Possible toxicity of chronic carbon dioxide exposure associated with mask use, particularly in pregnant women, children and adolescents – a scoping review

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ABSTRACT

Literature was systematically reviewed regarding CO_2 exposure and facemask use. Observational and experimental data are helpful for a risk-benefit assessment for masks as a popular non-pharmaceutical intervention against SARS-CoV2 in the populace. Masks impede breathing by increasing the resistance and dead space volume leading to a re-breathing of CO_2 with every breath taken. Fresh air has around 0.04% CO_2, while wearing masks more than 5 minutes bears a possible chronic exposure to carbon dioxide of 1.41% to 3.2% of the inhaled air. Although the buildup is usually within the short-term exposure limits, long-term consequences must be considered due to experimental data. US Navy toxicity experts set the exposure limits for submarines carrying female crews to 0.8% CO_2 based on animal studies indicating an increased risk for stillbirths. Additionally, in mammals chronically exposed to 0.3% CO_2 experimental data demonstrates teratogenicity with irreversible damage of neurons and reduced spatial learning caused by brainstem neuron apoptosis and a reduced blood level of the insulin-like growth factor 1. With significant impact on three readout parameters (morphological, functional, marker) this chronic 0.3% CO_2 exposure has to be defined as being toxic. Additional data exists on the exposure of chronic 0.3% CO_2 in adolescent mammals causing neuron destruction, which includes less activity, increased anxiety and impaired learning and memory. There is a possible negative impact risk by imposing extended mask mandates especially for vulnerable subgroups. Circumstantial evidence exists that extended mask use may be related to current observations of stillbirths and to reduced verbal motor and overall cognitive performance in children born during the pandemic. Extended masking in pregnant women, children and adolescents has not been thoroughly tested and studied. As a result of the animal experimental data available, a risk-benefit analysis is urgent and a need exists to rethink mask mandates, which provide appropriate warnings.

Keywords: carbon dioxide (CO_2) exposure, toxicity, personal protective equipment, masks, N95 face mask, surgical mask, risk, adverse effects, long-term adverse effects, health risk assessment, MIES-syndrome, children, adolescents, pregnant women

1. Introduction

Approximately 77% of the countries in the world introduced the requirement to wear masks in public spaces to contain SARS-CoV-2 making it commonplace in 2020. Simultaneously, it is one of the most important ubiquitous environmental factors directly affecting human breathing. Government data from the end of the year 2021 show that an estimated 4 496 149 755 people worldwide (58% of world population) have been confronted with a mask obligation. Given this and the significant role masks have played as a non-occupational, non-pharmaceutical public health intervention for the past 2 years, a rigorous scientific toxicological consideration is required. Children in schools in particular are heavily exposed to the mandatory wearing of masks for long periods. In this paper, we highlight the toxicological aspects of wearing a mask for special user groups resulting from a low level CO_2 exposure.

In medical environments, masks have been mandatory self-protective and third-party protective equipment for healthcare workers prior to COVID-19. There is no doubt about the efficacy of this medical device in reducing transmission of pathogens, especially bacteria. Masks belong in the hands of professionals in medical facilities and environments where symptomatic individuals are common. It should be noted that the authors of a recent systematic review evaluating six studies on antiviral mask efficacy concluded that wearing a mask might reduce the risk of COVID-19 infection, but predominantly in healthcare workers [1]. However, the evidence was limited due to the low statistical power and strength of the studies analysed. The topic of general mask mandates is currently the subject of much scientific debate, especially in the USA. It is widely believed that the use of masks – including in the general population – could be an important measure to combat SARS-CoV2 [2]. Yet moderate or strong empirical scientific evidence for the effectiveness of masks when used by the general population is lacking, and there is solid data questioning the definite antiviral effectiveness of masks [3-6], even from the Cochrane database analysing systematic reviews [7]. And even mask-supportive reviews include statements such as: „wearing a mask could reduce the risk of COVID-19-infection “, but „ more evidence is still needed to better define the protective effect of the mask on the wider population“[1]. An overview of systematic reviews on mask use against airborne viral diseases [8] found only one high quality study, which concluded „that compared with no facemask use, wearing a facemask may make little to no difference in how many people that catches a flu like illness“[7]. Furthermore, they stated: “It may seem that it makes little to no difference, what type of facemask is used“. Current evidence suggests that SARS-CoV-2 may be also transmitted via fecal transmission and fomite [9] between infected individuals and others. Altogether, from an evidence-based perspective, masks for the public are overrated in a pandemic response [10].

In contrast, it is known that masks bear several side effects and risks [11]. Among the many symptoms and physiological changes, an elevated blood carbon dioxide level is an important cornerstone of the so-called Mask-Induced Exhaustion Syndrome (MIES) [11]. There is a high risk of improper handling when the mask is used by the general population and by children [12,13]. Children and pregnant women are a special subgroup more susceptible to potential negative environmental factors [14].

There are several general short-term effects on human health due to low level CO_2-inhalation: Physiological changes occur already at levels between 0.05% and 0.5% carbon dioxide showing increased heart rate, increased blood pressure and overall increased circulation with the symptoms of headache, fatigue, difficulty concentrating, dizziness, rhinitis and dry cough [15]. While the effects of short-term exposure on cognitive performance begin at 0.1% CO_2 levels, with reduced cognitive performance, impaired decision-making and reduced speed of cognitive solutions, many other long-term effects are known at concentrations above 0.5% [15,16]. Exceeding the limit of 1% CO_2 the harmful effects include respiratory acidosis, metabolic stress, increased blood flow and decreased exercise tolerance [15]. Therefore, regarding low level CO_2 exposition an EN149:2001+A1 (European Standard Norm) and a NIOSH (National Institute for Occupational Safety & Health) norm exists. A health-critical limit is set at 15 minutes for 3% for short periods, while the 8-hour limit is set at 0.5% CO_2 [17].

