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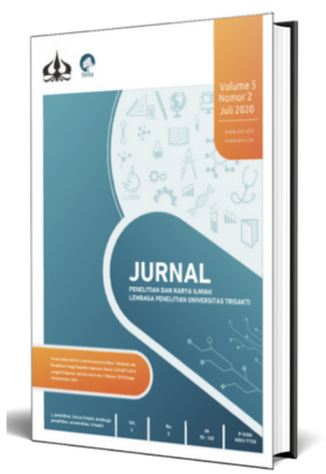

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CORRELATION BETWEEN CARBON DIOXIDE (CO2) AND RESPIRATORY ISSUES: A LITERATURE REVIEW

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ABSTRACT

The increasing levels of carbon dioxide (CO2) in the atmosphere due to human activities have raised concerns regarding potential health impacts, particularly on respiratory health. This literature review aims to examine the correlation between CO2 and respiratory issues by synthesizing the findings of relevant studies. A comprehensive search was conducted across academic databases, and studies were selected based on their relevance and methodological rigor. The review reveals that elevated CO2 levels are associated with respiratory symptoms, including coughing, wheezing, and shortness of breath, as well as the exacerbation of existing respiratory conditions. Additionally, exposure to increased CO2 concentrations can lead to respiratory acidosis, reduced lung function, and impaired gas exchange. Poorly ventilated indoor environments have been identified as potential hotspots for elevated CO2 levels, emphasizing the importance of monitoring indoor air quality. This review underscores the need for further research to elucidate the mechanisms underlying CO2-induced respiratory issues and to develop effective mitigation strategies. Understanding the correlation between CO2 and respiratory issues is crucial for public health interventions and policies aimed at minimizing the adverse impacts of elevated CO2 levels on respiratory health.

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- impaired gas exchange

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1. INTRODUCTION

In the last century, the massive increase in emissions of air pollutants due to the economic and industrial growth has made air quality a major problem in many industrialized countries, and an emerging problem for the rest of the world. Increased concentrations of greenhouse gases, especially CO_2, in the earth's atmosphere have already warmed the planet substantially, causing more severe and prolonged heat waves, temperature variability, air pollution, forest fires, droughts, and floods, all of which put respiratory health at risk. These changes in climate and air quality have a quantifiable impact, not only on the morbidity but also on the mortality for respiratory diseases (Permentier et al., 2017).

The rising levels of carbon dioxide (CO2) in the Earth's atmosphere due to human activities have raised concerns about potential health impacts (Permentier et al., 2017). This literature review aims to explore the correlation between CO2 and respiratory issues. Understanding this relationship is crucial for identifying the potential risks associated with elevated CO2 levels and developing appropriate mitigation strategies.

2. REVIEW

2.1 Background

Carbon dioxide (CO_2) is a product of combustion, fermentation, and respiration. In normal room air, carbon dioxide percentages are very low (around 0.04% or 400 ppm) (Küçükhüseyin, 2021; Azuma et al., 2018). At higher concentrations upwards of 1000 ppm, significant negative effects on the general well-being can occur (headaches, fatigue, lack of concentration) (Azuma et al., 2018). It is a colorless, tasteless, odorless, and nonflammable gas. It accumulates at lower space/ near the ground because CO_2 is 1.5 times heavier than air (Küçükhüseyin, 2021; Health Canada, 2021). These characteristics explain why enclosed environments are vulnerable for CO_2 buildup, displacing oxygen from the area, causing a deficiency of oxygen (Küçükhüseyin, 2021; Health Canada, 2021). The term "confined space hypoxic syndrome" has been proposed to describe confined space accidents occurring in water meter pits, tanks, holds of ships, mines, underground storage bins, and so forth, resulting from oxygen-deficient atmospheres (Küçükhüseyin, 2021).

Carbon dioxide does not only cause asphyxiation by hypoxia but also acts as a toxicant. At high concentrations, it has been showed to cause unconsciousness almost instantaneously and respiratory arrest within 1 minute (Küçükhüseyin, 2021).

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In 1987, Health Canada published *Exposure Guidelines for Residential Indoor Air Quality*, which set an acceptable long-term exposure range (ALTER) of ≤ 3500 ppm for CO_2 in residential indoor air. This value was derived from the lowest concentration at which adverse health effects had been observed in humans in the published literature available at that time. The proposed long-term exposure limit for CO_2 is 1000 ppm (based on a 24-hour average) (United States Environmental Protection Agency, 2023).

Since the publication of these guidelines, new information has become available regarding potential health effects of exposure to elevated CO_2 levels (particularly epidemiological and controlled human exposure studies) and indoor concentrations of CO_2 in Canada. The 1987 exposure guideline for CO_2 is therefore being revisited to reflect the most up-to-date science on health effects and indoor exposure levels for CO_2 (United States Environmental Protection Agency, 2023).

