



Review

Low Level Carbon Dioxide Indoors—A Pollution Indicator or a Pollutant? A Health-Based Perspective

Scott D. Lowther ^{1,†}, Sani Dimitroulopoulou ^{1,*}, Kerry Foxall ², Clive Shrubsole ^{1,‡}, Emily Cheek ¹, Britta Gadeberg ² and Ovnair Sepai ²

¹ Air Quality & Public Health Team, Environmental Hazards and Emergencies Department, Science Group, UK Health Security Agency Harwell Science and Innovation Campus, Chilton OX11 0RQ, UK; s.d.lowther@outlook.com (S.D.L.); drcliveshrubsole@gmail.com (C.S.); Emily.Cheek@phe.gov.uk (E.C.)

² Toxicology Department, Science Group, UK Health Security Agency, Harwell Science and Innovation Campus, Chilton OX11 0RQ, UK; Kerry.Foxall@phe.gov.uk (K.F.); Britta.Gadeberg@phe.gov.uk (B.G.); Ovnair.Sepai@phe.gov.uk (O.S.)

* Correspondence: sani.dimitroulopoulou@phe.gov.uk

† Now at Dyson, Environmental Care, RDD, Hullavington SN14 6GU, UK.

‡ Now retired.

Abstract: With modern populations in developed countries spending approximately 90% of their time indoors, and with carbon dioxide (CO₂) concentrations inside being able to accumulate to much greater concentrations than outdoors, it is important to identify the health effects associated with the exposure to low-level CO₂ concentrations (<5000 ppm) typically seen in indoor environments in buildings (non-industrial environments). Although other reviews have summarised the effects of CO₂ exposure on health, none have considered the individual study designs of investigations and factored that into the level of confidence with which CO₂ and health effects can be associated, nor commented on how the reported health effects of exposure correspond to existing guideline concentrations. This investigation aimed to (a) evaluate the reported health effects and physiological responses associated with exposure to less than 5000 parts per million (ppm) of CO₂ and (b) to assess the CO₂ guideline and limit concentrations in the context of (a). Of the 51 human investigations assessed, many did not account for confounding factors, the prior health of participants or cross-over effects. Although there is some evidence linking CO₂ exposures with health outcomes, such as reductions in cognitive performance or sick building syndrome (SBS) symptoms, much of the evidence is conflicting. Therefore, given the shortcomings in study designs and conflicting results, it is difficult to say with confidence whether low-level CO₂ exposures indoors can be linked to health outcomes. To improve the epidemiological value of future investigations linking CO₂ with health, studies should aim to control or measure confounding variables, collect comprehensive accounts of participants' prior health and avoid cross-over effects. Although it is difficult to link CO₂ itself with health effects at exposures less than 5000 ppm, the existing guideline concentrations (usually reported for 8 h, for schools and offices), which suggest that CO₂ levels <1000 ppm represent good indoor air quality and <1500 ppm are acceptable for the general population, appear consistent with the current research.

Keywords: CO₂; bio-effluents; cognitive effects; respiratory effects; neurological and irritation of upper airway system; physiological effects; guidelines



Citation: Lowther, S.D.; Dimitroulopoulou, S.; Foxall, K.; Shrubsole, C.; Cheek, E.; Gadeberg, B.; Sepai, O. Low Level Carbon Dioxide Indoors—A Pollution Indicator or a Pollutant? A Health-Based Perspective. *Environments* **2021**, *8*, 125. <https://doi.org/10.3390/environments8110125>

Academic Editor: Rosanna Mabilia

Received: 30 September 2021

Accepted: 1 November 2021

Published: 16 November 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

In indoor air, the primary source of carbon dioxide (CO₂) is human respiration, meaning that occupant density and ventilation are important determinants of indoor concentrations. In poorly ventilated indoor environments, CO₂ can accumulate to several times the background level, with potential health implications [1].

Given increasing energy costs and concerns about the environmental impact of buildings, ventilation rates are being reduced to minimise heat losses and improve energy efficiency [2]. However, this is allowing indoor air pollutants such as CO₂ to accumulate to much greater levels than before. Because CO₂ concentration, human occupancy and ventilation rates are linked to a great degree, CO₂ concentrations can be used to estimate ventilation rates and the concentrations of human bio-effluents indoors [1,3]. Currently, CO₂ is considered as an indicator for ventilation, as increased CO₂ levels indicate inadequate ventilation, which is often associated with poorer air quality [4].

As far back as 1881, Pettenkofer and Flügge proposed a concentration of 700–1000 parts per million (ppm) as the permissible indoor CO₂ concentration above which the air would be considered ‘contaminated’. However, there was no physiological basis to this criterion, with changes in respiration rates only seen with concentrations above 5000 ppm [5]. Eliseeva [6] made the first recorded investigation of the impacts of exposures to low levels of CO₂. Using a study with a small group, they investigated CO₂ exposures at concentrations of between 500 and 1000 ppm. They found that at a concentration of 1000 ppm, there was a marked change in respiration, with the amplitude of respiratory movements being reduced. An effect on the circulatory system was noted by an increase in peripheral blood flow. A study of cerebral electrical activity showed that at concentrations of 1000 ppm, CO₂ may influence the functional state of the cerebral cortex and may increase the amplitude of brain waves [6]. Although a very small-scale study, this formed part of a World Health Organization (WHO) report [5], which cautiously suggested that a CO₂ concentration of 1000 ppm in the indoor air may have a directly harmful effect. It was proposed that concentrations of CO₂ should therefore not be allowed to exceed 1000 ppm and the average concentration should be ≤500 ppm. However, this is not nowadays realistic to be achieved by natural ventilation indoors, as the global average outdoor CO₂ levels in 2019 were 410 ppm [7]. There are numerous industrial, national and international standards for CO₂ concentrations in various building types that have evolved with time and propose the average CO₂ levels during the period of occupancy (e.g., CIBSE [8]; UK Department for Education [9]). British Standard BS EN 16798-1: 2019 proposes the CO₂ concentrations above those of the outdoors that should be achieved by mechanical ventilation to maintain good indoor air quality (IAQ) [10].

Currently, within industry, academia and amongst policymakers, there is an increasing concern regarding the possible health impacts of CO₂ exposures on building occupants and the best strategies to mitigate these. Whilst the reported health impacts for higher concentrations of CO₂ (>20,000 ppm) are well established [11,12], the evidence of possible health effects at the average concentrations seen in buildings (typically ≤5000 ppm and often ≤1500 ppm) is unclear, although some emerging research suggests lower-level impacts may occur. Given that in developed countries people spend around 90% of their time indoors [13], it is important to clarify if any exposure to CO₂ could cause harm, as this would then act as an important modifier of population health.

A few recent reviews have investigated the effects of CO₂ exposure on human health [14–17]. The review of Azuma et al. [14] was short, looking at the impact of inhalation exposure to CO₂ at a wide range of concentrations (varying from 500 to >100,000 ppm). At low CO₂ levels, they focused on cognitive performance and concluded that exposure to CO₂ may affect it, starting at concentrations of around 1000 ppm for short-term exposure; they recommended further research on the impact of CO₂ exposure on cognitive performance, at low levels, from 500 to 3000 ppm. Jacobson et al. [16] reviewed primary research to assess the physiological changes, psychomotor performances and health symptoms associated with CO₂ exposure. They concluded that the evidence indicates potential risks at CO₂ exposures as low as 1000 ppm and made an urgent call for two types of studies: (a) controlled chamber studies, to identify the health effects of acute exposure at environmental CO₂ levels and (b) large, cohort-based longitudinal studies to evaluate the impacts of long-term chronic CO₂ exposure. Du et al. [15] focused more specifically on reviewing the evidence relating to indoor CO₂ concentrations and cognitive function. They identified

cognitive assessment methods, the study design, uncertainty in exposures and individual and population differences in subjects as major confounding factors. Seppänen et al. [17], provided a significant review of the effects of CO₂ concentrations and ventilation rates on health; however, this is now significantly dated, and requires updating.

Our review moves one step ahead from previous reviews, reviewing analytically the impact of exposure to low CO₂ levels, not only on cognitive performance, but also on respiratory impacts, neurological effects and irritation of the upper airway system, as well as on both human and animal physiological responses. We have identified a set of selected criteria related to study design and we assessed each of the reviewed studies against these criteria, to better understand the level of confidence we can have in results linking CO₂ and health. We also reviewed existing CO₂ guidelines from a number of countries and organisations, contextualised against the outcomes of our review. All the above work aimed to identify if CO₂ is only an indicator of ventilation and pollutant accumulation or is a pollutant itself at low levels (<5000 ppm).

2. Methods

2.1. Search Strategy

A systematic literature search was conducted using the following electronic databases: EMBASE, GlobalHealth and Scopus. In addition, a grey literature search was conducted including the WHO, Public Health England (PHE) and various worldwide standards to identify guidelines and recommended limits for CO₂ concentrations indoors.

A search strategy was developed incorporating key terms to explore the literature, restricted by publication language (English) and date (1990–2019).

Considering all populations, the search strategy was divided into the following concepts:

- Carbon dioxide terms;
- Health/effect terms;
- Location terms (indoor environments).

Using this framework, an initial set of keywords was developed to explore the literature. Additional terms and search strings revealed by the literature search were added and investigated. The search strings used are specified in Appendix A.

2.2. Initial Literature Search and Analysis

The search resulted in 1314 papers after duplicates were removed. All 1314 papers were screened independently by two reviewers by title and abstract and then were double-checked by a third reviewer. After exclusions from the first round of screening, the remaining papers (320) were sourced and screened by full text by two reviewers and verified by a third. The search was conducted up to January 2020.

To identify only the literature that was appropriate for making comparisons between indoor CO₂ concentrations and health effects, the following criteria had to be met for inclusion: the investigation must (a) contain primary research, (b) report CO₂ concentrations, with some being less than 5000 ppm, (c) compare CO₂ concentrations against measured health effects and (d) have CO₂ being measured in indoor environments. Figure 1 illustrates the systematic literature review process.

In addition to the systematic literature review, a grey literature review identified national and international CO₂ guidelines and limit concentrations for indoor environments, specifically looking for any health or toxicological information that was used to inform these.

2.3. Second Literature Search

A second literature search (using MEDLINE) was conducted to capture any papers investigating the physiological responses of animals and humans exposed to CO₂. To be included in the review, the identified papers had to (a) be human or animal laboratory studies examining the potential health effects of exposure to CO₂ and (b) have CO₂ exposure concentrations of ≤5000 ppm. Figure 2 illustrates the second literature search process.

Further papers were identified by reviewing the reference lists of the selected papers, in addition to those identified in the initial search, and these were then assessed against the inclusion criteria.

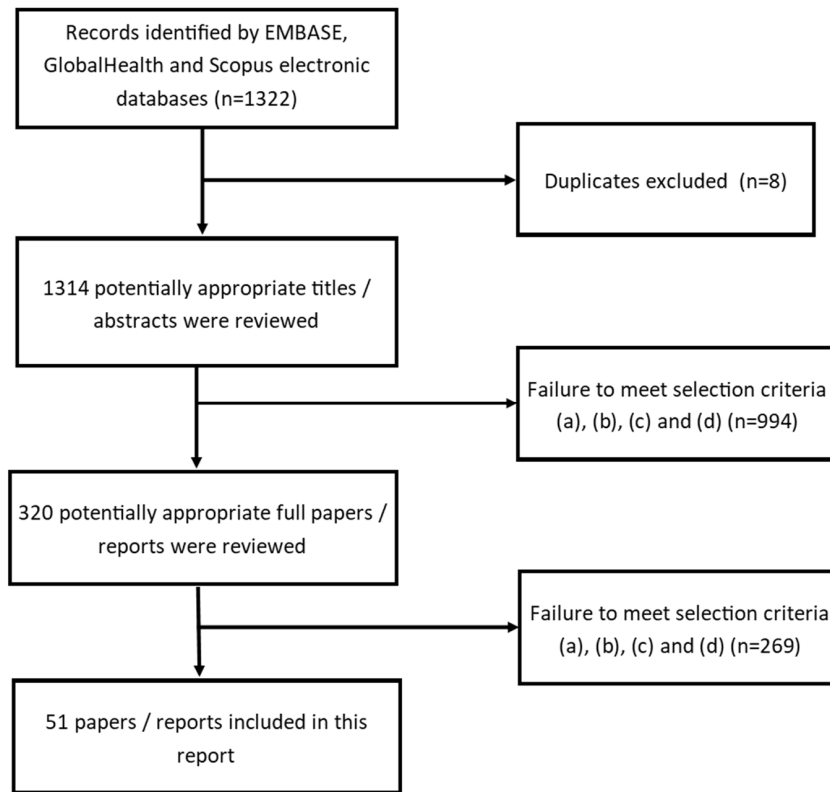


Figure 1. A flow chart illustrating the initial systematic literature search process.

