500 ppm was not statistically significant; however, the pilots were more likely to successfully perform five of the seven most difficult maneuvers at the lower CO₂ concentration (Allen et al., 2018). These findings suggest that there is a direct effect of low-level exposure to CO₂ on performance, which is independent of ventilation.

In another study, 10 healthy participants were exposed to CO₂ at 500 ppm and 5000 ppm (artificially elevated CO₂ concentrations) for 2.5 h in a low-emission stainless steel climate chamber. End-tidal CO₂ (ETCO₂) was higher at 5000 ppm than at 500 ppm. CO₂ concentration at 5000 ppm had no effect on acute health symptoms (respiratory, visual and skin-related, headache, and sensory) and performance in cognitive tests (Zhang et al., 2016). Twenty-five participants were

Table 1
Effects of exposure to CO₂ in indoor air.

| CO ₂ concentration | Physiological change | Psychomotor performance | Health symptoms |
|-------------------------------|---|---|---|
| Above 500 ppm | Increased pCO ₂ , increased heart rate, change in heart rate variability, increased blood pressure, increased peripheral blood circulation (Kajtár and Herczeg, 2012; MacNaughton et al., 2016; Vehviläinen et al., 2016; Zhang et al., 2017b) | | Building-related symptoms above 700 ppm ^a (Norbäck and Nordström, 2008 and supporting studies; Apte et al., 2000; Erdmann and Apte, 2004; Lu et al., 2015; MacNaughton et al., 2016; Seppänen et al., 1999; Tsai et al., 2012) |
| Above 1000 ppm | | Cognitive performance (decision making, problem resolution, speed of addition, number of correct link) (Satish et al., 2012; Allen et al., 2016; Allen et al., 2018; Zhang et al., 2017a) | Respiratory symptoms in school children ^a (Carreiro-Martins et al., 2014; Carreiro-Martins et al., 2016; Simoni et al., 2010) |
| Above 10,000 ppm | Increased respiratory rate, respiratory acidosis, metabolic stress (decreased blood calcium or urine phosphorus), increased brain blood flow, increased minute ventilation (ACGIH, 2017; DFG, 2012; HSDB, 2015; Rice, 2003) | | |
| Above 30,000 ppm | | Decreased exercise tolerance in workers when breathing against inspiratory and expiratory resistance (ACGIH, 2017; Rice, 2003) | |
| Above 50,000 ppm | | | Dizziness, headache, confusion, dyspnea (ACGIH, 2017; HSDB, 2015; Rice, 2003) |
| 80,000–100,000 ppm | | | Severe headache, dizziness, confusion, dyspnea, sweating, dim vision (ACGIH, 2017; HSDB, 2015; Rice, 2003) |
| Above 100,000 ppm | | | Unbearable dyspnea, followed by vomiting, disorientation, hypertension, and loss of consciousness (HSDB, 2015; Rice, 2003) |

^a These symptoms are likely to be caused by comorbid indoor pollutants.

exposed to CO₂ at 500, 1000, and 3000 ppm (artificially elevated CO₂ concentrations, outdoor air supply rate high enough to remove human bioeffluents) for 255 min in a low-emission stainless steel climate chamber. In two more conditions, the outdoor air supply rate was reduced to allow metabolically generated CO₂ by occupants to reach CO₂ concentrations of 1000 and 3000 ppm (bioeffluents were also increased). Exposures to CO₂ at concentrations of 3000 ppm, including bioeffluents, significantly increased the intensity of reported headache, fatigue, and sleepiness. In cognitive performance tests, the speed of addition was significantly reduced in CO₂ concentration at 3000 ppm including bioeffluents; the number of correct links made in the cue-utilization test was significantly reduced at 1000 ppm including bioeffluents. Both parameters tested were linearly correlated with increased CO₂ concentrations (500, 1000, and 3000 ppm) excluding bioeffluents (Zhang et al., 2017a). Exposures to CO₂ at 3000 ppm, including bioeffluents, significantly increased diastolic blood pressure and reduced nasal peak flow. Salivary α -amylase activity significantly increased during exposure to CO₂ at 1000 ppm including bioeffluents. ET_{CO2} and heart rate significantly increased during exposure to CO₂ under all conditions both including and removing bioeffluents (Zhang et al., 2017b).