The proposed Residential Indoor Air Quality Guidelines are intended to provide a proposed long-term indoor air exposure limit for CO_2 which would minimize risks to human health. The guideline document also shows that levels in some Canadian homes may exceed the proposed exposure limits, and recommends various risk mitigation measures to reduce exposure to CO_2 (United States Environmental Protection Agency, 2023).

2.2 Indoor Air Quality Concern

In the last several years, a scientific evidence has indicated that the air within homes and other buildings can be more seriously polluted than the outdoor air in even the largest and most industrialized cities. Indoor air is often reported to be severely polluted due to internal sources and infiltration of outdoor air pollution (Vardoulakis et al., 2020). Other research indicates that people spend approximately 90 percent of their time indoors. Thus, for many people, the risks to health may be greater due to exposure to air pollution indoors than outdoors (Vardoulakis et al., 2020; Tran et al., 2020; Erlandson G et al., 2019; Satish et al., 2020; Peterborough Public Health, 2022).

There is increasing awareness that the quality of the indoor environment affects our health and well-being. Indoor air quality (IAQ) in particular has an impact on multiple health outcomes, including respiratory and cardiovascular illness, allergic symptoms, cancers, and premature mortality (Health Canada, 2021; United States Environmental Protection Agency, 2023). According to the World Health Organization (WHO), indoor air pollution (IAP) is responsible for the deaths of 3.8 million people annually (Erlandson G et al., 2019).

People who may be exposed to indoor air pollutants for the longest periods of time are often those most susceptible to the effects of indoor air pollution. Such groups include the young, the elderly and the chronically ill, especially those suffering from respiratory or cardiovascular disease (Vardoulakis et

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al., 2020; Tran et al., 2020). Indoor air quality is an important aspect of human health and well-being. Poor indoor air quality can have adverse effects on human health, including respiratory problems, allergies, and even cancer. The World Health Organization (WHO) has developed guidelines on indoor air quality to help individuals, communities, and governments address this issue (World Health Organization, 2021). The WHO Indoor Air Quality Guidelines were first published in 2010 and updated in 2023. The guidelines provide recommendations on how to improve indoor air quality in both residential and non-residential settings. The guidelines cover a range of pollutants, including CO2, particulate matter, VOC, pressure, temperature, humidity, noise etc. (World Health Organization, 2021). The World Health Organization's Air quality guidelines (AQG) serve as a global target for national, regional and city governments to work towards improving their citizen's health by reducing air pollution (Government of Canada, 2021).

2.3 Sources of Indoor CO_2

Carbon dioxide is a pollutant found in indoor and outdoor air. Indoors, CO_2 is mainly produced through the respiration (breathing) of occupants (Azuma et al., 2018; Health Canada, 2021; United States Environmental Protection Agency, 2023; Erlandson G et al., 2019; Peterborough Public Health, 2022; Wong SK et al., 2022, Patel et al., 2022; Shigemura & Snajder, 2021). Carbon dioxide (CO_2) is a physiological gas produced as a consequence of aerobic metabolism (Patel et al., 2022; Shen G et al., 2020; Shigemura & Snajder, 2021). It is produced in the body's cells (at quantities of 0.7 kg per day) and diffuses from there to the surrounding capillaries. It is transported in the blood after chemically binding onto proteins such as haemoglobin, or in dissolved form. The carbon dioxide is exhaled via the alveolar membrane of the lung (Azuma et al., 2018; Peterborough Public Health, 2022; Drechsler & Morris, 2023). CO_2 can also come from occupants' activities, such as cooking, cigarette smoking, fireplaces, generators and other gasoline powered equipment, and outdoor air (United States Environmental Protection Agency, 2023; Erlandson G et al., 2019; Wong SK et al., 2022; Drechsler & Morris, 2023).

The level of CO_2 in indoor air depends on 3 main factors (Wong SK et al., 2022):

1) Ventilation
2) Indoor sources of CO2
3) The outdoor CO2 concentration

As the ventilation rate (i.e., rate of outdoor air supply to the indoors) per person decreases, the magnitude of the indoor–outdoor difference in CO_2 concentration increases (Peterborough Public Health, 2022). Consequently, peak indoor CO_2 concentrations, or the peak elevations of the indoor

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concentrations above those in outdoor air, have often been used as rough indicators for outdoor-air ventilation rate per occupant (Peterborough Public Health, 2022). The need to reduce energy consumption provides an incentive for low rates of ventilation, leading to higher indoor CO_2 concentrations (Peterborough Public Health, 2022).