2. Methods

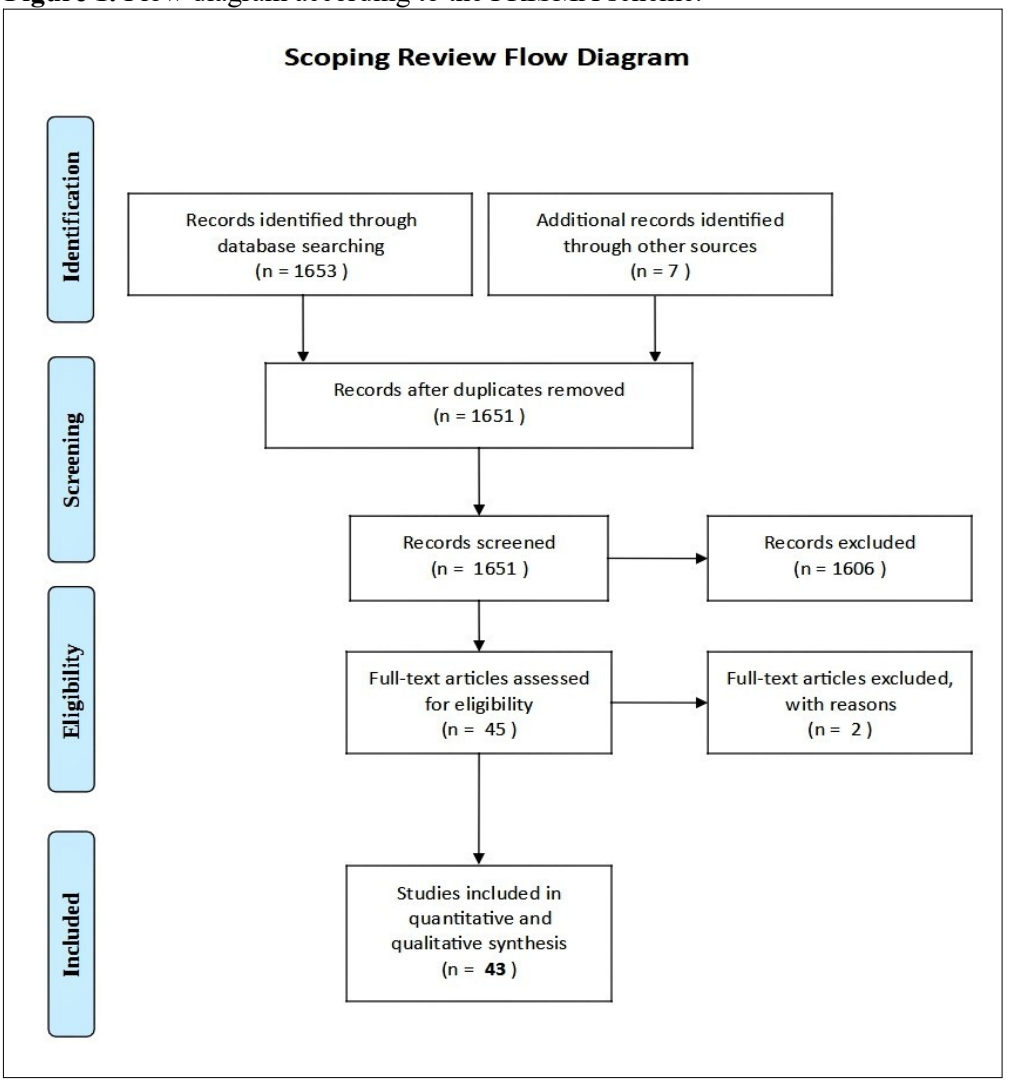
We conducted a systematic literature search in MEDLINE, Cochrane Library and the World Health Organization COVID-19 Database up until 30th November 2021 on toxic effects of low level

carbon dioxide including mask effects on carbon dioxide breathing. Medical surgical masks on the one hand and N95 masks (FFP2 masks) on the other were of interest here. Search terms were: “carbon dioxide”, “breathing” and “toxicity” as well as “carbon dioxide” and “mask”, including “surgical” and “N95”. We searched PubMed and Google Scholar for additional articles of interest. Two independent researchers identified and screened the eligible studies. The selected papers were checked by all authors for final eligibility. To expand the amount of published data further we reviewed citations from included articles to identify additional research. Only English- and German-language peer reviewed records were considered that explicitly described the toxicity of carbon dioxide at low concentrations as well as studies quantifying carbon dioxide when wearing masks under everyday conditions. Letters to the editor and case reports were not considered. Of the eligible papers, one with methodological weaknesses and one retracted paper were ultimately excluded.

3. Results

The search yielded 1651 papers, of which 43 publications were finally considered for evaluation according to the above criteria. In addition to 25 mask experiments in humans, we found 2 modeling and 2 test suite measurements of CO2 when using a mask. Four reviews describe the toxicity of inhaled low level CO2. From the referenced literature, two of the human and eight of the animal experiments examined the toxicity of carbon dioxide at low concentrations. The literature found demonstrates and quantifies in detail the effect of the face masks in terms of carbon dioxide rebreathing. It also describes in detail the effects of low concentration carbon dioxide toxicity. Figure 1 shows the flow chart of our scoping review.

Figure 1. Flow diagram according to the PRISMA scheme.



3.1. Effects of masks on carbon dioxide re-breathing

In the study of Ulrike Butz's dissertation [18] focusing on possible rebreathing of carbon dioxide in 15 healthy adult male volunteers, a carbon dioxide partial pressure of up to 21-24 mmHg was found under a surgical mask after 30 minutes [18]. This corresponds to about 2.8 - 3.2 % carbon dioxide of the inhaled air under the mask.

In Pifarrés mask-experiments in 8 adult females and males a health-critical value of carbon dioxide concentration (CO_2 Vol%) was measured in the air under the masks after few minutes. The concentrations of 14162 ppm with a mask versus 464 ppm without a mask were statistically significant with $p < 0.001$ increased by a high factor compared to the initial value (ambient air) and even more following exercise [19]. According to those experiments, masks can be responsible for a drastic increased CO_2 concentration of the inhaled air, which roughly corresponds to 1.41-1.7% carbon dioxide in inhaled air under the face mask ($p < 0.001$) [19].

A project at the University of Delft used a validated method that clearly demonstrated that carbon dioxide re-breathing under standardised laboratory conditions (test suite) after 1 minute is at least 0.9% CO_2 for N95/ FFP2 masks [20]. Those elevated carbon dioxide levels of inhaled air, particularly under N95 masks, have also been found in physiologic relevant short-time modeling studies. This confirms a constant increase leading to an averaged 1% inhaled CO_2 per breath during simulations of eight breathing cycles in 33.65 seconds [21] (see Figure 8 of mentioned publication with animation of CO_2 distribution with and without a respirator). Another modeling study shows that wearing N95 masks results in carbon dioxide accumulation, the volume fraction of CO_2 reaches 1.2% after 7 breathing cycles and is then maintained at 3.04% on average. The wearers re-inhale excessive CO_2 with every breath taken from the mask cavity [22].

In 2012 Sinkule already evaluated 30 different N95 respirators using the NIOSH Automated Breathing and Metabolic Simulator (ABMS) through 5 minute work rates and found elevated CO_2 levels in the inhaled air ranging between 1.28% and 3.52% [23]. These results are consistent with measurements of CO_2 in the dead space of the masks from experimental studies in humans with values of 2.8 [24] and 3.2 % [25].

