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A review of the effects of exposure to carbon dioxide on human health in indoor environment

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SUMMARY
Here, we review the scientific literature and other documents on pertaining to the effects of inhalation exposure to carbon dioxide (CO_2) on human health. Recent studies have reported linear physiological changes in circulatory, cardiovascular, and autonomic systems at CO_2 exposures ranging between 500 and 5,000 ppm; these effects are very evident. Recent experimental studies suggested that CO_2 might affect psychomotor performance including decision making or problem resolution, beginning at 1,000 ppm during short-time exposure, although bioeffluents emitted by human beings might also be associated with such effects. Many epidemiological studies have demonstrated a relationship between low-level exposure to CO_2 and sick building syndrome (SBS) symptoms, although other mixed hazardous chemicals might also involve such effects. Although such uncertainties exist, maintaining a CO_2 concentration below 1,000 ppm in the indoor environment of a building would represent an effective means of preventing effects upon human health and psychomotor performance. Further research on the long-term effects of low-level CO_2 exposure upon the autonomic system is now required.

KEYWORDS
carbon dioxide, indoor air, low-level exposure, physiological effect, psychomotor performance

INTRODUCTION
Since the 19th Century, the indoor carbon dioxide (CO_2) concentration has been used as an indicator of air quality in buildings. Several countries have established indoor air quality guidelines of 1,000 ppm for CO_2 in non-industrial buildings. CO_2 is naturally present in the atmosphere where the typical outdoor CO_2 concentrations are approximately 380 ppm, although outdoor levels in urban areas have been reported to be as high as 500 ppm. However, increasing CO_2 concentration has contributed to the greenhouse effect and has accelerated global warming. The main source of CO_2 in the non-industrial indoor environment is human metabolism, although an increase in the outdoor CO_2 concentration will also contribute to an increase in the indoor concentration of CO_2. In addition, the need to reduce energy consumption provides an incentive for low rates of ventilation, leading to higher indoor CO_2

concentrations. From these insights, the effects of low-level CO_2 exposure upon human health should be re-examined. This presentation reports a review of current literature pertaining to the association of low-level CO_2 exposure in non-industrial buildings with human health and related human responses.

MATERIALS and METHODS

"Carbon dioxide" was used as a search term in major databases, including PubMed, Google Scholar, CiNii, and J-Dream III for the period 1950–2016, and combined with two additional search terms; "health effect" or "sick building." References quoted in the literature and documents obtained from the above searches were then examined.

RESULTS

Traditional knowledge and national indoor air quality guideline

In 1968, the World Health Organization (WHO) reported two criteria relating to the health effects of CO_2 (Goromosov, 1968), which described physiological studies showing that, at concentrations greater than 5,000 ppm, CO_2 raises the respiration rate above the level required for gas exchange, imposing an additional load on the respiratory system. Pettenkofer and Flügge had proposed in 1881 that 700–1,000 ppm should be regarded as the permissible atmospheric concentration of CO_2. Although the latter criteria had no physiological basis, it proved of considerable practical value as an indirect index of the contamination of air in buildings. However, in 1964, Eliseeva (1964) reported a human experimental study, which showed that inhalation of 1,000 ppm CO_2 for a short time by six healthy individuals aged between 19 and 45 years caused marked changes in amplitude of the respiratory movement, increased peripheral blood flow, and changes in functional state of the cerebral cortex. Eliseeva concluded that the indoor concentration of CO_2 should not be allowed to exceed 1,000 ppm because the presence of a concentration of 1,000 ppm CO_2 in the air has a directly harmful effect. Subsequently, indoor air quality guidelines of 1,000 ppm for CO_2 were established in Japan (large buildings) in 1970, in Canada (office environments) in 1995, in Norway (residential spaces) in 1999, in Singapore (office buildings) in 1999, in China (housing and offices) in 2002, in Korea (large stores and medical facilities) in 2003, in Germany (guidance value to prevent harmful effects) in 2008, and in Taiwan in 2012; these were based on specific assessments in each country (Azuma, 2016a).