The amount of indoor CO_2 is often used (Wong SK et al., 2022):

1) As an indicator of general indoor air quality
2) To represent ventilation rate (the air changes per hour)

2.4 Sources of Outdoor CO_2

Outdoors CO_2 comes mainly from (United States Environmental Protection Agency, 2023):

1) Forest fires
2) Combustion of fossil fuels
3) Animal and plant respiration
4) Organic matter decomposition

2.5 How to lower exposure to CO2 in your home

You can lower levels of CO_2 indoors by increasing ventilation and controlling the sources of CO_2 (United States Environmental Protection Agency, 2023). You can increase ventilation by:

1) Opening windows when possible
   Check the outdoor air quality conditions in your region before opening windows at Air Quality Health Index
2) Using mechanical ventilation strategies. You can find more information on how to use both natural and mechanical ventilation to improve indoor air quality

You can control indoor sources of CO_2 by (United States Environmental Protection Agency, 2023):

1) Not smoking indoors
2) Avoiding crowded living situations, if possible
3) Using a range hood exhaust fan with outside venting when cooking
4) Ensuring fuel-burning appliances are in good working order and properly vented
5) Avoiding the use of unvented fuel-burning appliances (for example, space heaters) indoors.

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2.6 Health effects of CO_2

Elevated carbon dioxide (CO2) concentrations have been shown to significantly impact plant growth, leading to prolonged pollination periods. These changes in plant behavior can be attributed to various environmental pollutant effects, which not only act as irritants to the skin and mucous membranes but also alter the composition of allergen carriers, such as pollen, in the atmosphere. Consequently, allergens are released into the ambient air, contributing to the presence of allergen-containing aerosols (Permentier et al., 2017).

Pollen, traditionally known as an allergen carrier, has been found to release potent lipid mediators (pollen-associated lipid mediators) with pro-inflammatory and immunomodulating effects in allergy diseases. This dual role of pollen, both as an allergen carrier and a source of active lipid mediators, adds complexity to the understanding of respiratory health outcomes in response to environmental pollutants. Pollen allergy is generally used to evaluate the interrelation between air pollution and allergic respiratory diseases, such as rhinitis and asthma (Permentier et al., 2017). Further research is essential to fully comprehend the mechanisms behind these interactions and their implications for public health (Permentier et al., 2017).

CO_2 is viewed as a leading parameter for human-induced air pollution (Azuma et al., 2018). It is a crucial determinant of indoor air quality. Associations of higher indoor carbon dioxide (CO_2) concentrations with impaired work performance, increased health symptoms, and poorer perceived air quality have been attributed to correlation of indoor CO_2 with concentrations of other indoor air pollutants that are also influenced by rates of outdoor-air ventilation (Peterborough Public Health, 2022). Carbon dioxide does not only cause asphyxiation by hypoxia but also acts as a toxicant. At high concentrations, it has been showed to cause unconsciousness almost instantaneously and respiratory arrest within 1 min (Küçükhüseyin, 2021).

The present document reviews the epidemiological, toxicological, and exposure research on carbon dioxide (CO_2). The intent is to propose a new long-term exposure limit for CO_2 in residential indoor air, which would minimize risks to human health, and recommend various risk mitigation measures to reduce exposure to CO_2 (United States Environmental Protection Agency, 2023). Plasma CO_2 levels are tightly regulated under physiological conditions to maintain blood pH. CO_2 is mainly removed from the body via the lungs and can accumulate in lung pathologies (Patel et al., 2022).

A crucial physiological function of the carbon dioxide in the organism consists in its regulation of breathing via the chemical receptors of the aorta and the medulla oblongata, which stimulate the respiratory centre in the brain stem. Increased CO_2 concentrations in inhaled air increase the breathing

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frequency and the tidal volume. During this process, CO_2 has a dilatory effect on the bronchia, which causes an increase in the dead space volume (the space in the respiratory system which is not involved in gas exchange). However, the dilatory effect of the CO_2 on peripheral and central arterioles does not lead to a decrease of blood pressure, since an increased adrenalin production causes a compensatory vasoconstriction (Azuma et al., 2018).

CO_2 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 CO_2 accumulates in the blood, the blood pH decreases (acidity increases). Therefore, CO_2 is discharged from the human body for maintaining the acid–base balance in the blood (Health Canada, 2021). The CO_2 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 CO_2 passes from the blood into the lung alveoli to be exhaled into ambient air (external respiration) (Health Canada, 2021).