In a self-experiment in 2020 Geiss measured the air under masks under laboratory conditions and only found an accumulation of carbon dioxide between 0.22 and 0.29% within 5 minutes mainly under surgical masks [26]. However, this experiment has several limitations. Firstly, it is only a one-time measure performed by a man, which might not be representative. The anatomy of this volunteer does not reflect children or women. Secondly, the CO_2 sampling point chosen by Geiss above the tip of the nose on the bridge of the nose is suboptimal for mask measurements. This is because it is not close enough to the openings involved in breathing, which are shielded from the rest of the dead space of the mask by the protruding tip of the nose (see figure 1A in Geiss publication to illustrate the questionable placement of sensor [26] and compare it to the gas distribution video in Salati [21]). Thirdly, it is not optimal to place the sampling point at the highest point. This is because carbon dioxide is heavier than other air components (approximately 44 g/mol in CO_2 compared to 32 g/mol in O_2 and 28 g/mol in N_2) and could accumulate there over time to a lesser extent than in the lower parts of the dead space of the mask [21]. In contrast, Butz provided a positioning of the sensor close to the mouth attached to the cheek [18], like Blad [20] and Sinkule [23], who placed it close to the breathing orifice (mouth opening), while Rhee and Roberge chose the nasolabial fold [25,27].

In a prospective observational study in 2021, Rhee examined the carbon dioxide concentration of 11 healthy volunteers during regular breathing and sitting at rest while they put on different types of masks for 15 minutes. Serial CO_2 measurements were performed with a nasal cannula at a frequency of 1 Hz [27]. The measured 2.4-2.6% CO_2 concentration translates into a highly significant increase in CO_2 with a KN95 respirator and a valved respirator at the nasolabial fold ($p < 0.0001$), which is much greater than the NIOSH 8h threshold limit value [17]. The National Institute for Occupational Safety and Health (NIOSH) has an 8h threshold limit value – time-weighted average recommended exposure limit (TLV-REL) of 0.5% – and a 15 min threshold limit value – short-term exposure limit (TLV-STEL) of 3% for CO_2 – in workplace ambient air [17]. Rhee´s well designed reliable high quality study demonstrates a significant increase in end-tidal CO_2 concentrations among healthy volunteers while donning KN95 respirators. Consequently, the authors recommended further studies.

Table 1 summarizes the experimental findings concerning CO_2-re-breathing under face masks.

Table 1. Experimentally measured CO_2 concentrations in the inhaled air under masks.

Experimental mask study	Analyzer type	Placement CO_2 sensor / sampling	Inhaled Vol% of CO_2 (mask wearing time)	Factor of increase*
Blad 2020 [20] *FFP2/N95 and FFP3 masks*	GSS Sprint IR-WF-20	close to the breathing orifice	**0.42 - 0.94 %** *test suite* measurements (1 minute)	11 - 24
Butz 2005 [18] *surgical masks*	RADIMETER TCC3	close to mouth on cheek	**2.8 - 3.2 %** measurements on *humans* (**30 minutes**)	70 - 80
Geiss 2020 [26] *surgical masks*	TSI 7545 IAQ Meter	above nose tip, on nose bridge	**0.22 - 0.29 %** measurement on *human* (5 minutes)	6 - 7
Laferty 2006 [24] *N95 masks*	Control Technologies GEM-500	inner side of facepiece	**2.8 %** measurement on *humans* (7 minutes)	70
Pifarré 2020 [19] *mask type not given*	Multi-Rae gas analyzer	not given	**1.41 - 1.7 %** measurements on *humans* (5 to 7 minutes)	35 - 43
Rhee 2021 [27] *N95 masks*	GASLAB CM-0123 ExplorIR-W	at nasolabial fold	**2.4 - 2.6 %** measurements on *humans* (**15 minutes**)	60 - 65
Roberge 2010 [25] *N95 masks*	p61-B, AEI	at nasolabial fold	**2.8 -3.2 %** measurements on *humans* **(60 minutes)**	70 - 80
Sinkule 2012 [23] *N95 masks*	NIOSH ABMS	close to the breathing orifice	**1.28 - 3.52 %** *test suite* measurements (5 minutes)	32 - 88

**compared to normal air concentration with 0.04 Vol% CO_2.*

When masks are used elevated CO_2 concentrations are inhaled [18-27]. Despite the compensatory mechanisms that occur [28] an arterial $PaCO_2$ rise is inevitable in the long term [29]. For example, breathing air with an inspired CO_2 fraction of 1% (≈ 8 mmHg) will increase arterial carbon dioxide by 1 mmHg, which increases ventilation at rest [28]. In a recent scoping review numerous important studies which provide statistically significant evidence for such CO_2 retention under the mouth-nose protection have been presented [11] and we have found additional studies that reveal scientific evidence of a carbon dioxide increase in the blood when masks are used. In total, significant changes ($p<0.05$) could be found in most of the evaluated studies that measured body CO_2 content during mask use [18,29-44] (Table 2). Experiments with relatively short evaluation times [45] or questionable study design [46,47] showed no effects caused by masks. However, some well conducted studies also found no statistical difference between mask and no mask use, though measured CO_2 levels were continuously higher in mask wearers [25,48]. Some of these studies were conducted under extreme conditions and within selected user groups [49]. Overall, the most prominent rise in CO_2 was observed

while wearing N95 masks. This is due to the fact that the dead space volume is almost doubled and the breathing resistance is more than doubled, which leads to a significant re-breathing of CO_2 with every breathing cycle [11,21,22]. Due to compensatory mechanisms, carbon dioxide partial pressure ($PaCO_2$) in the blood is at a subthreshold generally in healthier people [28,29], but in sick people a partially pathological increase is detected [34]. However, all mask types like community masks, surgical mask, as well as N95 respirators can be responsible for a significant and comparable rise in the blood content of CO_2 [32].

The buildup of CO_2 behind the masks is predominantly within the short term exposure limits of NIOSH and EN149 [17,19,20,24,27], but even with values which do not go beyond this limit in the short term [20,21,27], a long-term pathological consequence with clinical relevance is to be expected [15-17,19,21-23,27,50,51]. This is as a result of the longer lasting effect with a subliminal impact and significant shift in the pathological direction. This pathogenetic damage principle, whereby a chronic low-dose exposure leads to disease or to disease relevant conditions in the long term [52,53] has been extensively studied and described in many aspects of environmental medicine [11].