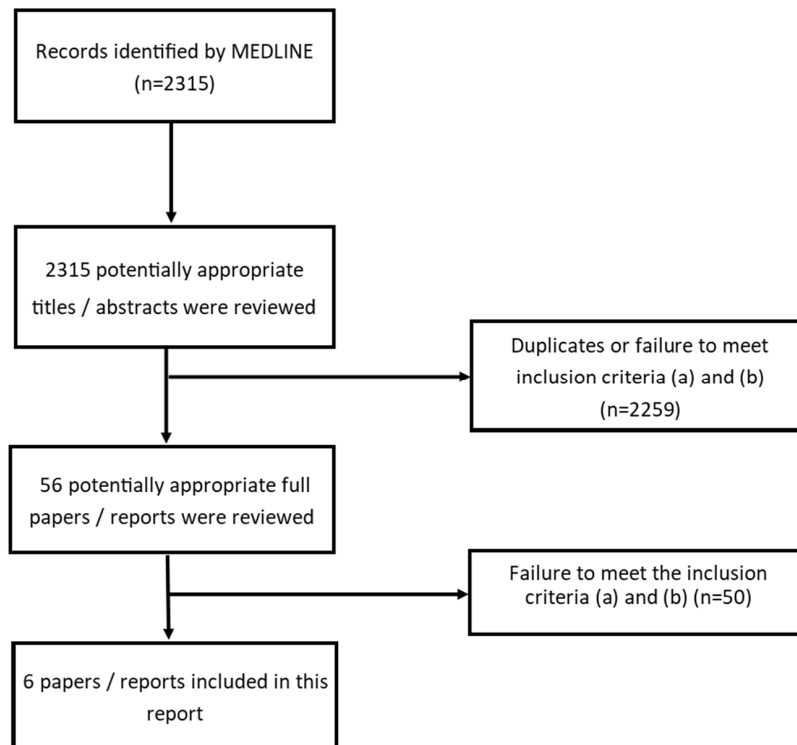


Figure 2. A flow chart illustrating the second literature search process.

3. Results and Discussion

3.1. CO₂ Concentration Guidelines and Recommended Limits

Table 1 shows existing guideline and limit concentrations for CO₂ in indoor environments ranging between 700 and 5000 ppm, as derived mainly from the grey literature. This includes standards for residential, non-residential, workplace and school indoor environments. Their consensus is that CO₂ concentrations ≤ 1000 ppm represent good or excellent indoor air quality (IAQ), 1000–1500 ppm represent acceptable or moderate IAQ and concentrations >1500 ppm represent poor IAQ. However, for the majority of standards, it is unclear how an acceptable CO₂ value is generated, and they are not based on robust epidemiological or toxicological evidence.

Table 1. A summary of current CO₂ concentration guidelines and limits in indoor environments for different countries and organisations. The colour coding corresponds with the consensus that ≤ 1000 ppm \approx good, 1000–1500 ppm \approx moderate and >1500 ppm \approx poor indoor air quality.

CO ₂ Guideline Concentration (ppm)	Country	Standard	Year	Description
750	Finland	Revised Finnish classification of indoor environment, Society of Indoor Air Quality and Climate (FISIAQ [18])	2018	Best quality, highest occupant satisfaction (S1 target value, <350 above outdoor level)
800	International	WELL Building Standard [19]	2016	(non-residential)
	Hong Kong	HKSAR-Indoor Air Quality Management Group [20]	2019	8 h average (excellent class) (non-residential)
950	Finland	Revised Finnish classification of indoor environment, Society of Indoor Air Quality and Climate (FISIAQ [18])	2018	Good indoor air quality (S2 target value, <550 above outdoor level)
950	International	BREEAM (Building Research Establishment Environmental Assessment Method) [21]	2019	High indoor air quality (non-residential)
1000	UK	British Standard (BS EN 16798-1:2019) [10]	2019	Good indoor air quality (residential and non-residential)
	UK	BB101—Department for Education (DfE [9])	2018	Good IAQ (schools)
1000	US	US EPA Facilities Manual Vol 2: Architecture and Engineering Guidelines [22]	2020	8 h average
	China	GB/T 18883-2002, Indoor air quality standard. Standards Press of China [23]	2002	24 h average (0.1% CO ₂ = 1000 ppm)
1000	Hong Kong	HKSAR-Indoor Air Quality Management Group [20]	2005	8 h average (good class)
	Germany	Federal Environment Agency (UBA) [24]	2008	Hygienically safe
1000	Singapore	Singapore Institute of Environmental Epidemiology (SAIQG) [25]	1996	8 h average
	Korea	Korea Occupational Safety and Health Agency (KOSHA), Guideline development for evaluation and management of office air quality (II) [26]	2005	8 h average (office)
1000	Malaysia	Industry COP on IAQ Malaysia (DOSHM) [27]	2010	8 h average

Table 1. Cont.

CO ₂ Guideline Concentration (ppm)	Country	Standard	Year	Description
1030	International	US Green Building Council (USGBC)—Leadership in Energy and Environmental Design (LEED) [28]	2010	
1100	ASHRAE	ANSI/ASHRAE 62.1-2019. Ventilation for acceptable indoor air quality [29]	2019	Acceptable (no greater about 700 ppm above outdoor levels)
1100	Canada	National Collaborating Centres for Public Health (NCCEH) [30]	2019	A surrogate for human comfort (odour) but not considered a health risk
1200	Finland	Revised Finnish classification of indoor environment, Society of Indoor Air Quality and Climate (FISIAQ [18])	2018	Acceptable (S3 target value, <800 above outdoor)
	UK	BB101—Department for Education (DfE [9])	2018	Acceptable (schools)
	UK	British Standard (BS EN 16798-1:2019) [10]	2019	Medium indoor air quality
	International	BREEAM (Building Research Establishment Environmental Assessment Method) [21]	2019	Medium indoor air quality (non-residential)
1250	Portugal	SAÚDE E AMBIENTE E AÇÃO CLIMÁTICA Portaria n.º 138-G/2021 (Diário da República, 1.ª série, 2021) [31]	2021	Protection threshold and tolerance margin (commercial buildings)
1500	UK	BB101—Department for Education (DfE [9])	2018	Acceptable max (schools)
1750	UK	BB101—Department for Education (DfE [9])	2018	Need for additional ventilation (schools)
	UK	British Standard (BS EN 16798-1:2019) [10]	2019	Poor indoor air quality (residential and non-residential)
	International	BREEAM (Building Research Establishment Environmental Assessment Method) [21]	2020	Moderate or low indoor air quality (non-residential)
1000–2000	Germany	Federal Environment Agency (UBA) [24]	2008	Hygienically noticeable
>2000	Germany	Federal Environment Agency (UBA) [24]	2008	Hygienically unacceptable
2800	UK	BB101—Department for Education (DfE [9])	2018	(schools)
5000	UK	HSE EH40/2005 Workplace exposure limits [32]	2018	Permissible exposure limit 8 h time (workplaces)
	Australia	National Occupational Health and Safety Commission (NOHSC) [33]	1995	8 h average working day (workplaces)
	International	Chartered Institute of Building Service Engineers (CIBSE) KS17 [8]	2011	8 h time-weighted average
	US	National Institute for Occupational Safety and Health (NIOSH) [34]	2019	
	Germany	Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK) [35]	2014	8 h average

3.2. CO₂ Concentration and Health

The findings of the studies were divided into five groups based on the key health effects, namely: cognitive performance effects, respiratory effects, neurological symptoms and irritation of the upper airway system (known as SBS—sick building syndrome symptoms), human physiological responses and animal physiological responses. A summary of the health findings of each study, and the concentrations at which these occur can be seen in Appendix B, Table A2 (cognitive performance effects), Table A3 (respiratory effects), Table A4 (neurological symptoms and irritation), Table A5 (human physiological responses) and Table A6 (animal physiological responses). Given the great variability in the reported health effects, and to have confidence in the results of the above studies, we assessed the human studies identified by the literature review against selected criteria; the criteria and the analysis of the study design are discussed in the following Section 3.3.

3.2.1. Cognitive Performance Effects

Ten of the reviewed studies [36–45] associated elevated levels of CO₂ with moderate reductions in cognitive function around and above 1000 ppm, decreased test performance (increased number of errors, reduced test scores and reductions in markers of decision making) at 1400–1500 ppm and reduced performance above 1800 ppm (Appendix B, Table A2). Gaihre et al. [46] and Kolarik et al. [47] associated an increase in the difference between indoor and outdoor CO₂ concentrations (dCO₂) of 100 ppm with a 0.2% decrease in annual attendance and 2% increase in sick leave, respectively. Similarly, Shendell et al. [48] associated a 1000 ppm increase in dCO₂ with a 0.5–0.9% decrease in annual average daily attendance in schools.

On the contrary, five studies, mainly performed in labs where confounding factors were controlled [46,49–52], reported no significant association between CO₂ concentration and cognitive performance, academic attainment or the amount and quality of work produced.

Although Kajtár and Herczeg [50] reported no significant association between CO₂ concentration and the amount and quality of work produced, at higher CO₂ concentrations (4000–5000 ppm), they reported significant increases in blood pressure, respiratory frequencies and volumes. Therefore, they postulated that it is likely that more mental effort was needed at higher CO₂ concentrations. This is consistent with the findings of Maula et al. [53], who found minimal significant impacts of 2200 ppm of CO₂ on cognitive performance, but found a significant increase in the perception of fatigue and workload in participants.

Both Jaber et al. [43] and Satish et al. [44] reported negative cognitive effects at 1000 ppm, with none of the reviewed papers reporting specific cognitive effects at concentrations lower than 1000 ppm. Three studies [54–56] significantly associated CO₂ concentrations with reduced ability to concentrate, whilst two studies [45,57] found no significant association between the two.

At 700–4000 ppm, Vehviläinen et al. [58] associated CO₂ with transcutaneously assessed partial pressure of CO₂ (pCO₂) in blood circulation, elevated CO₂ concentrations in tissues, changes in heart rate variation and an increase in peripheral blood circulation, which they noted could be linked to reductions in cognitive performance. However, Bloch-Salisbury et al. [49] found no association between pCO₂ levels in blood and cognitive performance or alertness.

Two of the most complete studies, in terms of accounting for almost all the confounding factors [59,60] which were performed in labs, concluded that there were no statistically significant effects on perceived air quality, acute health symptoms or cognitive performance during exposures when CO₂ was added. They concluded that the presence of moderate concentrations of bio-effluents (an atmospheric pollutant that emanates from humans or animals) and CO₂ at 3000 ppm will result in harmful effects on occupants during typical indoor exposures, but not pure CO₂.

Finally, on a different note, stressful activity may further increase CO₂ levels compared to a relaxing activity, as the recent work by Gall et al. [61] shows, which looked at the impact of cognitive tasks on human emission rates of CO₂ and isoprene.

3.2.2. Respiratory System Effects

From studies performed in schools, two [62,63] found a significant association between elevated CO₂ concentrations (above 2000 ppm) and wheezing, while four studies [64–67] found no significant association. Two studies [57,68] found no association between CO₂ concentration and difficulty breathing, while Mi et al. [65] significantly associated 500–1900 ppm of CO₂ with daytime breathlessness but not nocturnal breathlessness. Mi et al. [65] found a significant association between CO₂ and asthma, while Kim et al. [63] found no significant association between the two. Two school studies [62,69] found a significant association between CO₂ concentration and coughing (at levels >2100 and >1000, respectively), while Madureira et al. [64] found no significant association between the two, at levels between 1000–3000 ppm. At low concentrations of CO₂ (400–800 ppm) in an office environment, Mendell et al. [70] observed no significant association with respiratory illnesses, respiratory-illness-related absences, building-related symptoms or dissatisfaction with indoor air quality and odours. At levels above 2000 ppm, Shriram et al. [3], in a lab study, associated CO₂ with reductions in forced expiratory volume and forced vital capacity.

