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Review

The role of carbon monoxide in aerotoxic syndrome

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ABSTRACT

Chronic low-level exposure to toxic compounds in airplane cabin air may result in Aerotoxic Syndrome (AS). Aetiologic agents are organophosphates and numerous volatile organic hydrocarbons originating from leaks of engine oil and hydraulic fluids. Despite a documented history spanning decades, the role of carbon monoxide remains controversial. What evidence exists that carbon monoxide (CO), present in the cocktail of toxic compounds in bleed air, contributes to the AS?

We selected 22 publications encompassing 888 flights with 18 different aircraft types. In one study of 100 flights, fume events were confirmed in 38. Four studies were initialized after air quality incidents. The cabin CO concentrations could be categorized in three levels, 1) low (<5 ppm), without health implications, 2) moderate (5–10 ppm) with probably health implications in case of chronic exposure, and 3) high > 10 ppm, with health effects in case of acute and chronic exposure. These levels were recorded in 12, 6 and 4 studies respectively. In the six studies in category 2, max CO concentrations ranged from 5.8–9.4 ppm. The four studies with CO > 10 ppm comprised 376 of the 888 flights (42%) with six aircraft types. Toxic CO levels ranging between 13–60 ppm were identified in at least 129 of 888 (14.5%) flights. In one study with high CO levels four flight attendants were diagnosed with CO poisoning with elevated HbCO levels.

Max CO levels in aviation are either the same or higher than current occupational exposure limits (OEL) for ground-based workplace exposures or levels for urban street transport environments. Specific aspects of aviation should be taken into consideration: the effect of low(er) air pressure at high altitudes increasing the toxicity of CO, and the binding of CO to CYP enzymes, leading to impaired organophosphate detoxification.

We conclude that CO must be considered an important factor in the lubrication derived cocktail of airborne toxic compounds causing AS. In line with the WHO advice, a reduction of the OEL to 5 ppm over 8 hr time weighted average (TWA) for aircrew is strongly recommended. And we advocate continuous monitoring during all phases of flight and installation of CO detectors in the air supply ducts to the aircraft cabin.

1. Introduction

Over the last two decades several case studies and health surveys have been published describing adverse health effects reported by aircrew and passengers. Since these were thought to be related to exposure to contaminated air (Michaelis et al., 2017; Hageman et al., 2020a), the term Aerotoxic Syndrome (AS) has been proposed (Balouet and Winder, 1999). Symptoms frequently reported by aircrew include ENT- and airway-irritation, nausea, headaches, dizziness, palpitations, fatigue and cognitive impairment. Occasionally aircrew, including pilots, have been completely incapacitated by fumes and were forced to perform emergency landings (Burdon et al., 2023). Once exposure stops often resolution of symptoms is reported. In case of repeated exposure, it takes longer for aircrew to recover (Mackenzie Ross, 2008). Diagnostic criteria for AS include 1) all symptoms mentioned above. These symptoms have to correlate with flying hours and improve after cessation of flying, and reoccur only after flying, 2) objective evidence of exposure derived from air incident reports or engineering records. Or evidence arising from medical tests consistent with nervous system injury (brain MRI, elevated neuronal auto antibodies) (Reneman et al., 2016; Abou-Donia et al., 2013). Finally 3) other causes of ill health should be excluded, which also means a neuropsychological investigation excluding a depressive or somatisation disorder (Hageman et al., 2020b; Hageman et al., 2020a).

Cabin air on most commercial aircraft is supplied from the engines or auxiliary power unit (APU). The APU is a smaller gas-turbine powered