From a toxicological point of view, carbon dioxide is absorbed passively through the lungs from the breathed-in air. Human metabolism also produces carbon dioxide, which naturally requires elimination. Carbon dioxide is largely carried in the blood as bicarbonate, which is catalysed by the enzyme carbonic anhydrase. The excretion is accomplished mainly via the lungs although the kidneys also excrete small amounts. In expert literature, concentrations of >2% carbon dioxide in inhaled air are expected to cause adverse health effects [51]. At short exposure of CO_2 levels above 1% an increase in cardiac output is often seen. Inhalation of between 2.5–3.5% carbon dioxide for up to 10 minutes may increase cerebral blood flow up to 100% and a dilatation of cerebral blood vessels may be responsible for the severe headache produced by carbon dioxide inhalation [30,51]. Exposure to increased carbon dioxide concentrations causes hyperventilation. Interestingly, due to compensatory mechanisms, acclimatisation occurs to chronic low concentrations of carbon dioxide [28,50,51]. Acute features usually resolve despite continuing exposure as carbon dioxide at concentrations up to 3%. However, in healthy adults metabolic changes are responsible for slight long-term damages at concentrations of <5% [51].

Some mechanisms of human adaptation to low level exposure of CO_2 had been evaluated experimentally including levels of 1-2% [28, 50]. Regarding the referenced mask literature those carbon dioxide values of 1-2% can be assumed for masks [18,19,21-25,27]. In the human experiments with low level 1-2% CO_2 exposure an increased respiratory minute volume of more than 34% was detected [50]. Moreover, higher arterial $PaCO_2$ and bicarbonate levels produced an effective buffering of inhaled CO_2. A correlation could be shown between changes in plasma calcium level, pH, and CO_2, indicating that the bone CO_2 store is a determining factor in the extended time periods of CO_2 retention and elimination. Kidney and organ calcification was seen in animal studies frequently, emphasising the involvement of calcium metabolism in adaptation to elevated levels of carbon dioxide [50]. Recent studies raised interest in carbon dioxide in relationship with chronic and/or intermittent long-term exposure conditions that might induce pathologic states, in particular favour DNA alterations, nasal inflammation, and pulmonary inflammation [16].

Table 2 shows studies revealing evidence of carbon dioxide retention when masks are used.

Table 2. Demonstrated statistically significant increase in carbon dioxide levels in mask wearers under various conditions in scientific intervention studies.

Experimental mask study Author & Year	Parameter	CO_2 outcome in mmHg* No vs **Mask**	Rise mmHg	P-value
Bharatendu 2020 [30]	$PETCO_2$	N95 masks: 37.3 vs **40.4**	**+3.1**	<0.001
Butz 2005 [18]	$PtCO_2$	surgical masks: 40 vs **45.6**	**+ 5.6**	<0.05
	PCO_2	under surgical mask: 0.31 vs **22.49**	**+22.18**	<0.05
Dirol 2021 [42]	$PETCO_2$	surgical masks: 37.2 vs **38.7**	**+1.5**	<0.001
Epstein 2020 [31]	$PETCO_2$	surgical masks: 35 vs **40**	**+5**	<0.03
	$PETCO_2$	N95 masks: 35 vs **43**	**+8**	<0.001
Georgi 2020 [32]	$PtCO_2$	community masks: 38.4 vs **39.1**	**+0.7**	<0.001
	$PtCO_2$	surgical masks: 38.4 vs **39.9**	**+1.5**	<0.001
	$PtCO_2$	N95 masks: 38.4 vs **40.5**	**+2.1**	<0.001
Kim 2013 [43]	$PtCO_2$	N95 masks: 39.7 vs **42.7**	**+3**	<0.01
Kyung 2020 [33]	$PETCO_2$	N95 masks: 24.8 vs **25.7**	**+0.9**	<0.001
		34.0 vs **35.5**	**+1.5**	<0.001
Lubrano 2021 [39]	$PETCO_2$	N95 masks: 32 vs **39**	**+7**	<0.005
Mapelli 2021 [41]	$PETCO_2$	surgical masks: 33 vs **35.1**	**+2.1**	<0.05
		N95 masks: 33 vs **36.3**	**+3.3**	<0.05
Mo 2020 [34]	$PaCO_2$	surgical masks: 40.77 vs **49.75**	**+8.98**	<0.005
Pifarré 2020 [19]	PCO_2	under masks: 0.35 vs **10.76**	**+10.41**	<0.001
	PCO_2	under masks: 0.35 vs **12.92**	**+12.57**	<0.001
Rebmann 2013 [35]	$PtCO_2$	N95 masks: 32.4 vs **41.0**	**+8.6**	<0.01
Roberge 2012 [36]	$PtCO_2$	surgical masks: 39.31 vs **41.48**	**+2.17**	<0.001
Roberge 2014 [37]	$PtCO_2$	N95 masks: 31.3 vs **33.3**	**+2**	<0.05
Tong 2015 [38]	$FeCO_2$	N95 masks: 25.84 vs **28.12**	**+2.28**	<0.001
Zhang 2021 [40]	$PETCO_2$	surgical masks: 38.8 v**s 41.6**	**+2.8**	<0.001

$PaCO_2$=Arterial partial pressure of CO_2, PCO_2=Partial pressure of CO_2, $PETCO_2$=End-expiratory partial pressure of carbon dioxide, $PtCO_2$=Percutaneous CO_2, $FeCO_2$*=Exhaled CO_2.*

***If necessary, values have been standardised for comparability, assuming normal values of CO_2 content of room air (409 ppm) and normal air pressure (760 mmHg) according to the formula:*

$$\textit{Vapor Pressure (mmHg)} = \frac{\textit{Atmospheric Pressure}(\textit{mmHg})}{10^6} * \textit{ppm}.$$

Please Note: Breathing air with inspired CO_2 fraction of 1% (≈ 8 mmHg) will increase arterial carbon dioxide ($PaCO_2$) by 1 mmHg, [28]. $PETCO_2$ and PtCO2 measurements provide an estimation of $PaCO_2$ [54,55,56].

3.2. Low level inhaled carbon dioxide toxicity in animal studies

One principle of toxicological consideration of the risk of exposure to noxious agents to humans is the use of evidence from animal studies. Therefore, the most important animal studies on carbon dioxide respiration at low concentrations are presented. They provide information on possible mask effects. It should be mentioned that in a great work of toxicology [57] following statement on page 156 can be found: "Small laboratory animals (mice) cannot serve well as indicators for dioxide as they do for carbon monoxide, since they are much less sensitive to it than humans". Therefore, in an appropriate risk assessment it is necessary to apply an inter-species uncertainty factor.

3.2.1. Teratogenicity and stillbirth

From decades of studies on the toxicity of carbon dioxide it is known that just 0.5% carbon dioxide for a few minutes to an hour per day is capable of inducing stillbirth and teratogenic birth defects in guinea pigs [58] (Page 14 of the referred FDA document). People in positions of responsibility in the US Navy have been aware that this level of 0.5% carbon dioxide in submarines is often exceeded. They therefore set up a study in pregnant rats, the details of which have been published [59,60]. In rats the first signs of toxicity to pups were observed at a level of 3% carbon dioxide exposure for the pregnant dam with no signs of toxicity at 2.5% exposure. In the 3% CO_2 exposure group the findings were a statistically significant mean litter proportion of post-implantation loss (resorptions occurring in the early phase of pregnancy) and a corresponding statistically significant lower mean litter proportion of viable fetuses. Moreover, they found one fetus that had gastroschisis (stomach, several loops of the intestine and liver protruding through an opening in the ventral midline) and localised fetal edema was noted in 2 fetuses: one for hind limbs and the other for neck and thorax. With a safety factor between animals and humans of about three, the US Navy toxicity experts then set the exposure limits for submarines carrying female crews to 0.8% carbon dioxide as well as emergency exposure with a limit of 24 hours [59,60].