3.2.3. Neurological Symptoms and Irritation of the Upper Airway System

Several studies investigated the effects of increased CO₂ concentration on neurological symptoms (headaches, fatigue, stress, dizziness and insomnia), as well as irritation of the upper airway system (e.g., eye irritation: tired or strained eyes, dry, itching eyes; rhinitis; dry cough) (Appendix B, Table A3). Some studies [71–75] reported significant associations between CO₂ and a range of neurological symptoms as well as irritation of the upper airway system generally at CO₂ levels above 1000 ppm, whilst three studies [63,76,77] found no clear associations. Carreiro-Martins et al. [78], focussing on children in daycare centres, found conflicting results between the two phases of the project, regarding the CO₂ association with wheezing. Lu et al. [57] found an increase of 100 ppm in dCO₂ to be significantly associated with both neurological symptoms and irritation, i.e., dry throat, tiredness and dizziness, but not with eye dryness, nose itching, runny nose, stuffy nose, sneezing, skin dryness or irritability. Similarly, Norbäck and Nordström [68] significantly associated increases in CO₂ concentrations with headaches, but not with eye symptoms, sinusitis symptoms, dermal symptoms, tiredness or nausea. Chatzidiakou et al. [72] and MacNaughton et al. [74] associated 1000–2000 ppm of CO₂ and an increase of 1000 ppm in dCO₂ concentrations, respectively, with significant increases in dissatisfaction with perceived air quality and a lack of air movement.

3.2.4. Human Physiological Responses

Several studies also investigated human physiological responses to increased CO₂ concentrations (Appendix B, Table A5). Jung et al. [79] reported that increased CO₂ concentrations indoors were positively associated with allostatic load (the cumulative burden of chronic stress) on the neuroendocrine system, which may be linked to sick building syndrome (SBS). Lu et al. [80] associated 400–1500 ppm of CO₂ with higher levels of 8-OHdG (a biomarker of oxidative stress) in urine, which was then significantly associated with eye dryness, nose itching, sneezing, dry throat, skin dryness and dizziness. Similarly, Tomoda et al. [81] associated 700–1500 ppm of CO₂ with increases in urinary pH and bicarbonate levels. MacNaughton et al. [74] Zhang et al. [59] and Vehviläinen et al. [58] associated CO₂ concentrations with changes to heart rate and or increases in peripheral blood circulation. At CO₂ concentrations of 2000–3000 ppm, Shriram et al. [3] predicted an increase in the pCO₂ in the lungs of 3 mm Hg and a decrease in the partial pressure of oxygen of 7 mm Hg. However, this did not cause a significant reduction in oxygen saturation content in the blood. In Zhang et al. [59], exposure to 3000 ppm and bioeffluents, by restricting ventilation, significantly increased diastolic blood pressure and salivary α -amylase (biomarker of stress) levels compared to 500 ppm. However, no significant effects were observed when exposed to 3000 ppm generated by the addition of

pure CO₂. Zhang et al. [52] did not observe significant changes in the measured physiological responses, which included blood pressure, respiration rate and stress biomarkers. However, the two studies [52,59] found associations with increases in end tidal CO₂, the concentration of CO₂ in exhaled air. Finally, Vehviläinen et al. [58] also associated CO₂ concentrations with transcutaneously assessed pCO₂ (the partial pressure of CO₂) in blood circulation and elevated CO₂ concentrations in tissues, whilst Terleph et al. [82] associated CO₂ concentrations with elevated cortisol levels in children susceptible to CO₂-induced panic attacks.

3.2.5. Animal Physiological Responses

The animal physiological responses are summarised in Appendix B, Table A6. Thom et al. [83] reported inflammatory responses in mice exposed to 2000 or 4000 ppm CO₂ for two hours. The CO₂ exposures stimulated neutrophils to produce microparticles containing high concentrations of the pro-inflammatory cytokine interleukin-1 β . Inflammatory vascular damage was also observed, including vascular leaks in the brain, muscle and distal colon. There were no signs of compromised physical or gastrointestinal function and all changes were resolved 13 h post exposure [83]. Similarly, in an ex vivo study, human and murine neutrophils generated microparticles containing high levels of interleukin-1 β when incubated in a buffer equilibrated with 1000 to 4000 ppm CO₂ [84]. Increased expression of the inflammatory marker ICAM-1 (intercellular adhesion molecule 1) was observed in the bronchial epithelium of mice exposed to 5000 ppm CO₂ for six hours [85].

Rats exposed to 3000 ppm pure CO₂ for 30 days showed significant decreases in food intake, increased total body sodium and reduced adrenal mass, which is consistent with low-grade stress [86].

Young female rats exposed to 700 ppm pure CO₂ six hours per day for 15 days displayed changes in behaviour including increased inactivity and grooming and increased levels of corticosterone, which may be indicative of a stress response. Increased drinking and changes in muscle composition were also observed in the animals exposed to 700 ppm CO₂ [87].

Plasma calcium levels and kidney calcium content were significantly increased in guinea pigs exposed to 5000 ppm CO₂ for eight weeks. All values returned to control levels following an eight-week recovery period [88].

Exposure to 1000 ppm or 3000 ppm CO₂ in utero and during early development resulted in increased anxiety behaviour, elevated corticosterone levels and structural changes in the brains of adolescent rats. Blood and brain levels of insulin-like growth factor 1 (IGF-1), which plays a role in brain development, were reduced in animals exposed to 1000 ppm and 3000 ppm CO₂. Spatial learning and memory were also impaired in animals exposed to 3000 ppm CO₂ [89].

3.3. Analysis of Study Design

To better understand the level of confidence we can have in results linking CO₂ and health, the individual human study designs of investigations were assessed against selected criteria:

Were confounding factors that may have affected health outcomes controlled or accounted for? The confounding factors identified were temperature, humidity, noise, ventilation, human bio-effluents, lighting and indoor air pollutants.

Was the prior health of participants controlled or accounted for?

Were there potential cross-over effects from having multiple experiments over a short period?

Was the cohort large enough (more than five participants)?

Was the duration of CO₂ measurement sufficient to well characterise the range of CO₂ concentrations present?

Can we have confidence in the certainty of the CO₂ measurement equipment?

For each of the criteria, the studies were classed as “satisfactory”, “unclear” or “unsatisfactory”. Good study design is especially important when understanding health outcomes; for example, when there are several confounding factors in an environment, it is very difficult to identify with confidence which may be responsible for health outcomes.

The results of this analysis are shown in Table 2. Most of the experimental conditions are summarised in Du et al. [15], so are not repeated here.

Table 2. A comparison of each investigation against the study design criteria, green/✓ = satisfactory, yellow/~ = unclear and red/✗ = unsatisfactory. For the confounding factors, T = temperature, RH = relative humidity, N = noise, IAP = indoor air pollutants, V = ventilation, HB = human bio-effluents and Li = lighting. For the study type, L = laboratory or controlled setting, S = school or daycare based, O = office based and H = home based.

Source	Study Type	CO ₂ Levels (ppm)	Test Subjects								Prior Health of Participants	Cross-Over Effects	Duration of Measurement	Certainty in Measured CO ₂ Data	Statistically Significant Effects Reported
			T	RH	N	IAP	V	HB	Li						
Cognitive performance studies															
Bloch-Salisbury et al. [49]	L	N/A	~	~	~	✓	✓	✓	~	✓	✓	✓	N/A	N/A	✗
Hong et al. [40]	L	>1000	✓	✓	~	~	✓	~	~	✓	✗	✓	✓	✓	✓
Satish et al. [44]	L	1000, 2500	✓	✓	~	~	✓	✗	~	~	~	✓	N/A	✓	✓
Allen et al. [38]	L	945, 1400	✓	✓	~	~	✓	✗	✓	~	~	N/A	N/A	✓	✓
Maddalena et al. [37]	L	1800	✓	✓	✓	✓	✗	✗	✓	✓	✗	✗	N/A	~	✓
Maula et al. [53]	L	540, 2260	✓	✗	~	✓	✓	✓	~	✓	✓	✓	N/A	✓	✓
Allen et al. [39]	L	1500, 2500	✓	✓	~	~	✓	~	~	~	✗	~	N/A	✓	~
Snow et al. [51]	L	830, 2700	✓	✓	~	~	✓	~	~	~	~	~	N/A	✓	✗
Zhang et al. [52]	L	500, 5000	✓	✓	✓	✓	✓	✓	✓	✓	~	~	✓	✓	✗
Zhang et al. [59]	L	1000, 3000	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
Zhang et al. [60]	L	1500, 3500, 5000	✓	✓	✓	✓	✓	✓	✓	~	~	✓	N/A	✓	✗
Kajtar and Herczeg [50]	L	4000, 5000	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	N/A	✓	~
Lu et al. [57]	O	Increase of 100	✗	✗	✗	✗	✗	✗	✗	~	~	N/A	✓	✓	✓
Vehviläinen et al. [58]	O	700–4000	✗	✗	✗	✗	✓	✗	✗	~	~	N/A	✓	✓	✓
Gaihre et al. [46]	S	1000	✓	✓	✗	✗	✗	✗	✗	~	~	N/A	✓	✓	✓
Petersen et al. [42]	S	1500	✗	✗	✗	✗	✓	✗	✗	✗	✓	✓	✓	✓	✓
Madureira et al. [56]	S	500–1700	✗	✗	✗	✗	✗	✗	✗	✓	~	~	✓	✓	✓
Jaber et al. [43]	S	1000, 1800	✓	✓	✓	✗	✗	✗	✓	✗	~	~	N/A	✓	✓
Twardella et al. [45]	S	2115	✗	✗	✗	✗	✓	✗	✗	~	~	N/A	✓	✓	✓
Ferreira and Cardoso [55]	S	900–2500	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	N/A	✓	✓
Coley et al. [54]	S	2900	✓	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✓
Hutter et al. [41]	S	350–3000	✗	✗	✗	✗	✗	✗	✗	~	~	N/A	✓	~	~
Dorizas et al. [36]	S	N/A	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	N/A	✓	✓
Shendell et al. [48]	S	dCO ₂ 1000 ppm increase	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	N/A	✓	✓
Kolarik et al. [47]	S	Increase of 100 Variable, depending on ventilation	✗	✗	✗	✗	✗	✗	✗	~	~	N/A	✓	✓	✗
Respiratory system effects															
Shriram et al. [3]	L	2000, 3000	✓	✓	✓	~	✓	✗	~	~	~	✓	N/A	✓	✓
Mendell et al. [70]	O	400–800	✗	✗	✗	✗	✗	✗	✗	~	~	N/A	✓	✓	✗
Mohd Nor Rawi et al. [66]	S	579–784	✗	✗	✗	✗	✗	✗	✗	~	~	N/A	~	✓	✗
Simoni et al. [69]	S	>1000	✗	✗	✗	✗	✗	✗	✗	~	~	N/A	✓	✓	✓
Norbäck and Nordström [68]	S	700–1500	✗	✗	✗	✗	✓	✗	✗	~	~	✓	~	✓	✓

Table 2. Cont.