Biological effects of carbon dioxide

CO_2 is produced by cellular metabolism and enters the body during respiration when the atmospheric concentration exceeds the alveolar concentration. In the blood, CO_2 is transported in three ways: dissolved in solution; buffered with water as carbonic acid; and bound to proteins, particularly hemoglobin. Lowering the pH releases O_2 from oxyhemoglobin. Raising the partial pressure of CO_2 (pCO_2) also favors the release of O_2 from oxyhemoglobin (Arthurs, 2005). An increase of the pCO_2 delivered to the lungs, i.e., hypercapnia, induces an increase of pCO_2 in the alveoli (Guais, 2011). Because CO_2 freely diffuses through the alveolar membrane and into the blood, it results in an increase of CO_2 tension in arterial blood ($PaCO_2$). In turn, this increase in $PaCO_2$ results in an acute or chronic respiratory acidosis (lower blood pH), due to a lack of acido-basic balance (Guais, 2011). Acute (or acutely worsening chronic) respiratory acidosis causes headache, confusion, anxiety, drowsiness, and stupor (CO_2 narcosis). Slowly developing, stable respiratory acidosis may result in memory loss, sleep disturbances, excessive daytime sleepiness, and personality changes. Appearance of respiratory acidosis can be defined from exposure to a CO_2 concentration of 10,000 ppm for at least 30 minutes in a healthy adult with a moderate physical load (DFG, 2012). An increase in the inhaled CO_2 concentration can result in increased respiratory rate and brain

blood flow, headache, dizziness, confusion, dyspnea, sweating, dim vision, vomiting, disorientation, hypertension, and loss of consciousness (Rise, 2003).

Effects of low-level exposure to CO_2 in humans

Building-related symptoms

According to a review by Seppänen et al (1999), around half of the 21 studies on CO_2 suggested that the risk of sick building syndrome (SBS) symptoms continued to reduce significantly with decreasing CO_2 concentrations below 800 ppm. Apte et al (2000) observed significant associations between mucous membrane and lower respiratory SBS symptoms with increasing indoor minus average outdoor CO_2 (dCO_2) and maximum indoor 1 h moving average CO_2 minus outdoor CO_2 concentrations (dCO_2MAX) when workday average CO_2 levels were always below 800 ppm. Norbäck et al (2008) further reported that a 100 ppm increase in indoor CO_2 concentration (range, 674–1,450 ppm) was significantly associated with headache. Schoolchildren exposed to indoor CO_2 levels greater than 1,000 ppm also showed significantly higher risk for dry cough and rhinitis (Simoni et al, 2010). Office workers exposed to indoor CO_2 levels greater than 800 ppm also reported a significant increase in eye irritation and upper respiratory symptoms (Tsai et al, 2012). A 200 ppm increase in indoor CO_2 concentration (range, 1,000–2,000 ppm) in day care centers was significantly associated with reported wheezing (Carreiro-Martins et al, 2014). In earlier reports, we suggested that non-conformation to a CO_2 standard of 1,000 ppm in buildings was significantly associated with SBS symptoms in office workers (Azuma et al, 2014) and that a 100 ppm increase in CO2 was correlated with SBS symptoms (Azuma et al, 2016b).

Effects of autonomic function or psychomotor performance

Historically, CO_2 exposures below 5,000 ppm were not anticipated to affect blood CO_2 levels, but several recent studies have reported linear increases of pCO_2 in the blood as exposure to ambient CO_2 was increased from 500 to 4,000 ppm through changes in ventilation rate. These studies also reported other physiological responses, which were consistent with increased sympathetic stimulation including changes to heart rate variability, elevated blood pressure, and increases to peripheral blood circulation at CO_2 exposures in the range of 500 to 5,000 ppm (Kaitar 2012, MacNaughton et al, 2016; Vehviläinen et al, 2016). Autonomic dysfunction has a wide array of health impacts on cognitive, urinary, sexual, and digestive systems. Activation of the autonomic system through stress reduces strategic ability and working memory (Starcke et al, 2012), which supports finding by recent studies showing a decrease in decision making performance between 550 and 2,500 ppm of CO_2.

Twenty-two participants were exposed to CO_2 at 600, 1,000, and 2,500 ppm (three 2.5 h sessions, one day) in an office-like chamber. Statistically significant decrements occurred in psychomotor performance (decision making, problem resolution) starting at 1,000 ppm (Satish et al 2012). Twenty-four participants spent six full work days during two weeks in an environmentally controlled office space, blinded to different test conditions: concentrations of volatile organic compounds (VOCs), outdoor air ventilation rate, and artificially elevated CO_2 concentrations were independent of ventilation. VOCs and CO_2 were independently associated with cognitive scores in the groups exposed to CO_2 at 945 and 1,400 ppm compared with controls (Allen et al, 2016). In addition, the same research group reported additional results from the above experimental study, in which a 1,000 ppm increase in CO_2 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).