The exact mechanism of low level CO_2 toxicity for unborn life is not known in detail. Maternal and fetal mechanisms have to be taken into account. With regard to the adverse maternal changes an increased CO_2 and acidity in the blood (pH changes) trigger various compensatory mechanisms. These include pH buffering systems in the blood, increased breathing to reduce excess CO_2 in the bloodstream, increased excretion of acid by the kidneys to restore pH balance and nervous system stimulation due to changes of heart contractibility and vasodilation [61,62]. During respiratory acidosis the kidneys retain bicarbonate helping to normalize the pH of the blood. With prolonged CO_2 stress a metabolic acidosis occurs and the kidneys no longer respond in producing bicarbonate [63]. Thereafter –with further prolonged CO_2 burden – the body uses the bones to regulate the acid levels in the blood: Bicarbonate and a positive ion (Ca^{2+}, K^+, Na^+) are exchanged for H^+. The kidney tubule recovers filtered bicarbonate or secretes bicarbonate into the urine to help maintain the pH balance in the blood, which involves the Carbonic Anhydrase (CA) enzyme [64]. CA enzymes participate in metabolic reactions that convert CO_2 and result in the precipitation of calcium carbonate [65-67]. CA is involved in the calcification of human tissues including bone and soft-tissue calcification [65]. Carbon dioxide conversion by the CA enzyme provides bicarbonate and hydrogen ions that fuel the uptake of ionised calcium, which is then deposited in the body tissues as calcium carbonate. Increased CO_2 in the blood caused by breathing elevated levels of the gas could lower the pH enough to increase the activity of CA thereby potentially increasing calcium carbonate deposits [67]. Significant tissue calcification has been observed in animals after a 2-week exposure to 1% CO_2 or an 8-week exposure to 0.5% CO_2 with only slight reductions in pH [68]. This would occur by CA activity where tissues connect with plasma, e.g. arteries, kidneys or even the placenta. A placenta calcification is associated with a higher risk of adverse pregnancy outcomes [69-71]. This mechanism appears plausible as the final damaging step in the maternal body.

In addition, carbon dioxide is also known to play a role in oxidative stress caused by reactive oxygen species (ROS) [72]. This would impede fetal body development. In particular, oxidative damage to cellular DNA can lead to mutations [16,72].

Moreover, inflammation is a serious illness that is known to be caused by low-level CO_2 exposure in humans and animals [16,73-76]. CO_2 increases the result in higher levels of pro-inflammatory Interleukin-1β, a protein involved in regulating immune responses, which causes inflammation and vascular damage [73]. In this case, both fetal as well as maternal vascular damages are to be expected.

3.2.2. Neurotoxicity

To figure out the negative impact of poor indoor air quality on early brain development a research study exposed pregnant rats [77] to carbon dioxide levels of 0.1 to 0.3 %, which is unfortunately commonplace in poorly ventilated closed buildings [15]. At an exposure of 0.3% carbon dioxide for the pregnant rats the pups demonstrated reduced spatial learning and memory at the age of approx. 6 weeks [77]. This reduced spatial learning and memory was attributed to histologically proven damaged neurons in a part of the brain called the hippocampus [77]. This damage is irreversible and it affects mental health in the long term. When the pregnant rats were exposed to just 0.1% CO_2 the pups demonstrated increased anxiety [77], which is even more pronounced when the dams were exposed to 0.3% CO_2.

Carbon dioxide exposure, depending on its duration and intensity can cause oxidative stress [78]. Oxidative stress mediates apoptosis by forming lipid hydroperoxides that are highly toxic and cause DNA fragmentation [79]. This condition causes mitochondrial damage, which can lead to a release of Cytochrome C, Caspase activation and finally cell death [80].

Low indoor air quality in classrooms is well known to be associated with a negative impact on the learning capacity of school children [15,16,76]. To establish whether this only indicates a short-term effect or possible substantial damage to brain function, a study in mice was performed and published [81]. Adolescent mice were exposed 24 hours a day for 7 weeks to a level of 0.3% carbon dioxide, but with normal atmospheric levels of oxygen [81]. At the end of the study a so-called water maze exercise was performed. Here the mice have to find a life-saving platform in a water basin. This test distinguishes between impact on physical function and on mental function. Mice were tested on four consecutive days. On the first test day mice in all groups (carbon dioxide exposed and normal air exposed) typically needed around 40 seconds to find the platform. Healthy mice exposed to normal air learned to find the platform more quickly and after four days the healthy mice finally only needed 20 seconds to find the platform, whereas the carbon dioxide exposed mice were unable to learn the shortest way to the platform. Although the carbon dioxide exposed mice were able to swim as quickly as their healthy controls, they were not able to learn the shortest route. They swam around in a very disoriented manner day after day of the four test days. Histology tests demonstrated apoptosis of brainstem neurons in those 0.3% carbon dioxide exposed mice [81]. This is a very disturbing finding because this CO_2-induced loss of neurons is irreversible.

When exposure to low level CO_2 is prolonged (several hours to one week) the organism depletes its buffer systems [81-84]. The number of cells in the brain of adolescents is a result of the equilibrium of cell proliferation and apoptosis. External factors can affect both cell proliferation and death. In the case of prolonged low-level CO_2-exposure the latter occurs, especially under exercise or stress [85-88]. Blood carbon dioxide concentration exerts an important influence on intra- and extracellular pH, CO_2 passes quickly through the cell membranes to form carbonic acid with H_2O, which releases H^+ ions and, in excess, causes acidosis [89-91]. Acidosis decreases transmembrane Ca^{+2} conductivity and decreases the excitability of neurons [92,93]. Calcium overload causes excitotoxicity and apoptosis during hypoxia [94].