Thirty-six participants were exposed to condition A (outdoor air flow rate of 28.2 l/s person, CO₂ concentration 540 ppm) and condition B (outdoor air flow rate of 2.3 l/s person, CO₂ concentration 2260 ppm) during 4 h. Condition B had a weak negative effect on performance in the information retrieval tasks. Condition B slightly increased the workload and fatigue. No effects on health symptoms were noted (Maula et al., 2017). A crossover experimental study in primary school students suggested that the increase of outdoor air supply from an average of 1.7 to 6.6 l/s per person, which corresponds to decrease from 1500 to 900 ppm CO₂ concentrations, significantly improves the performance of children, including addition, number comparison, grammatical reasoning, and reading and comprehension (Petersen et al., 2016). In these studies, ventilation rates with outdoor air were reduced for increasing CO₂ levels. Thus, both CO₂ and other indoor air pollutants including bioeffluents may contribute to the negative effects on performance.

5. Effects of low-level CO₂ exposure in mice

Recent experimental studies using mice showed that microparticles (MPs) produced by neutrophils exposed to elevations of CO₂ in the range of 1000 to 4000 ppm for 2 h have increased the interleukin-1 β (IL-1 β) content, but these effects were biphasic and did not further increase at 10,000 and 20,000 ppm (Thom et al., 2017a). Mice exposed for 2 h to 2000 or 4000 ppm CO₂ also exhibited increases in IL-1 β , neutrophil and platelet activation, and diffuse inflammatory vascular injury, including vascular leaks in brain, muscle, and distal colon (Thom et al., 2017b). The authors suggest a novel mechanism for adverse effects associated with low-level exposure to CO₂ in which MPs would cause vascular injuries and neuropathological effects.

6. Concluding remarks and future perspectives

Effects of indoor exposure to CO₂ are summarized in Table 1. While epidemiological studies suggest a relationship between low-level exposure to CO₂ and BRs, the observed effects are likely influenced by other comorbid indoor pollutants. However, recent studies show clear linear physiological changes in circulatory, cardiovascular, and autonomic systems, including an increase of pCO₂ in the blood, elevated blood pressure, increased heart rate, increased peripheral blood circulation, and increased sympathetic stimulation at CO₂ exposures in the range of 500 to 5000 ppm.

Regarding the intrinsic effects of CO₂ on autonomic function, several experimental studies on humans suggest that CO₂ may affect cognitive performance (decision making, problem resolution, speed of addition, number of correct links) starting at concentrations of approximately 1000 ppm for short-term exposure to CO₂. The research group of Zhang et al. argues that bioeffluents emitted from humans may be associated with these effects. However, in their study, the speed of addition and the number of correct links in cognitive performance tests were linearly decreased with the CO₂ concentration increase in the range of 500 to 3000 ppm removing bioeffluents. These changes could be considered to be physiologically significance. A study on humans conducted under artificially elevated CO₂ concentrations at a constant outdoor air ventilation rate (corresponds to same conditions for

bioeffluents) suggests that the performances of decision making and problem resolution are affected starting at 1000 ppm CO₂. Further research on the effect of cognitive performance, especially long-term effects on the autonomic system under increased pCO₂ of low-level CO₂ exposure from 500 to 3000 ppm is required. Animal studies may provide further insights into the mechanism of neurobehavioral effects related to low-level exposure to CO₂ in future research. In particular, susceptible populations, such as children and elderly, may be more sensitive to the effects. Further research on susceptible population groups is also required. No study on elderly subjects was found in this review.

Although the effects of low-level exposure to CO₂ on cognitive performance may be sub-clinical and reversible, a reduced performance associated with labor productivity or learning may profoundly affect job competence and learning ability, which may have negative socio-economic repercussions. Therefore, precaution is warranted, particularly in the context of significant linear increase in the global ambient CO₂ concentration caused by anthropogenic activities and sources. Although the ambient CO₂ concentration will not be likely to exceed 1000 ppm owing to global efforts, the increase in ambient CO₂ makes it difficult to curb CO₂ levels in indoor environments as it necessarily entails ventilation with ambient air, which involves further energy consumption (e.g., air-conditioning). Therefore, suppressing the increase in atmospheric CO₂ concentration is a key imperative to prevent influx of CO₂ from ambient air to indoor environment.

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Conflict of interest

The authors declare that there is no conflict of interest.

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