Lowering the pH or raising the partial pressure of CO_2 (pCO_2) releases of oxygen (O_2) from oxyhemoglobin. An increase of pCO_2 delivered to the lungs, that is, hypercapnia, induces an increase of pCO_2 in the alveoli. CO_2 freely diffuses through the alveolar membrane and into the blood, resulting in an increase of CO_2 tension in arterial blood ($PaCO_2$). In turn, this increase in $PaCO_2$ (lower blood pH) results in an acute or chronic respiratory acidosis caused by the acid–base imbalance in the blood (Health Canada, 2021).

Respiratory acidosis corresponds to CO_2 accumulation. Acute or acutely worsening chronic respiratory acidosis causes headache, confusion, anxiety, drowsiness, and stupor (CO_2 narcosis). Slowly developing, stable respiratory acidosis may be well tolerated, but could result in memory loss, sleep disturbances, excessive daytime sleepiness, and personality changes. CO_2 rapidly diffuses into the brain across the blood–brain barrier. Symptoms and signs are the result of high CO_2 concentrations (low central nervous system pH) in the central nervous system and any accompanying hypoxemia (Health Canada, 2021; Wisconsin Department of Health Services, 2023).

Respiratory acidosis is defined as exposure to a CO_2 concentration of 10,000 ppm for at least 30 minutes in a healthy adult engaged in moderate physical activity. As the inhaled CO2 concentration increases, it can lead to elevated respiratory rate, metabolic stress, increased brain blood flow, and heightened minute ventilation (above 10,000 ppm). Beyond 30,000 ppm, it can cause decreased exercise tolerance in workers when breathing against inspiratory and expiratory resistance, while levels above 50,000 ppm may result in symptoms like headache, dizziness, confusion, and dyspnea. Extremely high concentrations above 100,000 ppm may induce sweating, dim vision, vomiting, disorientation, hypertension, and loss of consciousness (Health Canada, 2021).

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Recent studies by American academics have shown that exposure to ambient CO2 levels in indoor environments can have detrimental effects on the human body, even at much lower levels. Health problems such as inflammation, reduced cognitive performance, and kidney and bone issues can occur at CO2 levels as low as 1,000 parts per million (ppm), which is considerably lower than the previously accepted 5,000 ppm threshold (United States Environmental Protection Agency, 2023; Wong SK et al., 2022; Chrisodgen, 2019). Furthermore, mounting evidence suggests that health problems can emerge even with short-term exposure to CO2 levels as low as 1,000 ppm (Wisconsin Department of Health Services, 2023).

The findings, published in the journal *Nature Sustainability*, consolidate the growing body of research into health effects of CO_2, an area that has been relatively less explored compared to the effects of particulate matter (PM2.5) or nitrogen oxide (NOx)[20, 21]. This early evidence indicates potential health risks associated with CO_2 exposures as low as 1,000 ppm–a threshold that is already being surpassed in many indoor environments with increased room occupancy and reduced building ventilation rates (Chrisodgen, 2019).

Studies have observed CO_2 levels exceeding 1,000ppm in crowded and poorly ventilated rooms such as classrooms, offices, and bedrooms, and air-conditioned public transport and planes, where individuals often spend prolonged periods (Chrisodgen, 2019). WHO recommends maintaining a CO2 concentration of less than 1000 ppm (parts per million) in indoor spaces (World Health Organization, 2021). Combining the findings of numerous studies, the researchers concluded that acute exposure to high CO_2 levels can lead to 'adverse health outcomes', with inflammation and reduced cognitive performance being observed above 1,000ppm (Chrisodgen, 2019). Chronic exposure to levels between 2,000ppm and 3,000ppm can have even more severe impacts as this was linked to effects including kidney calcification and bone demineralisation (Chrisodgen, 2019). Wisconsin Department of Health Services provides a summary of CO_2 levels in the air and the potential health problems associated with them (Chrisodgen, 2019).

1) 400 ppm: average outdoor air level.
2) 400–1,000 ppm: typical level found in occupied spaces with good air exchange.
3) 1,000–2,000 ppm: level associated with complaints of drowsiness and poor air.
4) 2,000–5,000 ppm: level associated with headaches, sleepiness, and stagnant, stale, stuffy air. Poor concentration, loss of attention, increased heart rate and slight nausea may also be present.
5) 5,000 ppm: this indicates unusual air conditions where high levels of other gases could also be present. Toxicity or oxygen deprivation could occur. This is the permissible exposure limit for daily workplace exposures.

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6) 40,000 ppm: this level is immediately harmful due to oxygen deprivation.

CONCLUSION

The literature suggests a correlation between elevated CO_2 levels and respiratory issues. In conclusion, the discussed studies emphasize the critical impact of CO2 exposure on human health, with even lower concentrations than previously believed having adverse effects. Proper ventilation and control of indoor CO2 levels are vital to mitigate these health risks effectively.