3.2.3. Male reproductive toxicity

As a rise in carbon dioxide when wearing a mask is scientifically proven (Tables 1 and 2) [18-27,29-44], further information about the phenomenon of the toxicological influence of elevated carbon dioxide of inhaled air on male fertility needs to be discussed. The toxic effects of low level carbon dioxide exposure on male fertility have been studied extensively in animal experiments. The exposure of adolescent rats to a carbon dioxide level of 2.5% once for four hours induced pathological signs of diminished fertility in rat testes [95]. A correct estimation of an exposure limit from animal toxicity studies to humans requires implementation of a safety factor [59,60,96]. One has to consider that small laboratory animals, evolutionarily adapted to living in burrows and caves, are limited as indicators for carbon dioxide, since they are much less sensitive to it than humans [57]. As aforementioned, the US Navy was using a safety factor of 3 from a level with no adverse effects on rat pregnancies [59,60]. In the study referred to on rat testicular function of carbon dioxide no so-called NOAEL (No-Observed-Adverse-Effect-Level) was observed [95]. Using the 2.5% level with marked damage to testes function and a minimum safety factor of 5, an exposure limit for adolescent males needs to be set at 0.5% for a maximum of 4 hours a day [59,60,95,96].

The damaging mechanism of CO_2 affecting testicular tissues is based on the conditions of oxidative stress and acidosis with increased inflammation and apoptosis as described above [72,73-76,78,79]. Testes metabolism and cell respiration have been shown to be increasingly inhibited by rising levels of CO_2 [95]. It has to be pointed out here that this data on the toxicity of carbon dioxide on reproduction has been known for 60 years. Exposure limits have therefore typically been set at 0.5% CO_2 in working environments, e.g. according to a Safety Data Sheet by Linde Company on Exposure Limits [97]. These limits are based on EU Indicative Exposure Limit Values in Directives 91/322/EEC, 2000/39/EC, 2006/15/EC, 2009/161/EU, 2017/164/EU. An 8-hour exposure limit of 0.5% CO_2 has been defined in the NIOSH regulations [17]. Looking at the potential damage to the reproduction function by subacute or chronic carbon dioxide exposure proven in animal experiments makes it very clear why these limits exist.

Table 3 sums up the significant toxicity of inhaled carbon dioxide at low levels in animal studies.

Table 3. Significant toxicity of inhaled carbon dioxide at low levels in animal studies.

Experimental study, *species*	**Toxic CO_2-level (Vol%) [exposure duration]**	**Significant Outcome**
FDA Technical Reports 1979 [58] *guinea pigs*	**0.48 %** Exposure to pregnant [10 min over 20 days each]	Stillbirth and birth defects (67.5%)
Howard 2012 [59,60] *rats*	3% resp. **0.8 %*** Exposure to pregnant [chronically]	Stillbirth and birth defects ($p<0.01$)
Kiray 2014 [77] *rats*	**0.3 %** Exposure to unborn (pregnant) [chronically]	Neuron destruction in prefrontal cortex and hippocampus, decreased IGF-1 levels, increased anxiety after birth, impaired memory and learning ($p<0.05$)
Uysal 2014 [81] *mice*	**0.3 %** Exposure to adolescent [chronically]	Neuron destruction in gyrus dentatus and the prefrontal cortex, decreased IGF-1 levels, less activity, increased anxiety, impaired learning and memory ($p<0.05$)
Vandemark 1972 [95] *rats*	2.5 % resp. **0.5 %*** Exposure to male [4 hours]	Destruction of spermatid and Sertoli cells in testes, streaking & vacuolization of the tubular components, no maturation of spermatids (histopathological proof)

*calculated for humans with an interspecies safety factor, for further details see Howard et al [59,60,96].

4. Discussion

The above data including Table 1, Table 2 and Table 3 indicate that mandatory daily long-term use of masks, especially for pregnant women, children, adolescents and younger people can be expected to have negative effects. For example, the requirement that pupils wear masks throughout the entire school day is problematic. So does the extended N95 mask-wearing by pregnant women. With reliable measurements the experimentally determined CO_2 concentrations in the inhaled air under masks can reach – depending on exposure time – values of 0.42 up to 3.52 Vol% (Table 1) [18-20,23-25,27]. One has to remember, that in those experiments the time measured wearing a mask ranged from 1 minute to several minutes with a maximum of 60 minutes in a few studies, which is not always representative for real-world settings.

For pregnant women there is a metabolic need for a fetal-maternal CO_2 gradient. The mother's blood carbon dioxide level should always be lower than that of the unborn child. This is necessary to ensure the diffusion of CO_2 from the fetal blood into the maternal circulation via the placenta. Therefore, the hypercapnic gas shifts promoted by masks could, even with subliminal carbon dioxide increases, act as an interference variable of the fetal-maternal CO_2 gradient and increasing over time of exposure [11]. Thus, even if compensatory mechanisms are active, an additional risk for pregnant women and their unborn children must be considered. A study in 22 pregnant women shows that wearing N95-masks during 20 min of exercise leads to significantly higher percutaneous CO_2 values with average $PtcCO_2$ values of 33.3 mmHg compared to 31.3 mmHg without masks ($p = 0.04$) [37]. Another comparative study on pregnant women wearing N95 mask shows increased levels of CO_2 in expired air [38]. These results measuring the accumulation of CO_2 in the mother´s blood give evidence that a mask can lead to significant changes in the blood gas hemostasis of pregnant women (Table 2) despite the compensatory mechanisms [28,50] caused by the increased inhaled carbon dioxide. It is well-known from many disciplines that the toxicity of a pollutant depends on the one hand on the concentration and on the other on the duration of exposure. The frequency of exposure and time are of toxicological importance and there is the notion, that time is a variable equivalent to dose in toxicology [52,53]. According to Rozman, risk projecting should include time as a variable (including toxicokinetic, toxicodynamic, exposure frequency/duration). Adding time to dose as an independent variable in toxicology allows a risk assessment in which a single acute dose would represent the liminal case when the dose rate equals the dose. Consequently, a single high dose exposure will not be much different from exposure to proportionally smaller daily dose rates [52,53].
Additionally, one has to consider the special susceptibility of early life conceptual tissues with less well developed protective/conjugative pathways [14].

However, taking into account the above facts of increased carbon dioxide rebreathing under masks with values ranging from 0.22 to 3.52 vol% CO2 and in the majority of studies with values above 1% [18,19,21-25,27] including Table 1, it is clear even to laymen that carbon dioxide rebreathing, especially when using N95 masks, is above the 0. 8% CO2 limit set by the US Navy to reduce the risk of stillbirths and birth defects on submarines with female personnel who may be pregnant [58,59,60] (Table 3). One has to keep in mind that US Navy female submarine officers are of very high mental and physical fitness, incomparable to the level of physical health of pregnant women in the broad population. Nowadays all over the world masked pregnant women (especially those using N95 masks) are potentially exposed to carbon dioxide re-breathing levels that are prohibited by US Navy for female submarine officers because of the risk of stillbirth and birth defects. Analysis of online available data on mask mandates [98] show, according to our calculations, that most countries (150 out of 194) worldwide had a masking requirement (77.3%) roughly corresponding to 4 496 149 755 people worldwide accounting for 58% of the world population.