In another study, ten healthy participants were exposed to CO_2 at 500 ppm and 5,000 ppm (artificially elevated CO_2 concentrations) for 2.5 h in a low-emission stainless steel climate

chamber. End-tidal CO_2 ($ETCO_2$) at 5,000 ppm was increased in comparison with that at 500 ppm. CO_2 concentration at 5,000 ppm had no effect on acute health symptoms (respiratory, eyes and skin, headache, and sensory) and performance in cognitive tests (Zhang et al, 2016). Twenty-five participants were exposed to CO_2 at 500, 1,000 and 3,000 ppm (artificially elevated CO_2 concentrations, outdoor air supply rate was high enough to remove bioeffluents) for 255 min in a low-emission stainless steel climate chamber. In two further conditions, the outdoor air supply rate was reduced to reach CO_2 levels at 1,000 and 3,000 ppm by allowing metabolically generated CO_2 (in addition, bioeffluents also increased). Exposures to CO_2 at 3,000 ppm, including bioeffluents, significantly increased the intensity of reported headache, fatigue, and sleepiness. Cognitive performance was significantly reduced in exposure to CO_2 at 1,000 ppm including bioeffluents (Zhang et al, 2017a). Exposures to CO_2 at 3,000 ppm, including bioeffluents, significantly increased diastolic blood pressure and reduced nasal peak flow. Salivary α-amylase activity significantly increased during exposure to CO_2 at 1,000 ppm including bioeffluents. $ETCO_2$ and heart rate significantly increased during exposure to CO_2 under all conditions (Zhang et al, 2017b).

Table 1 Summary of the effects of exposure to CO_2 in indoor air and relevant exposure guidelines.

CO_2 concentration	Physiological effect	Psychomotor performance	Health symptoms	Guideline or standard
Above 500 ppm	pCO_2, heart rate, heart rate variability, blood pressure, peripheral blood circulation		SBS symptoms above 700 ppm	
Above 1,000 ppm		Cognitive performance (decision making, problem resolution)	Respiratory symptoms in school children	Recommended IAQ guideline for residential spaces
Above 5,000 ppm				Occupational limit (TWA)
Above 10,000 ppm	Respiratory rate, respiratory acidosis, metabolic stress, brain blood flow, minute ventilation			
Above 50,000 ppm	Dizziness, headache, confusion, dyspnea			
Above 100,000 ppm	Unbearable dyspnea, followed by vomiting, disorientation, hypertension, and loss of consciousness			Occupational limit (STEL)

Abbreviations: SBS, sick building syndrome; IAQ, indoor air quality; TWA, time-weighted average; STEL, short-term exposure limit. Occupational limit: American Conference of Governmental Industrial Hygienists, National Institute for Occupational Safety and Health, Occupational Safety and Health Administration.

DISCUSSION

It has been considered that exposure to CO_2 below a concentration of 5,000 ppm was not anticipated to affect blood CO_2 levels. However, several recent studies have reported linear increase of pCO_2 in the blood, elevated blood pressure, increased heart rate, and increased sympathetic stimulation at CO_2 exposures in the range of 500 to 5,000 ppm. Regarding the

intrinsic effects of CO_2 on autonomic function, several recent experimental studies on humans suggest that CO_2 may affect psychomotor performance (decision making, problem resolution) starting at a concentration of 1,000 ppm. Even though these effects are sub-clinical, the reduction of performance related to productivity of labor or learning has a profound effect on social economy or the community. Although bioeffluents emitted from humans might be associated with these effects during short-term exposure to CO_2 at 1,000 ppm, the quantitative and physiological evidence relating to this is not sufficient. Further research on the effects (especially long-term effects on the autonomic system under increased pCO_2) of low-level CO_2 exposure is needed.

The effects of low-level exposure to CO_2 on SBS symptoms may be influenced by other mixed hazardous chemicals. However, many epidemiological studies have demonstrated the relationship between low-level exposure to CO_2 and SBS symptoms. In addition, mucosal symptoms have been reported at a CO_2 exposure of 1,000 ppm during two weeks in an environmentally controlled office space. Maintaining CO_2 concentration below 1,000 ppm would, therefore, be effective in reducing the total health risk due to multiple low-level indoor pollutants in a building. Adverse effects on psychomotor performance could also be prevented.

CONCLUSIONS

Recent studies have shown clear linear physiological changes in circulatory, cardiovascular, and autonomic systems, including increased pCO2 in the blood, elevated blood pressure, increased heart rate, and increased sympathetic stimulation at CO_2 exposures in the range of 500 to 5,000 ppm. Recent short-term exposure studies have suggested that CO_2 might affect psychomotor performance such as decision making or problem resolution beginning at 1,000 ppm, and many epidemiological studies have demonstrated a relationship between low-level exposure to CO_2 and SBS symptoms. While other substances such as bioeffluents, or mixed hazardous chemicals, might also be associated with such effects, maintaining CO_2 concentration below 1,000 ppm would be effective in preventing effects on human health and psychomotor performance. Further research relating to the long-term effects of low-level CO_2 exposure from 500 to 3,000 ppm on the autonomic system is needed.

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