Source	Study Type	CO ₂ Levels (ppm)	Test Subjects										Duration of Measurement	Certainty in Measured CO ₂ Data	Statistically Significant Effects Reported	
			T	RH	N	IAP	V	HB	Li	Prior Health of Participants	Cross-Over Effects					
Mi et al. [65]	S	500–1900	×	×	×	×	×	×	×	×	×	~	N/A	~	✓	✓
Fraga et al. [62]	S	>2100	×	×	×	×	×	×	×	×	×	~	N/A	✓	✓	✓
Ferreira and Cardoso [76]	S	984–2942	×	×	×	×	×	×	×	×	×	~	N/A	✓	✓	~
Kim et al. [63]	S	900–4000	×	×	×	×	×	×	×	×	✓	N/A	✓	✓	✓	
Madureira et al. [64]	S	800–3000	×	×	×	×	×	×	×	×	~	N/A	✓	✓	×	
Sá et al. [67]	S	1700–4000	×	×	×	×	×	×	×	×	~	N/A	~	✓	×	
Neurological symptoms and irritation of the upper airway system																
Norback et al. [90]	H	850, 1020	×	×	×	×	×	×	×	×	✓	N/A	~	✓	✓	
Hill et al. [77]	O	<600	×	×	×	×	×	×	×	×	~	N/A	✓	✓	×	
Tsai et al. [75]	O	>800	✓	✓	×	✓	×	×	×	×	✓	N/A	✓	✓	✓	
Lu et al. [57]	O	467 to 2800 dCO ₂	✓	✓	×	✓	✓	×	×	×	×	N/A	✓	✓	✓	
Erdmann and Apte [71]	O	100 ppm increase	✓	✓	×	✓	✓	×	×	×	✓	N/A	✓	✓	✓	
Muscatiello et al. [91]	S	>1000	×	×	×	×	×	×	×	×	~	N/A	✓	✓	✓	
Carreiro-Martins et al. [78]	S	Median 1440 (1085–1970)	✓	✓	×	×	×	×	×	×	~	N/A	~	✓	~	
Chatzidiakou et al. [72]	S	Average 764–1206 Max: 2061	✓	✓	×	✓	✓	×	×	×	~	N/A	✓	✓	✓	
Jurado et al. [73]	S	1400	×	×	×	×	×	×	×	×	~	N/A	✓	✓	✓	
Kim et al. [63]	S	900–4000	×	×	×	×	×	×	×	×	✓	N/A	✓	✓	×	
Norbäck and Nordström [68]	U	Reduced air flow: 1030 to 1170 Increased air flow: 1200 to 920	✓	✓	×	✓	✓	×	✓	✓	✓	N/A	✓	✓	×	
Human Physiological Responses																
Zhang et al. [52]	L	500, 5000	✓	✓	✓	✓	✓	✓	✓	✓	✓	~	✓	✓	×	
Zhang et al. [59]	L	1000, 3000	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	
Lu et al. [92]	O	~400–1500	×	×	×	×	×	×	×	×	~	N/A	✓	✓	✓	
Vehviläinen et al. [58]	O	700–4000	×	×	×	×	✓	×	×	×	~	N/A	✓	✓	✓	
Jung et al. [79]	O	N/A	×	×	×	×	×	×	×	×	~	N/A	✓	✓	✓	
MacNaughton et al. [74]	O		✓	✓	×	✓	×	×	×	×	×	N/A	✓	✓	✓	
Tomoda et al. [81]	S	700–1500	×	×	×	×	×	×	×	×	×	N/A	N/A	✓	✓	

Firstly, from Table 2, it can be seen that many important confounding factors (temperature, humidity, noise, ventilation, human bio-effluents, lighting and other indoor air pollutants) are often not controlled or accounted for by all studies. They are more properly controlled in lab studies but not in indoor microenvironmental studies. Secondly, cross-over effects are often unaccounted for in many laboratory-based studies, with participants being subject to several exposure conditions over a single day. Thirdly, the prior health of participants is not reported sufficiently in a number of studies. Finally, there is limited concern surrounding the measurement accuracy and duration for CO₂ measurements (if the period is long enough to capture any effects in the lab experiments), with CO₂ being measured accurately with relative ease and low cost.

4. Discussion

4.1. CO₂ and Health

When considering the individual design of each study, and using that to determine our level of certainty in the results, alongside the conflicting results in research, overall, it is not possible to say with confidence what, if any, of the potential health effects associated with low-level (≤5000 ppm) exposure to CO₂ indoors may be.

Although it is difficult to understand with confidence what the health outcomes of exposure to low levels of CO₂ may be, there were physiological changes reported in both human and animal studies.

Human exposures to <5000 ppm CO₂ were associated with allostatic load on the neuroendocrine system [79] and increases in 8-OHdG, pH and bicarbonate in urine [80,81]. Associations were also found with changes in heart rate [58,59,74], increases in peripheral blood circulation, increased transcutaneously assessed pCO₂ in blood and elevated CO₂ concentrations in tissues [58]. Finally, increases in the partial pressure of CO₂ in the lungs [3], increases in salivary α -amylase (a stress biomarker) [59] and elevated cortisol levels in children susceptible to CO₂-induced panic attacks [82] were associated with CO₂ exposures.

There is some evidence of effects in laboratory animals exposed to CO₂ ranging from 700–5000 ppm. Effects reported include inflammation [84,85], stress responses, kidney calcification [89] and impaired spatial learning and memory [89]. In studies with a post-exposure recovery period, in normal CO₂ conditions, all changes resolved [85,89]. Some of the effects reported in these studies are at a cellular level, with no observable impact on the overall health of the animal. Each study varies considerably in study design including the endpoints investigated, animal model used, number of animals, exposure duration and source of CO₂. Animal laboratory test environments can more easily control for confounding factors such as temperature, ventilation, light, noise, humidity and other air pollutants. However, these environments are not typically representative of human indoor environments such as schools and offices. Overall, it is not possible to draw any definitive conclusions on the potential health effects of exposure to CO₂ (\leq 5000 ppm) from the animal data identified.

There is some evidence from epidemiological studies to suggest that exposure to <5000 ppm CO₂ is associated with reduced cognitive performance and sick building syndrome. However, some results are conflicting and when confounding factors are unaccounted for, as is the case for many of the non-laboratory investigations, it is very difficult to understand with confidence which of several factors may have been responsible for the reported health effects. For example, the temperature may have an effect on performance in standardised tests [40,43] and relative humidity can cause respiratory effects which resemble SBS [93]. In cognitive performance studies, the choice of cognitive function test may influence the study outcome as there are several different tests that assess different aspects of brain function. For example, Du et al. [15] found that in studies where pure CO₂ was added to the environment, effects on high-level decision-making performance were only reported when the Strategic Management Simulation (SMS) battery of tests was used. Finally, because CO₂ and other human bio-effluents are linked to a great degree, it is often difficult for researchers to differentiate between the health effects of exposures to each of these components individually.

In laboratory-based studies, it is often easier to control for confounding factors such as temperature, humidity, noise, ventilation, lighting and indoor air pollutants. However, laboratory-based investigations often perform multiple exposures to differing concentrations of CO₂ over a single day. This can potentially cause cross-over effects which makes it difficult to assess which health outcomes can be associated with which individual exposures. Some laboratory-based studies controlled well for a variety of confounding factors but had multiple participants occupying the test environment at the same time. Because humans produce a range of bio-effluents other than CO₂, which can potentially cause physiological effects [59], these will act as an additional confounding factor that needs to be controlled for.

4.2. Improving Study Design

There were two main types of studies identified by this critical review. Firstly, school or office-based studies where CO₂ is measured and health questionnaires are collected from participants occupying the environments, to determine whether there is a relationship between CO₂ and health. Secondly, laboratory or chamber-based studies where participants are exposed to varying concentrations of CO₂ in a controlled setting with health outcomes being measured.

In school or office-based studies, it is important to account for confounding factors. Ideally, if time and resources are unlimited, temperature, humidity, noise, ventilation, human bio-effluents, lighting and other indoor air pollutants could be controlled so that the only variable is CO₂ concentration. Where heating, ventilation, and air conditioning (HVAC) systems are available, temperature, humidity and ventilation rates should remain stable. HVAC systems also often contain MERV- or HEPA-type filters, which can also help to reduce particulate matter. When confounding factors are not easily controlled, measurement is an alternative option. If the temperature of a study environment cannot be controlled, measurements can help to understand the temperature variation, and therefore whether it is likely to be an important factor affecting health. For example, in some studies where the temperature could not be controlled, they measured and reported variations in temperature, and informed decisions can be made as to whether this is a factor likely to be affecting health or not. Allen et al. [38]] provide an example of where several confounding factors are carefully reported, making it easier to assess the epidemiological value of the investigation.

School- or office-based studies will often collect measurements in multiple schools or offices. When this is the case, it is necessary to consider the duration of the measurements. In some studies, only 30 min to two hours of CO₂ measurements were collected in each environment, and this may not be sufficient to represent the wide range of CO₂ concentrations experienced in that environment. The more measurements that can be collected within an environment, the better the understanding of the full range of CO₂ concentrations is and the better this can be linked to health outcomes.

For laboratory-based studies, it is essential to avoid cross-over effects by not having participants subjected to multiple different exposure conditions over a day. Additionally, having multiple participants in a single test environment should be carefully considered, as other human bio-effluents may act as confounding factors.

The studies identified by this review are short-duration studies, ranging from 1 day to a month. A longer-term study measuring potential health effects and CO₂ concentrations in a typical indoor working environment, such as a school or office, would give a better understanding of potential long-term health impacts. The home environment also needs to be considered, as it is the main working/living environment within the current pandemic situation.

4.3. CO₂ Guideline Concentrations

To summarise the existing CO₂ concentration guidelines, CO₂ levels ≤1000 ppm represent good or excellent indoor air quality, 1000–1500 ppm represent acceptable or moderate IAQ and concentrations >1500 ppm represent poor IAQ. These levels appear consistent with the existing literature, which reports effects starting at as low as 1000 ppm CO₂ [38,43,44,46]. Two human studies investigating lower concentrations (~400–800 ppm) [66,70] found no significant correlation with health outcomes. Only one of the 51 papers reviewed reported significant effects at <1000 ppm [75]. Recent scientific evidence indicates a support of the initial studies [5,6] in the 1960s, which were used to inform the guidance. However, we cannot be confident that the health effects informing the guidelines are due solely to exposure to CO₂, due to the limited toxicological/physiological evidence and shortcomings in study design.

5. Conclusions

Within the current project, we carried out a systematic literature search to identify primary research considering the relationship between CO₂ and health effects. We investigated the grey literature to identify CO₂ guideline and limit concentrations and assessed whether they corresponded well with the existing research. This investigation evaluated the reported health effects of exposure to less than 5000 ppm of CO₂ and the potential physiological links between CO₂ and health effects.

While assessing the study designs of investigations, it was found that many did not account and control for confounding factors such as temperature, humidity, noise, ventilation, human bio-effluents, lighting and other indoor air pollutants. Especially in the case of the home environment used as an office, the ventilation behaviour of the occupants should be considered. There is little concern surrounding the accuracy of CO₂ monitoring, with CO₂ being measured with relative ease and at low cost.

Although several investigations associated low CO₂ concentrations (≤ 5000 ppm) with effects on health, others did not, and given the shortcomings of study design, it is difficult at present to accurately link CO₂ exposure below 5000 ppm with any health effects. Given that CO₂ is commonly linked with other human bio-effluents, which may have effects on health [74], it is difficult to say whether CO₂ itself is directly responsible for the health effects observed.

In the future, in school- or office-based studies, confounding factors should ideally be controlled, with CO₂ being the only variable. If this is not feasible, investigations should aim to measure and report the variation in confounding factors to allow health scientists to understand whether these are likely to impact the measured health outcomes or not. While measuring in a variety of indoor environments, the exposure period is crucial; it is essential to measure for a long enough duration to fully represent the variability in CO₂ concentrations that may be present.

In laboratory-based studies, it is essential to ensure that participants are not exposed to varying concentrations in a single day, as this can lead to cross-over effects, making the interpretation of results complex. Finally, it should be carefully considered as to whether other human bio-effluents will act as confounding factors when multiple participants are occupying the test environment at once.

Although it is not possible to say with confidence whether CO₂ alone is responsible for health effects at low exposures (≤ 5000 ppm) and whether it is itself a pollutant, the existing guideline CO₂ concentrations can be indicative of ventilation, human bio-effluent and indoor air pollution concentrations, and therefore, the current consensus that ≤ 1000 ppm, 1000–1500 ppm and >1500 ppm represent good, moderate and poor indoor air quality, respectively, seems appropriate.

Author Contributions: Conceptualization, S.D.; Methodology, S.D., S.D.L.; Formal Analysis, S.D.L., K.F., C.S.; Investigation, S.D.L., K.F., C.S.; Data Curation, S.D.L., E.C., K.F., C.S.; Writing—Original Draft Preparation, S.D.L., K.F.; Writing—Review and Editing, S.D., B.G., O.S.; Supervision, S.D.; Project Administration, S.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Table A1. Search strings used for the literature review.