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unit delivering rotating shaft power and compressor air during ground operations. All modern commercial aircrafts, except for the Boeing 787 Dreamliner, are designed to "bleed" (extract) air compressed within the engine or APU for ventilation. Outside air is heated and pressurised to a breathable level before being 'bled off' and pumped into the aircraft (see Fig. 1). Since this bleed air is not filtered AS may develop as a result of toxic compounds from engine oil and hydraulic fluids leaking past "wet engine seals" (Megson et al., 2016). The use of oil-bearing seals reliant on pressurized air enables small leakages of synthetic engine oils to the compressor, in case of 1) transient power changes, 2) overfilling of oil reservoirs or 3) failure of bearings or seals. So "fume events" can occur at low level leakage during normal operations or in failure scenarios, resulting in acute high-level exposures (Hageman et al., 2022; Burdon et al., 2023). A fume event is defined as an incident involving either engine oil or hydraulic fluid contamination in the aircraft ventilation supply air, that may impair the health of the passengers and aircrew (Anderson, 2021; CEN (Comite Europeen de Normalisation), 2022). The contaminated ventilation air may contain organophosphates, volatile organic compounds and black carbon (Chen et al., 2021; Gerber et al., 2023; Hayes et al., 2021). Aircraft engine oils and hydraulic fluids contain various additives to enhance lubrication, anti-corrosion, flame retardant and pressure-transferring properties (Gerber et al., 2023). Tricresylphosphate (TCP), an antiwear additive, has long been regarded as the primary contaminant of interest (Schindler et al., 2013; de Ree et al., 2014; de Boer et al., 2015). Air quality monitoring studies have concluded that levels of (individual) inhaled chemicals, even on a chronic basis, were too low to cause adverse effects (Chen et al., 2021; Crump et al., 2011; Solbu et al., 2011; Houtzager et al., 2013, 2021; Schuchardt et al., 2017, 2019; Shehadi et al., 2019). In these studies, not only TCP, but various organophosphates, and (semi) volatile organic compounds were measured and were lower than permissible levels of air quality standards and guidelines for aircraft cabins (Chen et al., 2021). Additional sources of contamination of cabin air may be kerosene fumes emitted during taxiing or (waiting for) take-off, de-icing products (ethylene glycol, propylene glycol), insecticides, and polybrominated phenylesters (flame retardants) (Chen et al., 2021; Hageman et al., 2022).

Concerns about aircrew exposure to carbon monoxide (CO), a byproduct of incomplete hydrocarbon combustion, have been raised for many years (Armstrong, 1939; Howlett and Shepard, 1973; van Netten, 2005). Subjected to high engine temperatures above 300 °C, lubricating and hydraulic oil generate several degradation products including CO, which may enter cabin air. It is well known that small, piston-powered aircraft (Cessna, Piper) have the highest risk of CO distribution in the cabin during flight, due to cracks or insufficiently fitting components in the exhaust system (Salazar, 2005). The contribution of CO intoxications to fatal accidents in piston-powered aircraft is not negligible and is estimated at 0.5–2% (Zelnick et al., 2002). In large jet and turboprop aircraft, for a long time CO concentrations have not been considered a risk to flight crew, assumably based on relatively low concentrations. Indeed, in many studies, CO concentrations in aircraft cabin air are below those associated with health effects. However, existing data rarely reflect concentrations during a fume event. And CO is just one compound of a complex mixture which can include other (additive) asphyxiants such as hexane and phenyl-naphthylamine (PAN) (Chen et al., 2021; Winder and Balouet, 2002). For instance, PAN can also displace oxygen from hemoglobin, forming methemoglobin, contributing to hypoxemia (Skold et al., 2011; WHO, 1998; Iolascon et al., 2021). Furthermore, the effects of chronic low-level CO exposure are not well-defined.

The most common symptoms following *acute* exposure to CO are headache, nausea, vomiting, vertigo, alteration in consciousness and subjective weakness. The cherry-red discoloration of the skin and cyanosis described in classical publications is rarely observed (Prockop, 2005). This only appears in case of a lethal carboxyhemoglobin (COHb)-level outshining the darker red of oxy-Hb (Hampson et al., 2012). Symptoms of severe poisoning include confusion, myocardial infarction, seizures, coma and death. In acute CO intoxication, CO diffuses rapidly across the alveolar capillary membrane and binds tightly to iron centers in hemoglobin (Piantadosi, 2002). The affinity of CO for hemoglobin is 250 times greater than that of oxygen. As the concentration COHb in blood increases, the body attempts to compensate for a lower oxygen level by increasing the respiration rate. Overt signs of toxic effects usually appear at COHb levels of 15–20% (Piantadosi, 2002; Chaturvedi, 2010). COHb decreases the blood oxygen content leading to tissue hypoxia, especially for organs with high oxygen demands such as the brain and the heart. Neurotoxicity is not only the direct effect of hypoxia, but also the consequence of arterial hypotension, and disruption of mitochondrial function, mediated by cytochrome C oxidase (Townsend and Maynard, 2002; Rutchik and Ratner, 2022). CO also binds to intracellular myoglobin in the myocardium. In addition, a secondary inflammatory response is initiated during reperfusion (after the event), when oxygen levels increase in hypoxic tissues. This leads to free radical release and may cause longer lasting symptoms (Townsend and Maynard, 2002).