This review underscores the need for further research to elucidate the mechanisms underlying CO2-induced respiratory issues and to develop effective mitigation strategies. Understanding the correlation between CO2 and respiratory issues is crucial for public health interventions and policies aimed at minimizing the adverse impacts of elevated CO2 levels on respiratory health.

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CORRELATION BETWEEN CARBON DIOXIDE (CO2) AND RESPIRATORY ISSUES

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CORRELATION BETWEEN CARBON DIOXIDE (CO2) AND RESPIRATORY ISSUES: A LITERATURE REVIEW

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ABSTRACT

The increasing levels of carbon dioxide (CO2) in the atmosphere due to human activities have raised concerns regarding potential health impacts, particularly on respiratory health. This literature review aims to examine the correlation between CO2 and respiratory issues by synthesizing the findings of relevant studies. A comprehensive search was conducted across academic databases, and studies were selected based on their relevance and methodological rigor. The review reveals that elevated CO2 levels are associated with respiratory symptoms, including coughing, wheezing, and shortness of breath, as well as the exacerbation of existing respiratory conditions. Additionally, exposure to increased CO2 concentrations can lead to respiratory acidosis, reduced lung function, and impaired gas exchange. Poorly ventilated indoor environments have been identified as potential hotspots for elevated CO2 levels, emphasizing the importance of monitoring indoor air quality. This review underscores the need for further research to elucidate the mechanisms underlying CO2-induced respiratory issues and to develop effective mitigation strategies. Understanding the correlation between CO2 and respiratory issues is crucial for public health interventions and policies aimed at minimizing the adverse impacts of elevated CO2 levels on respiratory health.

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1. INTRODUCTION

In the last century, the massive increase in emissions of air pollutants due to the economic and industrial growth has made air quality a major problem in many industrialized countries, and an emerging problem for the rest of the world. Increased concentrations of greenhouse gases, especially CO_2, in the earth's atmosphere have already warmed the planet substantially, causing more severe and prolonged heat waves, temperature variability, air pollution, forest fires, droughts, and floods, all of which put respiratory health at risk. These changes in climate and air quality have a quantifiable impact, not only on the morbidity but also on the mortality for respiratory diseases (Permentier et al., 2017).

The rising levels of carbon dioxide (CO2) in the Earth's atmosphere due to human activities have raised concerns about potential health impacts (Permentier et al., 2017). This literature review aims to explore the correlation between CO2 and respiratory issues. Understanding this relationship is crucial for identifying the potential risks associated with elevated CO2 levels and developing appropriate mitigation strategies.

2. REVIEW

2.1 Background

Carbon dioxide (CO_2) is a product of combustion, fermentation, and respiration. In normal room air, carbon dioxide percentages are very low (around 0.04% or 400 ppm) (Küçükhüseyin, 2021; Azuma et al., 2018). At higher concentrations upwards of 1000 ppm, significant negative effects on the general well-being can occur (headaches, fatigue, lack of concentration) (Azuma et al., 2018). It is a colorless, tasteless, odorless, and nonflammable gas. It accumulates at lower space/ near the ground because CO_2 is 1.5 times heavier than air (Küçükhüseyin, 2021; Health Canada, 2021). These characteristics explain why enclosed environments are vulnerable for CO_2 buildup, displacing oxygen from the area, causing a deficiency of oxygen (Küçükhüseyin, 2021; Health Canada, 2021). The term "confined space hypoxic syndrome" has been proposed to describe confined space accidents occurring in water meter pits, tanks, holds of ships, mines, underground storage bins, and so forth, resulting from oxygen-deficient atmospheres (Küçükhüseyin, 2021).

Carbon dioxide does not only cause asphyxiation by hypoxia but also acts as a toxicant. At high concentrations, it has been showed to cause unconsciousness almost instantaneously and respiratory arrest within 1 minute (Küçükhüseyin, 2021).

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In 1987, Health Canada published *Exposure Guidelines for Residential Indoor Air Quality*, which set an acceptable long-term exposure range (ALTER) of ≤ 3500 ppm for CO_2 in residential indoor air. This value was derived from the lowest concentration at which adverse health effects had been observed in humans in the published literature available at that time. The proposed long-term exposure limit for CO_2 is 1000 ppm (based on a 24-hour average) (United States Environmental Protection Agency, 2023).

Since the publication of these guidelines, new information has become available regarding potential health effects of exposure to elevated CO_2 levels (particularly epidemiological and controlled human exposure studies) and indoor concentrations of CO_2 in Canada. The 1987 exposure guideline for CO_2 is therefore being revisited to reflect the most up-to-date science on health effects and indoor exposure levels for CO_2 (United States Environmental Protection Agency, 2023).