#	Database	Search Term
1	EMBASE	(((CO ₂ OR "carbon dioxide").ti,ab OR "CARBON DIOXIDE"/) AND ((effect * OR symptom * OR health OR impact).ti,ab OR (headache * OR migrain *).ti,ab OR (sleep * OR drows * OR tired * OR fatigue * OR exhaust *).ti,ab OR (respirat * OR asthma * OR breath *).ti,ab OR (lung OADJ1 (function * OR behavio?r)).ti,ab OR (attendance OR absence *).ti,ab OR (neurodevelopmental OR neurolog * OR cognit * OR neurobehavioral OR neurophysiological).ti,ab OR (performance OR "decision making" OR concentrat * OR confusion).ti,ab OR (dizz * OR disorient *).ti,ab OR (hypercapnia).ti,ab OR (cardiovascular OR heartbeat OR arrhythmia OR "heart rate").ti,ab OR (depress * OR paranoi * OR anxiety OR anxious OR "panic attack *").ti,ab OR (physiolog * ADJ1 (response OR change *)).ti,ab OR (blood OADJ1 (pressure OR circulation)).ti,ab OR (muscle * ADJ1 twitch *).ti,ab OR (skin ADJ3 flush *).ti,ab OR (development * OR "nervous system" OR inflam * OR consciousness OR seizure).ti,ab)) AND (indoor OR building * OR workplace * OR (work ADJ1 environment *) OR office * OR occupation * OR profession * OR home * OR house * OR accommodation OR residen * OR dwell * OR tenant * OR nurser * OR ("day care" ADJ1 (centre * OR center *)) OR school * OR schoolchild * OR classroom * OR student * OR pupil * OR college * OR universit *).ti
2	Scopus	(TITLE-ABS-KEY (CO ₂ OR "carbon dioxide")) AND (((ABS (effect * OR symptom * OR health OR impact)) OR (ABS (headache * OR migrain *)) OR (ABS (sleep * OR drows * OR tired * OR fatigue * OR exhaust *)) OR (ABS (respirat * OR asthma * OR breath *)) OR (ABS (respirat * OR asthma * OR breath *)) OR (ABS (lung W/1 (function * OR behavio?r))) OR (ABS (attendance OR absence *)) OR (ABS (neurodevelopmental OR neurolog * OR cognit * OR neurobehavioral OR neurophysiological)) OR (ABS (performance OR "decision making" OR concentrat * OR confusion)) OR (ABS (dizz * OR disorient *))) OR ((ABS (hypercapnia)) OR (ABS (cardiovascular OR heartbeat OR arrhythmia OR "heart rate"))) OR (ABS (depress * OR paranoi * OR anxiety OR anxious OR "panic attack *")) OR (ABS (physiolog * W/1 (response OR change *))) OR (ABS (blood W/1 (pressure OR circulation))) OR (ABS (muscle * W/1 twitch *)) OR (ABS (skin W/3 flush *)) OR (ABS (development * OR "nervous system" OR inflam * OR consciousness OR seizure))) AND ((TITLE (indoor OR building * OR workplace *) OR (TITLE (office * OR occupation * OR profession * OR home * OR house * OR accommodation OR residen * OR dwell * OR tenant * OR nurser *) OR (TITLE (school * OR schoolchild * OR classroom * OR student * OR pupil * OR college * OR universit *) OR (TITLE (work W/1 environment *) OR (TITLE ("day care" W/1 (centre * OR center *))))))
3	Global Health	TI (CO ₂ OR "carbon dioxide") OR SU (CO ₂ OR "carbon dioxide")
4	Global Health	AB (effect * OR symptom * OR health OR impact) OR AB (headache * OR migrain *) OR AB (sleep * OR drows * OR tired * OR fatigue * OR exhaust *) OR AB (respirat * OR asthma * OR breath *) OR AB (lung w1 (function * OR behavio?r)) OR AB (attendance OR absence *) OR AB (neurodevelopmental OR neurolog * OR cognit * OR neurobehavioral OR neurophysiological) OR AB (performance OR "decision making" OR concentrat * OR confusion) OR AB (dizz * OR disorient *) OR AB hypercapnia OR AB (cardiovascular OR heartbeat OR arrhythmia OR "heart rate") OR AB (depress * OR paranoi * OR anxiety OR anxious OR "panic attack *")
5	Global Health	AB (physiolog * n1 (response OR change *)) OR AB (blood w1 (pressure OR circulation)) OR AB muscle * n1 twitch * OR AB skin n3 flush * OR AB (development * OR "nervous system" OR inflam * OR consciousness OR seizure)
6	Global Health	TI (indoor OR building * OR workplace *) OR TI work n1 environment * OR TI (office * OR occupation * OR profession * OR home * OR house * OR accommodation OR residen * OR dwell * OR tenant * OR nurser *) OR TI ("day care" n1 (centre * OR center *)) OR TI (school * OR schoolchild * OR classroom * OR student * OR pupil * OR college * OR universit *)
7	Global Health	4 or 5
8	Global Health	3 and 6 and 7

Table A1. Cont.

#	Database	Search Term
9	Medline	((toxic *).ti,ab OR ((adverse OR health) ADJ2 effect *).ti,ab OR (“immune response”).ti,ab OR (“serum bicarbonate”).ti,ab OR (“end tidal CO ₂ ” OR “end-tidal CO ₂ ”).ti,ab OR (Acidosis).ti,ab OR (“acid-base” OR “acid base”) ADJ1 (disturbance OR alteration)).ti,ab OR (“elevated plasma calcium”).ti,ab OR (inflammation).ti,ab OR (“vascular damage”).ti,ab OR (adaptive ADJ1 (change OR compensation)).ti,ab OR (bone ADJ1 (demineralization OR deposition)).ti,ab OR (“kidney calcification”).ti,ab OR (“Oxidative stress”).ti,ab OR (“Reactive oxygen species”).ti,ab OR (“Endothelial dysfunction”).ti,ab OR ((vulnerable OR sensitive) AND population).ti,ab OR (“CO ₂ hypersensitivity”).ti,ab OR (“brain development”).ti,ab OR (“impaired learning” OR memory).ti,ab OR (elevat * ADJ2 (corticosterone OR corticosteroid)).ti,ab OR (“growth reduction”).ti,ab OR (“apoptotic activity” AND brain).ti,ab OR (hypercapnia).ti,ab) AND (*“CARBON DIOXIDE”/OR (“Carbon dioxide” OR CO ₂ OR CO ₂).ti)) [DT 2000-2020] [Languages English]

Appendix B

Table A2. A summary of primary research associating CO₂ with cognitive performance effects.

Source	CO ₂ Concentration (ppm)	Health Effects/Comments
Bloch-Salisbury, 2000	N/A	Lab: High partial pressure of CO ₂ in arterial blood has no significant effects on cognitive function or alertness. Low partial pressure of CO ₂ in arterial blood has no significant effects on cognitive function or alertness.
Hong et al., 2018	>1000	Lab: Statistically significant decreases in task performances observed.
Satish et al., 2012	1000	Lab: Moderate and statistically significant reductions were seen for 6 out of 9 markers of decision-making performance relative to 600 ppm.
	2500	Lab: Large and statistically significant reductions were seen for 7 out of 9 of the markers. Two markers, “Focused Activity” and “Information search” did not seem to be significantly affected by changes in CO ₂ concentration.
Allen et al., 2016	945	Lab: For seven out of nine cognitive function domains, average scores decreased as CO ₂ concentrations increased. Aggregate cognitive scores dropped by 15%.
	1400	For seven out of nine cognitive function domains, average scores decreased as CO ₂ concentrations increased. Aggregate cognitive scores dropped by 50%.
Maddalena et al., 2015	1800	Lab: Reduced performances in decision-making tests relative to 900 ppm.
Maula et al., 2017	540	Lab: Office workers: High ventilation rate (28.1 l/s/p). No health symptoms were found to office workers.
	2260	Low ventilation rate (2.31 l/s/p). Exposure of office workers had a weak negative effect on performance only in the information retrieval tasks and slightly increased subjective workload and perceived fatigue. No effects on health symptoms were found.
Allen et al., 2019	1500	Lab: Pilot’s odds of passing a manoeuvre was 1.52 times larger when exposed to 1500 ppm rather than 2500 ppm.
	2500	Pilot’s odds of passing a manoeuvre was 1.69 times larger when exposed to 700 ppm rather than 2500 ppm.
Snow et al., 2019	830, 2700	Lab: 31 volunteers; experiment of <60 min; reported no significant association between CO ₂ concentrations, cognitive performance, academic attainment and quality of work produced. The addition of CO ₂ may have influenced aspects of cognitive performance only after certain periods. There was absence of clear physiological drivers.
Zhang et al., 2016	500, 5000	Lab: 2.5 h exposure to artificially raised CO ₂ up to 5000 ppm compared to 500 ppm did not cause any significant change in perceived air quality, acute health symptoms or the performance of tasks (typical office work).

Table A2. Cont.

Source	CO ₂ Concentration (ppm)	Health Effects/Comments
Zhang et al., 2017	1000, 3000	Lab: 25 subjects were exposed for 255 min to each condition. Subjective ratings, physiological responses and cognitive performance were measured. No statistically significant effects on perceived air quality, acute health symptoms or cognitive performance were seen during exposures when CO ₂ was added. Exposures to bio-effluents with CO ₂ at 3000 ppm reduced perceived air quality; increased the intensity of reported headache, fatigue, sleepiness, and difficulty in thinking clearly; and reduced speed of addition, the response time in a redirection task, and the number of correct links made in the cue-utilization test. This suggests that moderate concentrations of bio-effluents, but not pure CO ₂ , will result in deleterious effects on occupants during typical indoor exposures.
Zhang et al., 2020	1500, 3500, 5000	Lab: For the subjective mental workload, there were no significant differences at different CO ₂ conditions. The MATB (Multi-attribute Task Battery) task performance declined significantly when the CO ₂ concentration increased from 1500 ppm to 3500 ppm, but there was no significant difference between 3500 ppm and 5000 ppm, or 1500 ppm and 5000 ppm.
Kajtar and Herczeg, 2012	4000	Lab: Participants struggled with maintaining concentration over the 2–3 h period, reporting high scores on the tiredness scales and showing decreased mental performance.
	5000	Subjects perceived the environment as more unpleasant and exhausting. At 5000 ppm, a small but significant increase in diastolic blood pressure was observed. At 5000 ppm, the majority of subjects experienced greater respiratory frequency and volumes. This indicates that although the work output and quality was not significantly affected by CO ₂ concentration, more mental effort was required at higher CO ₂ concentrations.
Lu et al., 2015	Increase of 100	Office workers: Not significantly associated with difficulties in concentrating
Vehviläinen et al., 2016	700–4000	Office workers: Associated with an elevated CO ₂ level in transcutaneously assessed pCO ₂ in blood circulation, elevated CO ₂ concentrations in tissues, changes in heart rate variation and an increase in peripheral blood circulation. This may be associated with reductions in functional ability.
	600–5000	Amount and quality of work produced by subjects was not significantly impacted by the degree of CO ₂ concentration.
Gaihre et al., 2014	1000	School children: time-weighted CO ₂ average was significantly associated with decreased attendance but was not associated with academic attainments.
	Increase of 100	Significantly associated with a reduced annual attendance of 0.2%.
Petersen et al., 2016	1500	School children: Associated with decreased numbers of correct answers and increased numbers of errors in four performance tests compared to 900 ppm.
Madureira et al., 2009	500–1700	School children: Associated with concentration difficulties.
Riham Jaber et al., 2017	1000	School children: Statistically significant decrease in accuracy in performance in all tasks relative to 600 ppm (5.3% errors).
	1800	Statistically significant decrease in accuracy in performance in all tasks relative to 600 ppm (12.16% errors).
Twardella et al., 2012	2115	School children: No significant effect on participants concentration performance or amount of work completed compared to 1045 ppm. However, a significant increase in the total number of errors was observed 1.65 (95% CI 0.42–2.87).
Ferreira and Cardoso, 2014	~900–2500	School children: Lack of concentration significantly correlated with CO ₂ concentrations.
Coley et al., 2007	2900	School children: Statistically significant decrease in power of attention of approximately 5% relative to 690 ppm.

Table A2. Cont.

Source	CO ₂ Concentration (ppm)	Health Effects/Comments
Hutter et al., 2013	350–3000	School children: Significantly decreased cognitive performance observed.
Dorizas et al., 2015	N/A	School children: 17% increase in indoor CO ₂ associated with a statistically significant reduction in test performance of 16%.
Shendell et al., 2004	Increase of 1000 dCO ₂	School children: 1000 ppm increase above the outdoor concentration was associated with a 0.5–0.9% decrease in annual average daily attendance (ADA) of students, corresponding to a relative 10–20% increase in student absence. Annual ADA was 2% higher in traditional than in portable classrooms.
Kolarik et al., 2016	Increase of 100 dCO ₂	School children: Associated with a 2% increase in sick leave (not statistically significant).

Table A3. A summary of primary research associating CO₂ with respiratory system effects.