So one has to ask: May there be a link between an increased mask-related (pandemic) global carbon dioxide re-breathing since 2020 and the current reported rise in stillbirths worldwide [99] of disturbing 28%? In a prospective registry of 263 infants of 179 infected mothers the authors found no evidence that a SARS-CoV-2 infection is associated with significant higher risk of damage to unborn life [100]. However, current data on the new Delta variant, imply a possible slightly higher risk of stillbirths (prepandemic stillbirth rate of 0.59% versus 0.98% in COVID-19–affected deliveries and 2.70% during the Delta period), but the evaluation was not able to separate SARS-CoV2 exposure from higher mask exposure in those women [101]. Interestingly, recent data from Australia shows that

lockdown restrictions and other measures (including masks that have been mandatory in Australia), in the absence of high rates of COVID-19 disease, were associated with
a significant increase in preterm stillbirths [102]. May there be also a link between the pandemic driven excessive mask-use and the fact that 42% of female USA surgeons surveyed between November 2020 and February 2021 [103] lost a pregnancy according to a recent study? During a pandemic, surgeons are likely to have the heaviest mask exposure compared to the general population. Data from Italy show with statistical significance three-fold increase in stillbirths in the general population during lockdown period (March-April-May) 2020 compared to the same period in 2019 [104]. A recent rapid review and meta-analysis gives clues about the severity of the indirect influence of COVID-19 lockdown implementations [105]. The authors found that lockdown measures were associated with a significant risk of stillbirth with RR=1.33 (95% CI 1.04, 1.69) when compared to before lockdown period [105]. It is well known that lockdown measures include mask mandates as well [2].

Among the few countries that do not require the wearing of masks in public is Sweden. Interestingly, despite similar pandemic measures and SARS-CoV2 presence in the media and in the real world, no increased risk of stillbirths was observed in Sweden. A Swedish nationwide study „did not find any associations between being born during a period when many public health interventions aimed at mitigating the spread of COVID-19 were enforced and the risk for any of the preterm birth categories or stillbirth (adjusted OR 0.78, CI 0.57 to 1.06)“[106]. Although society was not completely closed, Swedish authorities enforced many policies to mitigate the spread of COVID-19, such as promotion of general hygiene measures and social distancing (including remote working), ban of nonessential travel, prohibition of gatherings of more than 50 people and the closure of upper secondary schools and universities [106].

A look at Table 3 shows that the results of the FDA (1979) [58] and Howard experiments (2012) [59,60] on toxic CO_2 levels may explain the increase in the incidence of stillbirths found in the above studies. Moreover, wearing N95 masks that are linked to a higher carbon dioxide re-breathing (Table 2) [31,32,41] is significantly more associated with higher gestational age than surgical masks [107].

Interestingly, a recent publication realised a large on-going longitudinal study of child neurodevelopment in Rhode Island, an USA state with mask mandates, examining general childhood cognitive scores in 2020 and 2021 vs. the preceding decade, 2011-2019 [108]. The scientists found that children born during the pandemic have significantly reduced verbal, motor, and overall cognitive performance compared to children born pre-pandemic with consistent and significant reductions ($p<0.001$) showing lower cognitive skills [108]. Could there be a connection between the increased use of N95 masks by pregnant women [107], higher carbon dioxide re-breathing levels (Tables 1&2) [18-25,27,31,32,41] and the results [108] of this recent study? Fresh outdoor air has around 0.04% carbon dioxide [15,16] and the level of re-breathed CO_2 under masks can rise to levels far higher than 1% as mentioned above [18,19,21-25,27], especially when masks are worn in closed buildings additionally worsening the sick building syndrome [15,16]. A look at Tables 1 and 3 shows that the results of the Kiray 2014 [77] experiments could be an explanation of these findings due to the fact that most human studies prove CO_2 exposition of higher than 0.3% while using a face mask. After low-level exposure of 0.3% CO_2 to the pregnant dams, Kiray was able to detect neuron destruction in prefrontal cortex and hippocampus, decreased IGF-1 levels, increased anxiety and impaired memory and learning after birth [77] of the offspring.

The problem of prolonged mask use in children and in schools needs to be discussed as well. One has to consider that children are not just small adults. This means that exposure criteria should be based on information relevant to predicting risks to children and should account for such toxicokinetic differences occurring with development [14]. It is necessary to evaluate the psychological and neurological effects when masks are compulsory at school [15,16, 18-25,27,76]. A statement was made in a recent scoping review on masks that “the long-term sociological, psychological and educational consequences of a comprehensive masking requirement extended to schools are unpredictable with regard to the psychological and physical development of healthy children “[11]. In this psychological, neurological and pediatric context it is crucial to discuss the toxicological impact of prolonged mask wearing and the concomitant elevation in re-breathed carbon dioxide (Tables 1, 2 and 3). Regarding the experimentally measured CO_2 concentrations in the inhaled air under masks from Table 1 with values ranging from 0.22% to 3.52% being mostly above 0.3% [18-27], the results from Table 3 [81,95] are remarkable. In 2014 Uysal could demonstrate with his experiments that a mere 0.3 % CO_2 exposure to

adolescent brain neurons can cause destruction in the gyrus dentatus and the prefrontal cortex with decreased IGF-1 levels resulting in less activity, increased anxiety and impaired learning and memory [81]. Already in 1972 Vandemark revealed – only after a 4-hour low level CO_2 exposure – a carbon dioxide dependent destruction of spermatid and Sertoli cells in testes, streaking & vacuolization of the tubular components with no maturation of spermatids [95]. Calculated with a human safety factor [59,60,96], the carbon dioxide content of the inhaled air should be at least below 0.5% CO_2 for a 4-h exposure to avoid these adverse effects on testicular tissue. According to data from Table 1, when wearing masks – for example in schools– this seems difficult to achieve in many cases [18-25,27] especially when room air (in crowded classrooms) already has an increased CO_2 content [15,16,76].

Altogether, there is disturbing experimental evidence for a possible negative impact risk on the mental and reproductive health of children, adolescents and pregnant women due to chronic carbon dioxide re-breathing since the introduction of mask mandates (Table 1 and Table 3). Indeed, masks (being a medical device) for general and long term use in the populace should be evaluated more thoroughly according to the German Medical Devices Act (Medizin-Produkte-Gesetz), the European MDR (Medical Device Regulation) and the FDA [17,109,110].

In summary, benefits and risks of masks have to be assessed according to the WHO especially for children, pregnant women, the elderly and the ill [11,111]. Therefore, the justification of the mask mandate for the general public must be critically and scientifically questioned.

On the one hand there is no clear high-quality empirical data providing moderate or strong evidence that mask use in the general population could have a relevant impact on SARS-CoV2 virus transmission rates [3-8,10]. An overview of systematic reviews on mask use against airborne virus diseases [8] did find only one high quality study [7]. Moreover, they concluded that „wearing a mask may make little to no difference".