The proposed Residential Indoor Air Quality Guidelines are intended to provide a proposed long-term indoor air exposure limit for CO_2 which would minimize risks to human health. The guideline document also shows that levels in some Canadian homes may exceed the proposed exposure limits, and recommends various risk mitigation measures to reduce exposure to CO_2 (United States Environmental Protection Agency, 2023).

2.2 Indoor Air Quality Concern

In the last several years, a scientific evidence has indicated that the air within homes and other buildings can be more seriously polluted than the outdoor air in even the largest and most industrialized cities. Indoor air is often reported to be severely polluted due to internal sources and infiltration of outdoor air pollution (Vardoulakis et al., 2020). Other research indicates that people spend approximately 90 percent of their time indoors. Thus, for many people, the risks to health may be greater due to exposure to air pollution indoors than outdoors (Vardoulakis et al., 2020; Tran et al., 2020; Erlandson G et al., 2019; Satish et al., 2020; Peterborough Public Health, 2022).

There is increasing awareness that the quality of the indoor environment affects our health and well-being. Indoor air quality (IAQ) in particular has an impact on multiple health outcomes, including respiratory and cardiovascular illness, allergic symptoms, cancers, and premature mortality (Health Canada, 2021; United States Environmental Protection Agency, 2023). According to the World Health Organization (WHO), indoor air pollution (IAP) is responsible for the deaths of 3.8 million people annually (Erlandson G et al., 2019).

People who may be exposed to indoor air pollutants for the longest periods of time are often those most susceptible to the effects of indoor air pollution. Such groups include the young, the elderly and the chronically ill, especially those suffering from respiratory or cardiovascular disease (Vardoulakis et

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al., 2020; Tran et al., 2020). Indoor air quality is an important aspect of human health and well-being. Poor indoor air quality can have adverse effects on human health, including respiratory problems, allergies, and even cancer. The World Health Organization (WHO) has developed guidelines on indoor air quality to help individuals, communities, and governments address this issue (World Health Organization, 2021). The WHO Indoor Air Quality Guidelines were first published in 2010 and updated in 2023. The guidelines provide recommendations on how to improve indoor air quality in both residential and non-residential settings. The guidelines cover a range of pollutants, including CO2, particulate matter, VOC, pressure, temperature, humidity, noise etc. (World Health Organization, 2021). The World Health Organization's Air quality guidelines (AQG) serve as a global target for national, regional and city governments to work towards improving their citizen's health by reducing air pollution (Government of Canada, 2021).

2.3 Sources of Indoor CO_2

Carbon dioxide is a pollutant found in indoor and outdoor air. Indoors, CO_2 is mainly produced through the respiration (breathing) of occupants (Azuma et al., 2018; Health Canada, 2021; United States Environmental Protection Agency, 2023; Erlandson G et al., 2019; Peterborough Public Health, 2022; Wong SK et al., 2022, Patel et al., 2022; Shigemura & Snajder, 2021). Carbon dioxide (CO_2) is a physiological gas produced as a consequence of aerobic metabolism (Patel et al., 2022; Shen G et al., 2020; Shigemura & Snajder, 2021). It is produced in the body's cells (at quantities of 0.7 kg per day) and diffuses from there to the surrounding capillaries. It is transported in the blood after chemically binding onto proteins such as haemoglobin, or in dissolved form. The carbon dioxide is exhaled via the alveolar membrane of the lung (Azuma et al., 2018; Peterborough Public Health, 2022; Drechsler & Morris, 2023). CO_2 can also come from occupants' activities, such as cooking, cigarette smoking, fireplaces, generators and other gasoline powered equipment, and outdoor air (United States Environmental Protection Agency, 2023; Erlandson G et al., 2019; Wong SK et al., 2022; Drechsler & Morris, 2023).

The level of CO_2 in indoor air depends on 3 main factors (Wong SK et al., 2022):

1) Ventilation
2) Indoor sources of CO2
3) The outdoor CO2 concentration

As the ventilation rate (i.e., rate of outdoor air supply to the indoors) per person decreases, the magnitude of the indoor–outdoor difference in CO_2 concentration increases (Peterborough Public Health, 2022). Consequently, peak indoor CO_2 concentrations, or the peak elevations of the indoor

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concentrations above those in outdoor air, have often been used as rough indicators for outdoor-air ventilation rate per occupant (Peterborough Public Health, 2022). The need to reduce energy consumption provides an incentive for low rates of ventilation, leading to higher indoor CO_2 concentrations (Peterborough Public Health, 2022).