Source	CO ₂ Concentration (ppm)	Health Effect
Shriram et al., 2019	2000	Lab: Statistically significant reduction in forced expiratory volume and forced vital capacity relative to 1000 ppm.
	3000	Statistically significant reduction in forced expiratory volume and forced vital capacity relative to 1000 ppm. A predicted increase in the partial pressure of CO ₂ in the lungs of 3 mm Hg and a decrease in the partial pressure of O ₂ of 7 mm Hg. This did not cause a significant reduction in oxygen saturation content in the blood.
Mendell et al., 2015	400–800	Office workers: Not significantly associated with respiratory illnesses and respiratory-illness-related absences, building-related symptoms and dissatisfaction with indoor air quality and odours. However, this may be due to relatively high ventilation rates and low CO ₂ concentrations.
Mohd et al., 2015	579–784	School children: Not significantly associated with decreased lung function or wheezing.
Simoni et al., 2010	>1000 Increase of 100	School children: Significantly associated with dry cough (OR 2.99, 95% CI 1.65–5.44) and rhinitis (OR 2.07, 95% CI 1.14–3.73). Significantly associated with dry cough (OR 1.06, 95% CI 1.00–1.13) and rhinitis (OR 1.06, 95% CI 1.00–1.11).
Mi et al., 2006	500–1900	Schools: Significantly associated with asthma and need for asthma medication as well as daytime breathlessness. Not significantly associated with wheezing or nocturnal breathlessness.
Fraga et al., 2008	>2100	School children: Statistically significant association with exercise-induced wheeze (OR = 1.86 (95%CI:1.20–2.89)) and night cough (OR = 1.40 (4.20–2.89))
Ferreira and Cardoso, 2014 a	984–2942	School children: Decreased spirometry values.
Kim et al., 2011	900–4000	School children: Significantly associated with wheeze (OR = 1.03 (1.001–1.06)), but not with doctor diagnosed asthma (OR = 1.01 (0.97–1.04)).
Madureira et al., 2015	800–3000	School children: No clear relationship between CO ₂ concentration and wheezing, nasal allergy, cough episodes or phlegm episodes.
Sa et al., 2019	1700–4000	School children: No significant association with wheezing.

Table A4. A summary of primary research associating CO₂ with neurological symptoms and irritation of the upper airway system.

Source	CO ₂ Concentration (ppm)	Health Effect
Norback et al., 1995	850 and 1020	Home: Significantly associated with nocturnal chest tightness.
Hill et al., 1992	<600	Office workers: CO ₂ concentrations had no significant effect on a variety of health outcomes.
Tsai et al., 2015	>800	Office: Compared with workers exposed to CO ₂ concentrations of less than 500 ppm, office workers exposed to CO ₂ concentrations of >800 ppm were more likely to report SBS symptoms: "eye irritation" and "upper respiratory symptoms", and more specifically, "tired or strained eyes", "dry, itching, or irritated eyes" and "difficulty in remembering things or in concentrating". Headache was marginally increased at CO ₂ levels >800 ppm. Female workers were more likely to report SBS than male workers, and more specifically "eye irritation", "nonspecific symptoms", "higher respiratory symptoms" and "skin irritation". Workers with a history of allergies tended to report more "eye irritation," "nonspecific symptoms" and "lower respiratory symptoms".
Lu et al., 2015	467 to 2800	Office workers: After controlling for personal and environmental variables, per 100 ppm increase in dCO ₂ had significant associations with dry throat, tiredness, dizziness and non-specific syndrome, but had a protective association with eye irritation.
Erdmann and Apte, 2004	dCO ₂ (difference between I/O CO ₂) increased per 100 ppm	Office workers: Covariate-adjusted odds ratios per 100 ppm increases in dCO ₂ were statistically significant for dry eyes, sore throat, nose/sinus, sneeze and wheeze symptoms and ranged from 1.1 to 1.2.
Muscatiello et al., 2015	>1000	School teachers: Non-significantly associated with increased reporting of neuro-physiological (i.e., headache, fatigue, difficulty concentrating) symptoms.
Carreiro-Martins et al., 2014	Median 1440 (1085–1970)	Children in daycare centres. Phase I: exposure of 3186 children (mean age 3.1 ± 1.5 years) to indoor CO ₂ concentration was associated with reported wheezing in the past 12 months (27.5%) (adjusted odds ratio (OR) for each increase of 200 ppm. Phase I: the association in the subsample of 1196 children seen in 19 out of the initial 45 DCCs was not significant.
Chatzidiakou et al., 2014	Average: 764–1206 Max: 2061	Schoolchildren: Significantly related to neurological symptoms (headaches, fatigue, malaise) and dissatisfaction with perceived IAQ. Subjective air quality perception was significantly related to indoor environmental conditions such as temperature and CO ₂ levels, higher concentrations of airborne dust (PM10), exposure to microbial parameters, such as <i>Penicillium</i> spp./ <i>Aspergillus</i> spp., cat allergen (Der f 1), and <i>Streptomyces</i> spp. and exposure to high VOC levels, such as formaldehyde and limonene. Prevalence of dermal and mucosal symptoms, often associated with SBS symptoms, were slightly higher in an urban school, while eczema prevalence was slightly higher in a suburban school.
Jurado et al., 2014	~1400	Schools: Statistically significant associations with eye irritation, nasal irritation, throat irritation, headaches, difficulties in concentration and fatigue.
Norback and Nordstrom, 2008	Variable, depending on ventilation Reduced air flow: 1030 to 1170 Increased air flow: 1200 to 920	University room temperatures and CO ₂ levels were positively associated with different types of SBS symptoms. After mutual adjustment, independent effects of room temperature could be demonstrated, while the associations between CO ₂ levels and symptoms were reduced and mostly no longer statistically significant. Headache and tiredness were most prevalent; mucous membrane symptoms were less prevalent.
Kim et al., 2011	900–4000	Not significantly associated with headaches (OR 1.00, 95% CI 0.97–1.02) or tiredness (OR 1.01, 95% CI 1.00–1.03)

Table A5. A summary of primary research associating CO₂ with human physiological responses.

Source	CO ₂ Concentration (ppm)	Health Effect
Shriram et al., 2019	2000 3000	Lab: Statistically significant reduction in forced expiratory volume and forced vital capacity relative to 1000 ppm. Statistically significant reduction in forced expiratory volume and forced vital capacity relative to 1000 ppm. A predicted increase in the partial pressure of CO ₂ in the lungs of 3 mm Hg and a decrease in the partial pressure of O ₂ of 7 mm Hg. This did not cause a significant reduction in oxygen saturation content in the blood.
Zhang, Wargocki and Lian [74]	500, 3000	Lab: Exposure to 3000 ppm and bio-effluents, by restricting ventilation, significantly increased diastolic blood pressure and salivary α-amylase (biomarker of stress) levels compared to 500 ppm. They only found associations with ET _{CO2} .
Zhang et al. (2016)	500, 5000	Lab: Compared to CO ₂ at 500 ppm, 2.5 h exposures to artificially raised CO ₂ up to 5000 ppm increased ET _{CO2} slightly more. No other significant changes were seen in the measured physiological responses that included blood pressure, respiration rate and stress biomarkers.
Lu et al., 2007	~400–1500	Office: Associated with higher levels of 8-OHdG in urine. Higher levels of 8-OHdG in urine were significantly associated with eye dryness, nose itching, sneezing, dry throat, skin dryness and dizziness.
Vehviläinen et al., 2016	700–4000	Office workers: Associated with an elevated CO ₂ level in transcutaneously assessed pCO ₂ in blood circulation, elevated CO ₂ concentrations in tissues, changes in heart rate variation and an increase in peripheral blood circulation, through changes in ventilation rate.
Jung et al., 2014	N/A	Office: CO ₂ concentrations, the difference in concentration between indoor and outdoor and the ratio of indoor and outdoor CO ₂ concentrations had a statistically significant association with allostatic load on the neuroendocrine system, with allostatic load on the neuroendocrine system being hypothesised to be related to increased incidence of sick building syndrome. This may provide a mechanism by which CO ₂ is related to sick building syndrome.
MacNaughton et al., 2016	Increase of 1000	Office workers: Participants who perceived a lack of air movement would report on average 67% more symptoms each day. The 1000 ppm increase was associated with a 43% increase in reported symptoms per person per day and a 2.3bpm statistically significant increase in heart rate, after accounting for potential confounding factors.
Tomoda et al., 1995	700–1500	School: Associated with increases in urinary pH and bicarbonate levels

Table A6. A summary of primary research associating CO₂ with animal physiological responses.

Animal Physiological Responses			
Source	CO ₂ Concentration (ppm)	Animal	Health Effect
Martrette et al., 2017	700	Young female rats	Lethargy, increased grooming and drinking, changes in muscle composition and increased plasma corticosterone levels.
Kiray et al., 2014	1000 and 3000	Postnatal rats	At 1000 and 3000 ppm increased anxiety behaviour, structural changes in the brain, elevated corticosterone levels and reduced insulin-like growth factor 1 levels in the blood and brain. At 3000 ppm spatial learning and memory impaired
Schaefer et al., 1979	5000	Guinea pigs	Increase in plasma calcium and kidney calcium content. All values returned to control levels following an 8-week recovery period

Table A6. Cont.

Animal Physiological Responses			
Source	CO ₂ Concentration (ppm)	Animal	Health Effect
Schneberger et al., 2017	5000	Mice	Increased expression of inflammatory marker ICAM-1 (intercellular adhesion molecule 1). Co-exposure to CO ₂ and hog barn dust resulted in a dose-dependent increase in expression of other pro-inflammatory markers
Thom et al., 2017	1000, 2000 and 4000	Ex vivo—human and murine neutrophils	At 1000–4000 ppm, increased human and murine neutrophil production of microparticles that contain high levels of Interleukin-1 β
Thom et al., 2017	1000, 2000 and 4000	Mice	At 2000–4000 ppm, increased neutrophil production of microparticles that contain high levels of Interleukin-1 β . Signs of inflammatory vascular damage in various tissues which resolved 13 h post exposure
Wade et al., 2000	3000	Rat	At 3000 ppm, decreases in food intake, increased total body sodium and reduced adrenal mass

References

- Lu, T.; Knuutila, A.; Viljanen, M.; Lu, X. A novel methodology for estimating space air change rates and occupant CO₂ generation rates from measurements in mechanically-ventilated buildings. *Build. Environ.* **2010**, *45*, 1161–1172. [CrossRef]
- Persily, A.; Emmerich, S. Indoor Air Quality in Sustainable, Energy Efficient Buildings. *HVAC&R Res.* **2011**, *18*. [CrossRef]
- Shriram, S.; Ramamurthy, K.; Ramakrishnan, S. Effect of occupant-induced indoor CO₂ concentration and bioeffluents on human physiology using a spirometric test. *Build. Environ.* **2019**, *149*, 58–67. [CrossRef]
- Seppänen, O.A.; Fisk, W.J. Summary of human responses to ventilation. *Indoor Air* **2004**, *14* (Suppl. 7), 102–118. [CrossRef] [PubMed]
- Goromosov, M.S. *The Physiological Basis of Health Standards for Dwellings*; World Health Organization: Geneva, Switzerland, 1968.
- Eliseeva, O.V. On the determination of maximum permissible carbon dioxide concentrations in the air of apartment buildings and public buildings. *Gig. Sanit.* **1964**, *29*, 10–15. [PubMed]
- NOAA. Climate Change: Atmospheric Carbon Dioxide. Available online: <https://www.climate.gov/news-features/understanding-climate/climate-change-atmospheric-carbon-dioxide> (accessed on 1 December 2020).
- CIBSE. *KS17 Indoor Air Quality and Ventilation*; Chartered Institution of Building Services Engineers, October 2011; ISBN 9781906846190. Available online: <https://www.cibse.org/knowledge/knowledge-items/detail?id=a0q2000008I7gSAAS> (accessed on 1 November 2021).
- BB101—Department for Education (DfE). Guidelines on Ventilation, Thermal Comfort and Indoor Air Quality in Schools, UK. 2018. Available online: <https://www.gov.uk/government/publications/building-bulletin-101-ventilation-for-school-buildings> (accessed on 1 September 2021).
- British Standard. *BS EN 16798-1:2019—Energy Performance of Buildings—Ventilation for Buildings—Part 1: Indoor Environmental Input Parameters for Design and Assessment of Energy Performance of Buildings Addressing Indoor Air Quality, Thermal Environment, Lighting and Acoustics—Module M1-6*; BSI: London, UK, 2019; ISBN 978 0 580 85868 0. Available online: <https://shop.bsigroup.com/products/energy-performance-of-buildings-ventilation-for-buildings-indoor-environmental-input-parameters-for-design-and-assessment-of-energy-performance-of-buildings-addressing-indoor-air-quality-thermal-environment-lighting-and-acoustics-module> (accessed on 1 November 2021).
- Langford, N.J. Carbon dioxide poisoning. *Toxicol. Rev.* **2005**, *24*, 229–235. [CrossRef]
- PHE. Carbon Dioxide: Health Effects and Incident Management. Available online: <https://www.gov.uk/government/publications/carbon-dioxide-properties-and-incident-management> (accessed on 2 September 2021).
- Klepeis, N.E.; Nelson, W.C.; Ott, W.R.; Robinson, J.P.; Tsang, A.M.; Switzer, P.; Behar, J.V.; Hern, S.C.; Engelmann, W.H. The National Human Activity Pattern Survey (NHAPS): A resource for assessing exposure to environmental pollutants. *J. Expo. Anal. Environ. Epidemiol.* **2001**, *11*, 231–252. [CrossRef]
- Azuma, K.; Kagi, N.; Yanagi, U.; Osawa, H. Effects of low-level inhalation exposure to carbon dioxide in indoor environments: A short review on human health and psychomotor performance. *Environ. Int.* **2018**, *121*, 51–56. [CrossRef]
- Du, B.; Tandoc, M.C.; Mack, M.L.; Siegel, J.A. Indoor CO₂ concentrations and cognitive function: A critical review. *Indoor Air* **2020**, *30*, 1067–1082. [CrossRef]
- Jacobson, T.A.; Kler, J.S.; Hernke, M.T.; Braun, R.K.; Meyer, K.C.; Funk, W.E. Direct human health risks of increased atmospheric carbon dioxide. *Nat. Sustain.* **2019**, *2*, 691–701. [CrossRef]