On the other hand, empirically, the assumption that asymptomatic persons are significant virus spreaders cannot be supported [112,113] and systematic reviews do not provide moderate or strong evidence for the asymptomatic as significant spreaders [114-116]. Thus, if asymptomatic people are not the focus of infection according to these findings a mask for the asymptomatic must be questioned. Even if the mask were to work its widespread use should be questioned because of the lack of literature clearly demonstrating the infectiousness of symptomless SARS-CoV2 infected individuals [113]. Therefore, the argumentation to make a mask mandatory in places where symptomatic individuals are excluded (tests, admission control, restrictions etc.) in order to contain SARS-CoV2 spreading cannot be substantiated [112,113].

In addition, the infectivity [117] and average lethality risk of SARS-CoV-2 ranging from 0.1 to 0.14% must be considered when recommending universal mask use [118,119]. This figure is far lower for children and fertile young women [120]. In a recent study, no healthy children between 5 and 18 years of age were found to have died from COVID [121].

Indeed, if the potential adverse effects and possible long-term consequences of masks [11] are taken into account (Table 3) even greater doubts arise regarding masks as a defensible, effective and harmless means of combating SARS-CoV2 in widespread use, especially regarding our referenced data with possible deleterious effects for children, adolescents and pregnant women [18-25,27,58-60,77,81,95]. The background of the political decisions on far-reaching mandatory mask use is difficult to understand scientifically [120]. According to the medical principle of "primum nihil nocere" (at first do not harm) and in view of the presented findings, the mask would have to be scientifically re-evaluated as a SARS-CoV2 pandemic control. The credo of all those involved in the containment of the crisis, including politicians, should be to prevent the damage caused by precautionary or therapeutic measures at all costs so as not to exceed the damage caused by the disease. When it comes to medical decision-making in a sick person, the assessment of therapeutic measures for the benefit of the patient against the side effects of the therapy is to be evaluated differently than a prophylactic procedure in healthy people. If wrong decisions are made in the selection of preventive measures in healthy people or if they are improperly applied, the consequences are usually much more severe and liability claims are often unavoidable. In view of the possible toxicological mask effects of re-breathed carbon dioxide in pregnant women, children and adolescents, and in view of the limited scientific evidence for masks as an effective pandemic measure, there is need to re-evaluate and rethink mask mandates especially for these vulnerable subgroups.

5. Conclusions

It is widely believed that the use of masks - including in the general population - could be an important measure to combat SARS-CoV2 [2] and a huge number of publications on this topic cannot be overlooked. However, elevated blood carbon dioxide levels are an important cornerstone of the so called Mask-Induced Exhaustion Syndrome (MIES) (Table 2) [11]. A significant rise in carbon dioxide occurring while wearing a mask is scientifically proven in many studies [11,18-25,27,30-44], especially for N95-masks (Table 2) [20,23-25,27,30-33,35,37-39,41,43,44], due to their higher deadspace and breathing resistance [11].

Fresh air has around 0.04% CO_2 while masks bear a possible chronic exposure to low level carbon dioxide of 0.42 to 3.52% in laboratory test suites [20,23], of 1% to 3.05% in modeling studies [21,22] and reliable human measurements even yield values of 1.41 to 3.2% CO_2 of the inhaled air (Table 1) [18,19,24,25,27].

Animal experimental data shows deleterious proven effects of elevated CO_2 of inhaled air in the long term with threshold values of above 0.3%, 0.5% and 0.8% (Table 3) [58-60,68,77,81,95]. The risk for children's mental development starts at levels of above 0.3% [77,81], to adolescent male sexual development at levels of above 0.5% [95], as well as to unborn life at levels of above 0.8 % [58-60] resulting in reduced cognitive performance, reduced fertility and stillbirths (Table 3).

There is circumstantial evidence that popular mask use may be related to current observations of a significant rise of 28% to 33% in stillbirths worldwide and a reduced verbal, motor and overall cognitive performance of two full standard deviations in scores in children born during the pandemic [99,102-105,108]. Assuming that time is a toxicological variable equivalent to dose [52,53] long term everyday mask use cannot be claimed as harmless, as exposure to smaller daily doses will not be much different from exposure to a single high dose. Instead of worrying only about the potential risks of a future harmful long-term CO_2 increase in the atmosphere with impact on human health [76,122,123], the focus of research should also be on the current mask-related CO_2 increase in breathing air (Table 1) with its numerous effects. In this article we only focused on CO_2, however, other noxious agents in the masks contribute to toxicological long term effects like the inhalation of synthetic microfibers, carcinogenic compounds and volatile organic compounds could also play a role [124,125].

It must be remembered that the increased carbon dioxide content of the breathing air behind the mask may also lead to a displacement of oxygen. In this case, in addition to hypercapnia, hypoxia could also have an effect, which would certainly be very important for the teratogenetic aspects (e.g. spinal malformations due to hypoxia) [126]. The fact that in this context (toxic effect of carbon dioxide versus hypoxia) no sharp distinction is made it can lead up to the mixing of sequelae, which was mentioned by Hubert Meesen [127].

The general extended masking requirement, especially for children and pregnant women [14], is a measure that has not been thoroughly tested and studied. According to the literature found, masks bear some toxicological unpredictable risks with respect to carbon dioxide [11,18-25,27]. Unfortunately, wearing of N95 masks, that are linked to a higher carbon dioxide re-breathing (Table 1&2) [32,32,41] has a considerable association with an advanced gestational week than surgical masks [107].

Consequently, it should be the task of governments in conjunction with their responsible health authorities to perform an appropriate benefit risk assessment of the mandatory use of masks in each country. This is the fundamental basis of all approvals for chemicals, medical devices and drugs aimed to protect humans, animals and the environment.

Reliable studies on possible carbon dioxide re-breathing while wearing a mask in real-world scenarios are necessary to exclude possible damaging effects [99,102-105,108]. Therefore, health authorities should organise and perform further toxicological studies focusing on masks in specific user groups according to Good-Clinical-Practice and Good-Laboratory-Practice.

So far, such mandatory activities by governments and health authorities are not visible globally. Regarding the referenced literature, low level CO_2 exposure can be related to mask use. Keeping in mind the weak antiviral mask efficacy, the current behavior of the media, science and politics vehemently forcing mask mandate even for the vulnerable subgroups appears highly unethical and not in line with the obligation in particular to protect born or unborn children from potential harmful influences [14]. The actual – so called „ preventive “– proceeding concerning mask obligations in many countries around the world and especially in schools is not in line with the Helsinki Declaration [128], the Lisbon Declaration [129] and the Nuremberg Code [130].

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