The amount of indoor CO_2 is often used (Wong SK et al., 2022):

1) As an indicator of general indoor air quality
2) To represent ventilation rate (the air changes per hour)

2.4 Sources of Outdoor CO_2

Outdoors CO_2 comes mainly from (United States Environmental Protection Agency, 2023):

1) Forest fires
2) Combustion of fossil fuels
3) Animal and plant respiration
4) Organic matter decomposition

2.5 How to lower exposure to CO2 in your home

You can lower levels of CO_2 indoors by increasing ventilation and controlling the sources of CO_2 (United States Environmental Protection Agency, 2023). You can increase ventilation by:

1) Opening windows when possible
   Check the outdoor air quality conditions in your region before opening windows at Air Quality Health Index
2) Using mechanical ventilation strategies. You can find more information on how to use both natural and mechanical ventilation to improve indoor air quality

You can control indoor sources of CO_2 by (United States Environmental Protection Agency, 2023):

1) Not smoking indoors
2) Avoiding crowded living situations, if possible
3) Using a range hood exhaust fan with outside venting when cooking
4) Ensuring fuel-burning appliances are in good working order and properly vented
5) Avoiding the use of unvented fuel-burning appliances (for example, space heaters) indoors.

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2.6 Health effects of CO_2

Elevated carbon dioxide (CO2) concentrations have been shown to significantly impact plant growth, leading to prolonged pollination periods. These changes in plant behavior can be attributed to various environmental pollutant effects, which not only act as irritants to the skin and mucous membranes but also alter the composition of allergen carriers, such as pollen, in the atmosphere. Consequently, allergens are released into the ambient air, contributing to the presence of allergen-containing aerosols (Permentier et al., 2017).

Pollen, traditionally known as an allergen carrier, has been found to release potent lipid mediators (pollen-associated lipid mediators) with pro-inflammatory and immunomodulating effects in allergy diseases. This dual role of pollen, both as an allergen carrier and a source of active lipid mediators, adds complexity to the understanding of respiratory health outcomes in response to environmental pollutants. Pollen allergy is generally used to evaluate the interrelation between air pollution and allergic respiratory diseases, such as rhinitis and asthma (Permentier et al., 2017). Further research is essential to fully comprehend the mechanisms behind these interactions and their implications for public health (Permentier et al., 2017).

CO_2 is viewed as a leading parameter for human-induced air pollution (Azuma et al., 2018). It is a crucial determinant of indoor air quality. Associations of higher indoor carbon dioxide (CO_2) concentrations with impaired work performance, increased health symptoms, and poorer perceived air quality have been attributed to correlation of indoor CO_2 with concentrations of other indoor air pollutants that are also influenced by rates of outdoor-air ventilation (Peterborough Public Health, 2022). Carbon dioxide does not only cause asphyxiation by hypoxia but also acts as a toxicant. At high concentrations, it has been showed to cause unconsciousness almost instantaneously and respiratory arrest within 1 min (Küçükhüseyin, 2021).

The present document reviews the epidemiological, toxicological, and exposure research on carbon dioxide (CO_2). The intent is to propose a new long-term exposure limit for CO_2 in residential indoor air, which would minimize risks to human health, and recommend various risk mitigation measures to reduce exposure to CO_2 (United States Environmental Protection Agency, 2023). Plasma CO_2 levels are tightly regulated under physiological conditions to maintain blood pH. CO_2 is mainly removed from the body via the lungs and can accumulate in lung pathologies (Patel et al., 2022).

A crucial physiological function of the carbon dioxide in the organism consists in its regulation of breathing via the chemical receptors of the aorta and the medulla oblongata, which stimulate the respiratory centre in the brain stem. Increased CO_2 concentrations in inhaled air increase the breathing

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frequency and the tidal volume. During this process, CO_2 has a dilatory effect on the bronchia, which causes an increase in the dead space volume (the space in the respiratory system which is not involved in gas exchange). However, the dilatory effect of the CO_2 on peripheral and central arterioles does not lead to a decrease of blood pressure, since an increased adrenalin production causes a compensatory vasoconstriction (Azuma et al., 2018).

CO_2 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 CO_2 accumulates in the blood, the blood pH decreases (acidity increases). Therefore, CO_2 is discharged from the human body for maintaining the acid–base balance in the blood (Health Canada, 2021). The CO_2 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 CO_2 passes from the blood into the lung alveoli to be exhaled into ambient air (external respiration) (Health Canada, 2021).

Lowering the pH or raising the partial pressure of CO_2 (pCO_2) releases of oxygen (O_2) from oxyhemoglobin. An increase of pCO_2 delivered to the lungs, that is, hypercapnia, induces an increase of pCO_2 in the alveoli. CO_2 freely diffuses through the alveolar membrane and into the blood, resulting in an increase of CO_2 tension in arterial blood ($PaCO_2$). In turn, this increase in $PaCO_2$ (lower blood pH) results in an acute or chronic respiratory acidosis caused by the acid–base imbalance in the blood (Health Canada, 2021).