17. Seppänen, O.A.; Fisk, W.J.; Mendell, M.J. Association of ventilation rates and CO₂ concentrations with health and other responses in commercial and institutional buildings. *Indoor Air* **1999**, *9*, 226–252. [CrossRef] [PubMed]
18. Ahola, M.; Säteri, J.; Sariola, L. Revised Finnish classification of indoor climate 2018. *E3S Web Conf.* **2019**, *111*, 6. [CrossRef]
19. WELL. WELL Building Standard v1 with May 2016 Addenda. Available online: <https://resources.wellcertified.com/articles/well-building-standard-v1-addenda-update-may-2016/> (accessed on 2 September 2021).
20. HKSAR-Indoor Air Quality Management Group. *A Guide on Indoor Air Quality Certification Scheme for Offices and Public Places*; The Government of the Hong Kong Special Administrative Region. Available online: https://www.iaq.gov.hk/media/65346/new-iaq-guide_eng.pdf (accessed on 2 September 2021).
21. BREEAM. *In-Use International Commercial Technical Manual V6*; Building Research Establishment. Available online: <https://www.breeam.com/discover/technical-standards/breeam-in-use/> (accessed on 2 September 2021).
22. U.S. Environmental Protection Agency (USEPA). EPA Facilities Manual: Volume 2 Architecture and Engineering Guidelines. 2020. Available online: https://www.epa.gov/sites/production/files/2018-03/documents/ae_guidelines_508.pdf (accessed on 17 December 2020).
23. Hao, J.; Zhu, T.; Fan, X. Indoor Air Pollution and Its Control in China. *Indoor Air Pollut.* **2018**, *64*, 145–170. [CrossRef]
24. Federal Environment Agency (UBA). *Guidelines for Indoor Air Hygiene in School Buildings*; Federal Environment Agency (UBA): Berlin, Germany, 2008. Available online: <https://www.umweltbundesamt.de/sites/default/files/medien/publikation/long/4113.pdf> (accessed on 1 December 2020).
25. SAIQG. *Guidelines for Good Indoor Air Quality in Office Premises*; Institute of Environmental Epidemiology Ministry of the Environment: Singapore, 1996. Available online: https://www.bca.gov.sg/greenmark/others/NEA_Office_IAQ_Guidelines.pdf (accessed on 2 September 2021).
26. KOSHA. *Guideline Development for Evaluation and Management of Office Air Quality(II)*; Reported in Jeong, J.Y. *Recently Issues on Indoor Air Quality in Korea 2006*; Korea Occupational Safety and Health Agency, 2005. Available online: <http://www.zyaura.com/quality/Archives/Recently%20issues%20on%20Indoor%20air%20quality%20in%20Korea%5B1%5D.pdf> (accessed on 1 December 2020).
27. Department of Occupational Safety and Health Ministry of Human Resources Malaysia. *Industry Code of Practice on Indoor Air Quality 2010*. Available online: <https://www.dosh.gov.my/index.php/chemical-management-v/indoor-air-quality> (accessed on 17 December 2020).
28. US Green Building Council. *LEED v4.1 Building Operations and Maintenance*; 2019. Available online: <https://www.usgbc.org/leed> (accessed on 1 November 2021).
29. ANSI/ASHRAE 62.1-2019. *Ventilation for Acceptable Indoor Air Quality*. American Society of Heating, Refrigerating and Air-Conditioning Engineers. 2019. Available online: <https://www.ashrae.org/technical-resources/standards-and-guidelines/read-only-versions-of-ashrae-standards> (accessed on 2 September 2021).
30. NCCEH. *Carbon Dioxide in Indoor Air*; National Collaborating Centres for Public Health: Canada, 2010. Available online: <https://nccch.ca/documents/practice-scenario/carbon-dioxide-indoor-air> (accessed on 2 September 2021).
31. SAÚDE E AMBIENTE E AÇÃO CLIMÁTICA Portaria n.º 138-G/2021 (Diário da República, 1.ª Série, Ministry of Health, Portugal, 2021). Available online: <https://dre.pt/dre/analise-juridica/portaria/138-g-2021-166296490> (accessed on 1 November 2021).
32. HSE. *EH40/2005 Workplace Exposure Limits*; Health and Safety Executive: UK, 2005; ISBN 9780717667031. Available online: <https://www.hse.gov.uk/pubns/priced/eh40.pdf> (accessed on 2 September 2021).
33. NOHSC. *Adopted National Exposure Standards for Atmospheric Contaminants in the Occupational Environment*; National Occupational Health and Safety Commission: Australia, 1995. Available online: https://www.safeworkaustralia.gov.au/system/files/documents/1702/adoptednationalexposurestandardsatmosphericcontaminants_nohsc1003-1995_pdf.pdf (accessed on 2 September 2021).
34. NIOSH. *Carbon Dioxide*; National Institute for Occupational Safety and Health: USA, 2019. Available online: <https://www.cdc.gov/niosh/npg/npgd0103.html> (accessed on 4 January 2021).
35. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. *List of MAK and BAT Values Report No. 50*; Wiley: Germany, 2014.
36. Dorizas, P.V.; Assimakopoulos, M.N.; Santamouris, M. A holistic approach for the assessment of the indoor environmental quality, student productivity, and energy consumption in primary schools. *Environ. Monit. Assess.* **2015**, *187*, 1–18. [CrossRef]
37. Maddalena, R.; Mendell, M.J.; Eliseeva, K.; Chan, W.R.; Sullivan, D.P.; Russell, M.; Satish, U.; Fisk, W.J. Effects of ventilation rate per person and per floor area on perceived air quality, sick building syndrome symptoms, and decision-making. *Indoor Air* **2015**, *25*, 362–370. [CrossRef]
38. Allen, J.G.; MacNaughton, P.; Satish, U.; Santanam, S.; Vallarino, J.; Spengler, J.D. 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*, 805–812. [CrossRef] [PubMed]
39. Allen, J.G.; MacNaughton, P.; Cedeno-Laurent, J.G.; Cao, X.; Flanagan, S.; Vallarino, J.; Rueda, F.; Donnelly-McLay, D.; Spengler, J.D. Airplane pilot flight performance on 21 maneuvers in a flight simulator under varying carbon dioxide concentrations. *J. Expo. Sci. Environ. Epidemiol.* **2019**, *29*, 457–468. [CrossRef] [PubMed]
40. Hong, T.; Kim, J.; Lee, M. Integrated task performance score for the building occupants based on the CO₂ concentration and indoor climate factors changes. *Appl. Energy* **2018**, *228*, 1707–1713. [CrossRef]

41. Hutter, H.P.; Haluza, D.; Piegler, K.; Hohenblum, P.; Frohlich, M.; Scharf, S.; Uhl, M.; Damberger, B.; Tappler, P.; Kundi, M.; et al. Semivolatile compounds in schools and their influence on cognitive performance of children. *Int. J. Occup. Med. Environ. Health* **2013**, *26*, 628–635. [[CrossRef](#)]
42. Petersen, S.; Jensen, K.L.; Pedersen, A.L.S.; Rasmussen, H.S. The effect of increased classroom ventilation rate indicated by reduced CO₂ concentration on the performance of schoolwork by children. *Indoor Air* **2016**, *26*, 366–379. [[CrossRef](#)]
43. Jaber, A.R.; Mumovic, D.; Ucci, M. The Effect of Indoor Temperature and CO₂ Levels on Cognitive Performance of Adult Females in a University Building in Saudi Arabia. *Energy Procedia* **2017**, *122*, 451–456. [[CrossRef](#)]
44. Satish, U.; Mendell, M.J.; Shekhar, K.; Hotchi, T.; Sullivan, D.; Streufert, S.; Fisk, W.J. Is CO₂ an indoor pollutant? direct effects of low-to-moderate CO₂ concentrations on human decision-making performance. *Environ. Health Perspect.* **2012**, *120*, 1671–1677. [[CrossRef](#)] [[PubMed](#)]
45. Twardella, D.; Spegel, H.; Hendrowarsito, L.; Matzen, W.; Fromme, H.; Lahrz, T.; Burghardt, R.; Frenzel, A.C. Effect of classroom air quality on students' concentration: Results of a cluster-randomized cross-over experimental study. *Indoor Air* **2012**, *22*, 378–387. [[CrossRef](#)] [[PubMed](#)]
46. Gaihare, S.; Semple, S.; Miller, J.; Fielding, S.; Turner, S. Classroom carbon dioxide concentration, school attendance, and educational attainment. *J. Sch. Health* **2014**, *84*, 569–574. [[CrossRef](#)]
47. Kolarik, B.; Moller, E.; Brauner, E.V.; Andersen, Z.J.; Ibfelt, T.; Engelund, E.H. Ventilation in day care centers and sick leave among nursery children. *Indoor Air* **2016**, *26*, 157–167. [[CrossRef](#)] [[PubMed](#)]
48. Shendell, D.G.; Prill, R.; Fisk, W.J.; Apte, M.G.; Blake, D.; Faulkner, D. Associations between classroom CO₂ concentrations and student attendance in Washington and Idaho. *Indoor Air* **2004**, *14*, 333–341. [[CrossRef](#)]
49. Bloch-Salisbury, E.; Lansing, R.; Shea, A.S. Acute changes in carbon dioxide levels alter the electroencephalogram without affecting cognitive function. *Psychophysiology* **2000**, *37*, 418–426. [[CrossRef](#)]
50. Kajtár, L.; Herczeg, L. Influence of carbon-dioxide concentration on human well-being and intensity of mental work. *Időjárás* **2012**, *116*, 145–169.
51. Snow, S.; Boyson, A.S.; Paas, K.H.W.; Gough, H.; King, M.-F.; Barlow, J.; Noakes, C.J.; Schraefel, M.C. Exploring the physiological, neurophysiological and cognitive performance effects of elevated carbon dioxide concentrations indoors. *Build. Environ.* **2019**, *156*, 243–252. [[CrossRef](#)]
52. Zhang, X.; Wargocki, P.; Lian, Z. Human responses to carbon dioxide, a follow-up study at recommended exposure limits in non-industrial environments. *Build. Environ.* **2016**, *100*, 162–171. [[CrossRef](#)]
53. Maula, H.; Hongisto, V.; Naatula, V.; Haapakangas, A.; Koskela, H. The effect of low ventilation rate with elevated bioeffluent concentration on work performance, perceived indoor air quality, and health symptoms. *Indoor Air* **2017**, *27*, 1141–1153. [[CrossRef](#)] [[PubMed](#)]
54. Coley, D.A.; Greeves, R.; Saxby, B.K. The effect of low ventilation rates on the cognitive function of a primary school class. *Int. J. Vent.* **2007**, *6*, 107–112. [[CrossRef](#)]
55. Ferreira, A.M.; Cardoso, M. Indoor air quality and health in schools. *J. Bras. Pneumol. Publicacao Soc. Bras. Pneumol. Tisiologia* **2014**, *40*, 259–268. [[CrossRef](#)]
56. Madureira, J.; Alvim-Ferraz, M.C.M.; Rodrigues, S.; Goncalves, C.; Azevedo, M.C.; Pinto, E.; Mayan, O. Indoor air quality in schools and health symptoms among portuguese teachers. *Hum. Ecol. Risk Assess.* **2009**, *15*, 159–169. [[CrossRef](#)]
57. Lu, C.Y.; Lin, J.M.; Chen, Y.Y.; Chen, Y.C. Building-related symptoms among office employees associated with indoor carbon dioxide and total volatile organic compounds. *Int. J. Environ. Res. Public Health* **2015**, *12*, 5833–5845. [[CrossRef](#)]
58. Vehviläinen, T.; Lindholm, H.; Rintamäki, H.; Pääkkönen, R.; Hirvonen, A.; Niemi, O.; Vinha, J. High indoor CO₂ concentrations in an office environment increases the transcutaneous CO₂ level and sleepiness during cognitive work. *J. Occup. Environ. Hyg.* **2016**, *13*, 19–29. [[CrossRef](#)]
59. Zhang, X.; Wargocki, P.; Lian, Z. Physiological responses during exposure to carbon dioxide and bioeffluents at levels typically occurring indoors. *Indoor Air* **2017**, *27*, 65–77. [[CrossRef](#)]
60. Zhang, J.; Pang, L.; Cao, X.; Wanyan, X.; Wang, X.; Liang, J.; Zhang, L. The effects of elevated carbon dioxide concentration and mental workload on task performance in an enclosed environmental chamber. *Build. Environ.* **2020**, *178*, 106938. [[CrossRef](#)]
61. Gall, E.T.; Mishra, A.K.; Li, J.; Schiavon, S.; Laguerre, A. Impact of Cognitive Tasks on CO₂ and Isoprene Emissions from Humans. *Environ. Sci. Technol.* **2021**, *55*, 139–148. [[CrossRef](#)] [[PubMed](#)]
62. Fraga, S.; Ramos, E.; Barros, H.; Martins, A.; Samudio, M.J.; Silva, G.; Fernandes, E.O.; Guedes, J. Qualidade do ar interior e sintomas respiratorios em escolas do Porto—Indoor air quality and respiratory symptoms in Porto schools. *Rev. Port. Pneumol.* **2008**, *14*, 487–507. [[CrossRef](#)]
63. Kim, J.L.; Toren, K.; Elfman, L.; Wieslander, G.; Norback, D.; Ferm, M. Respiratory health among Korean pupils in relation to home, school and outdoor environment. *J. Korean Med. Sci.* **2011**, *26*, 166–173. [[CrossRef](#)]
64. Madureira, J.; Paciencia, I.; Rufo, J.; de Oliveira Fernandes, E.; Ramos, E.; Barros, H.; Teixeira, J.P. Indoor air quality in schools and its relationship with children's respiratory symptoms. *Atmos. Environ.* **2015**, *118*, 145–156. [[CrossRef](#)]
65. Mi, Y.H.; Norbäck, D.; Tao, J.; Mi, Y.L.; Ferm, M. Current asthma and respiratory symptoms among pupils in Shanghai, China: Influence of building ventilation, nitrogen dioxide, ozone, and formaldehyde in classrooms. *Indoor Air* **2006**, *16*, 454–464. [[CrossRef](#)]

66. Mohd Nor Rawi, N.A.; Jalaludin, J.; Chua, P.C. Indoor air quality and respiratory health among malay preschool children in Selangor. *BioMed Res. Int.* **2015**, *2015*, 248178. [CrossRef] [PubMed]
67. Sá, J.P.; Branco, P.T.B.S.; Alvim-Ferraz, M.C.M.; Martins, F.G.; Sousa, S.I.V. Children's exposure to indoor air in schools: Impact on wheezing. *WIT Trans. Ecol. Environ.* **2019**, *236*, 205–212. [CrossRef]
68. Norbäck, D.; Nordström, K. Sick building syndrome in relation to air exchange rate, CO₂, room temperature and relative air humidity in university computer classrooms: An experimental study. *Int. Arch. Occup. Environ. Health* **2008**, *82*, 21–30. [CrossRef] [PubMed]
69. Simoni, M.; Viegi, G.; Cancianie, M.; Sestini, P.; Annesi-Maesano, I.; Sigsgaard, T.; Norback, D.; Wieslander, G.; Nystad, W. School air quality related to dry cough, rhinitis and nasal patency in children. *Eur. Respir. J.* **2010**, *35*, 742–749. [CrossRef]
70. Mendell, M.J.; Eliseeva, E.A.; Spears, M.; Chan, W.R.; Cohn, S.; Sullivan, D.P.; Fisk, W.J. A longitudinal study of ventilation rates in California office buildings and self-reported occupant outcomes including respiratory illness absence. *Build. Environ.* **2015**, *92*, 292–304. [CrossRef]
71. Erdmann, C.A.; Apte, M.G. Mucous membrane and lower respiratory building related symptoms in relation to indoor carbon dioxide concentrations in the 100-building BASE dataset. *Indoor Air Suppl.* **2004**, *14*, 127–134. [CrossRef]
72. Chatzidiakou, L.; Mumovic, D.; Summerfield, A.J.; Hong, S.M.; Altamirano-Medina, H. A Victorian school and a low carbon designed school: Comparison of indoor air quality, energy performance, and student health. *Indoor Built Environ.* **2014**, *23*, 417–432. [CrossRef]
73. Jurado, S.R.; Bankoff, A.D.P.; Sanchez, A. Indoor air quality in Brazilian universities. *Int. J. Environ. Res. Public Health* **2014**, *11*, 7081–7093. [CrossRef] [PubMed]
74. MacNaughton, P.; Spengler, J.; Vallarino, J.; Santanam, S.; Satish, U.; Allen, J. Environmental perceptions and health before and after relocation to a green building. *Build. Environ.* **2016**, *104*, 138–144. [CrossRef] [PubMed]
75. Tsai, D.H.; Lin, J.S.; Chan, C.C. Office workers' sick building syndrome and indoor carbon dioxide concentrations. *J. Occup. Environ. Hyg.* **2012**, *9*, 345–351. [CrossRef] [PubMed]
76. Ferreira, A.M.; Cardoso, S.M. Effects of Indoor Air Quality on Respiratory Function of Children in the 1st Cycle of Basic Education of Coimbra. In *Occupational Safety and Hygiene II*; CRC Press: Boca Raton, FL, USA, 2014; pp. 347–350, ISBN 9780429227349. Available online: <https://www.taylorfrancis.com/chapters/edit/10.1201/b16490-63/effects-indoor-air-quality-respiratory-function-children-1st-cycle-basic-education-coimbra-portugal-ferreira-cardos> (accessed on 2 September 2021).
77. Hill, B.A.; Craft, B.F.; Burkart, J.A. Carbon dioxide, particulates, and subjective human responses in office buildings without histories of indoor air quality problems. *Appl. Occup. Environ. Hyg.* **1992**, *7*, 101–111. [CrossRef]
78. Carreiro-Martins, P.; Viegas, J.; Papoila, A.L.; Aelenei, D.; Caires, I.; Araújo-Martins, J.; Gaspar-Marques, J.; Cano, M.M.; Mendes, A.S.; Virella, D.; et al. CO₂ concentration in day care centres is related to wheezing in attending children. *Eur. J. Pediatrics* **2014**, *173*, 1041–1049. [CrossRef] [PubMed]
79. Jung, C.-C.; Liang, H.-H.; Lee, H.-L.; Hsu, N.-Y.; Su, H.-J. Allostatic Load Model Associated with Indoor Environmental Quality and Sick Building Syndrome among Office Workers. *PLoS ONE* **2014**, *9*, e95791.
80. Lu, C.Y.; Ma, Y.C.; Lin, J.M.; Li, C.Y.; Lin, R.S.; Sung, F.C. Oxidative stress associated with indoor air pollution and sick building syndrome-related symptoms among office workers in Taiwan. *Inhal. Toxicol.* **2007**, *19*, 57–65. [CrossRef]
81. Tomoda, A.; Yamanaka, S.; Kawai, H.; Itoh, H.; Katsumata, M.; Minami, M.; Hashimoto, T.; Tani, H.; Hashimoto, K. Variation of urinary pH and bicarbonate concentrations of students in metropolitan and rural areas of Japan. *Arch. Environ. Health* **1995**, *50*, 457–461. [CrossRef]
82. Terleph, T.A.; Klein, R.G.; Roberson-Nay, R.; Mannuzza, S.; Moulton, J.L., 3rd; Woldehawariat, G.; Guardino, M.; Pine, D.S. Stress responsivity and HPA axis activity in juveniles: Results from a home-based CO₂ inhalation study. *Am. J. Psychiatry* **2006**, *163*, 738–740. [CrossRef]
83. Thom, S.R.; Bhopale, V.M.; Hu, J.; Yang, M. Increased carbon dioxide levels stimulate neutrophils to produce microparticles and activate the nucleotide-binding domain-like receptor 3 inflammasome. *Free Radic. Biol. Med.* **2017**, *106*, 406–416. [CrossRef]
84. Thom, S.R.; Bhopale, V.M.; Hu, J.; Yang, M. Inflammatory responses to acute elevations of carbon dioxide in mice. *J. Appl. Physiol.* **2017**, *123*, 297–302. [CrossRef] [PubMed]
85. Schnerberger, D.; DeVasure, J.M.; Bailey, K.L.; Romberger, D.J.; Wyatt, T.A. Effect of low-level CO₂ on innate inflammatory protein response to organic dust from swine confinement barns. *J. Occup. Med. Toxicol.* **2017**, *12*, 9. [CrossRef] [PubMed]
86. Wade, C.E.; Wang, T.J.; Lang, K.C.; Corbin, B.J.; Steele, M.K. Rat growth, body composition, and renal function during 30 days increased ambient CO₂ exposure. *Aviat. Space Environ. Med.* **2000**, *71*, 599–609. [PubMed]
87. Martrette, J.M.; Egloff, C.; Clement, C.; Yasukawa, K.; Thornton, S.N.; Trabalon, M. Effects of prolonged exposure to CO₂ on behaviour, hormone secretion and respiratory muscles in young female rats. *Physiol. Behav.* **2017**, *177*, 257–262. [CrossRef] [PubMed]
88. Schaefer, K.E.; Douglas, W.H.J.; Messier, A.A.; Shea, M.L.; Gohman, P.A. Effect of Prolonged Exposure to 0.5-Percent CO₂ on Kidney Calcification and Ultrastructure of Lungs. *Undersea Biomed. Res.* **1979**, *6*, S155–S161. [PubMed]
89. Kiray, M.; Sisman, A.R.; Camsari, U.M.; Evren, M.; Dayi, A.; Baykara, B.; Aksu, I.; Ates, M.; Uysal, N. Effects of carbon dioxide exposure on early brain development in rats. *Biotech. Histochem.* **2014**, *89*, 371–383. [CrossRef]
90. Norback, D.; Bjornsson, E.; Janson, C.; Widstrom, J.; Boman, G. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. *Occup. Environ. Med.* **1995**, *52*, 388–395. [CrossRef]

91. Muscatiello, N.; McCarthy, A.; Kielb, C.; Hsu, W.H.; Hwang, S.A.; Lin, S. Classroom conditions and CO₂ concentrations and teacher health symptom reporting in 10 New York State Schools. *Indoor Air* **2015**, *25*, 157–167. [[CrossRef](#)]
92. Lu, C.Y.; Ma, Y.C.; Lin, J.M.; Sung, F.C.; Chuang, C.Y. Oxidative DNA damage estimated by urinary 8-hydroxydeoxyguanosine and indoor air pollution among non-smoking office employees. *Environ. Res.* **2007**, *103*, 331–337. [[CrossRef](#)]
93. Apte, M.G. Associations between indoor CO₂ concentrations and sick building syndrome symptoms in U.S. office buildings: An analysis of the 1994–1996 BASE study data. *Indoor Air* **2000**, *10*, 246–257. [[CrossRef](#)]