Respiratory acidosis corresponds to CO_2 accumulation. Acute or acutely worsening chronic respiratory acidosis causes headache, confusion, anxiety, drowsiness, and stupor (CO_2 narcosis). Slowly developing, stable respiratory acidosis may be well tolerated, but could result in memory loss, sleep disturbances, excessive daytime sleepiness, and personality changes. CO_2 rapidly diffuses into the brain across the blood–brain barrier. Symptoms and signs are the result of high CO_2 concentrations (low central nervous system pH) in the central nervous system and any accompanying hypoxemia (Health Canada, 2021; Wisconsin Department of Health Services, 2023).

Respiratory acidosis is defined as exposure to a CO_2 concentration of 10,000 ppm for at least 30 minutes in a healthy adult engaged in moderate physical activity. As the inhaled CO2 concentration increases, it can lead to elevated respiratory rate, metabolic stress, increased brain blood flow, and heightened minute ventilation (above 10,000 ppm). Beyond 30,000 ppm, it can cause decreased exercise tolerance in workers when breathing against inspiratory and expiratory resistance, while levels above 50,000 ppm may result in symptoms like headache, dizziness, confusion, and dyspnea. Extremely high concentrations above 100,000 ppm may induce sweating, dim vision, vomiting, disorientation, hypertension, and loss of consciousness (Health Canada, 2021).

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Recent studies by American academics have shown that exposure to ambient CO2 levels in indoor environments can have detrimental effects on the human body, even at much lower levels. Health problems such as inflammation, reduced cognitive performance, and kidney and bone issues can occur at CO2 levels as low as 1,000 parts per million (ppm), which is considerably lower than the previously accepted 5,000 ppm threshold (United States Environmental Protection Agency, 2023; Wong SK et al., 2022; Chrisodgen, 2019). Furthermore, mounting evidence suggests that health problems can emerge even with short-term exposure to CO2 levels as low as 1,000 ppm (Wisconsin Department of Health Services, 2023).

The findings, published in the journal *Nature Sustainability*, consolidate the growing body of research into health effects of CO_2, an area that has been relatively less explored compared to the effects of particulate matter (PM2.5) or nitrogen oxide (NOx)[20, 21]. This early evidence indicates potential health risks associated with CO_2 exposures as low as 1,000 ppm–a threshold that is already being surpassed in many indoor environments with increased room occupancy and reduced building ventilation rates (Chrisodgen, 2019).

Studies have observed CO_2 levels exceeding 1,000ppm in crowded and poorly ventilated rooms such as classrooms, offices, and bedrooms, and air-conditioned public transport and planes, where individuals often spend prolonged periods (Chrisodgen, 2019). WHO recommends maintaining a CO2 concentration of less than 1000 ppm (parts per million) in indoor spaces (World Health Organization, 2021). Combining the findings of numerous studies, the researchers concluded that acute exposure to high CO_2 levels can lead to 'adverse health outcomes', with inflammation and reduced cognitive performance being observed above 1,000ppm (Chrisodgen, 2019). Chronic exposure to levels between 2,000ppm and 3,000ppm can have even more severe impacts as this was linked to effects including kidney calcification and bone demineralisation (Chrisodgen, 2019). Wisconsin Department of Health Services provides a summary of CO_2 levels in the air and the potential health problems associated with them (Chrisodgen, 2019).

1) 400 ppm: average outdoor air level.
2) 400–1,000 ppm: typical level found in occupied spaces with good air exchange.
3) 1,000–2,000 ppm: level associated with complaints of drowsiness and poor air.
4) 2,000–5,000 ppm: level associated with headaches, sleepiness, and stagnant, stale, stuffy air. Poor concentration, loss of attention, increased heart rate and slight nausea may also be present.
5) 5,000 ppm: this indicates unusual air conditions where high levels of other gases could also be present. Toxicity or oxygen deprivation could occur. This is the permissible exposure limit for daily workplace exposures.

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6) 40,000 ppm: this level is immediately harmful due to oxygen deprivation.

CONCLUSION

The literature suggests a correlation between elevated CO_2 levels and respiratory issues. In conclusion, the discussed studies emphasize the critical impact of CO2 exposure on human health, with even lower concentrations than previously believed having adverse effects. Proper ventilation and control of indoor CO2 levels are vital to mitigate these health risks effectively.

This review underscores the need for further research to elucidate the mechanisms underlying CO2-induced respiratory issues and to develop effective mitigation strategies. Understanding the correlation between CO2 and respiratory issues is crucial for public health interventions and policies aimed at minimizing 11 the adverse impacts of elevated CO2 levels on respiratory health.

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