The European Food Safety Authority (EFSA) defines *chronic* exposure as a long-term constant or intermittent exposure to a substance which may have an impact on health over time (EFSA, 2023). CO intoxication is defined as chronic in case of repeated exposure to relatively low concentrations (Wright, 2002). In chronic exposure, individuals may experience both short periods of mild acute CO intoxication and long-term effects of low-level exposure. This may occur during a long-haul flight, or during successive flights. Mild CO intoxication can be associated with minor neurological sequelae such as dizziness and headache, or concentration difficulty and confusion (Annane et al., 2001; Ely et al., 1995). Most studies have found that more severe neuropsychological sequelae are confined largely to those who have loss of consciousness at some stage (Rutchik and Ratner, 2022). Concentration

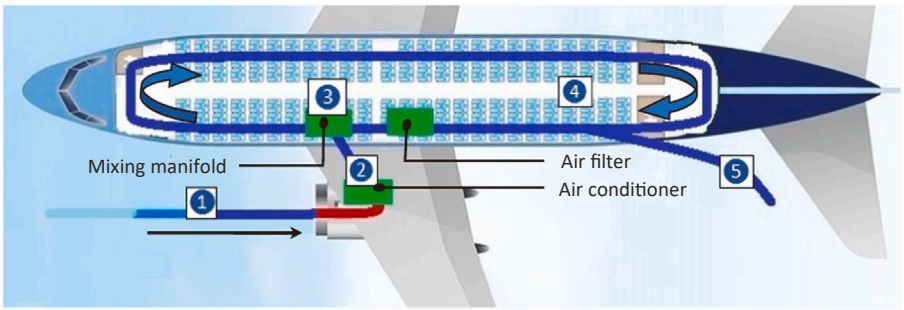

Fig. 1. bleed air. 1. Air enters the compressor stage of the aircraft's jet engine, where it becomes very hot as it is pressurized. 2. The hot, compressed air then passes to air conditioning units where it is cooled. 3. The outside air is passed to the mixing manifold, where it is mixed 50/50 with recirculated cabin air that has been cleaned with high-efficiency filters. 4. Air from the mixing manifold is supplied to the cabin on a continuous basis from the overhead outlets. 5. As outside air enters the aircraft, an equal amount of air is discharged. The air in the entire cabin is replaced every two to three minutes.

and memory deficits have been found though in patients after chronic low to moderate level CO exposure without a history of loss of consciousness (Ryan, 1990). In a case series, seven patients with chronic low-level CO exposure (1–18 months) presented with memory loss, dizzy spells, tremor, alterations in sleep pattern, headache and emotional lability. Neuropsychological testing showed motor slowing and memory problems (Myers et al., 1998). Symptoms from chronic low level CO exposure cannot be explained by phenomena during acute exposure; hypoxia, hypoxemia and measured COHb are quickly compensated by various physiological mechanisms. Rather chronic effects are caused by non-hypoxic, cellular mechanisms, including binding to intracellular proteins, nitric oxide (NO) generation and lipid peroxidation (Hampson et al., 2012; Rutchik and Ratner, 2022; Weaver, 2009). Since COHb level only reflects initial CO uptake, a better measure for chronic intoxication is recommended: the product [CO concentration] x [duration of exposure] (Weaver, 2009; WHO, 2021).

There are several exposure standards for CO, of which three are specific for aviation: the American National Standards Institute (ANSI) - the American Society of Heating, Refrigerating and Air-conditioning Engineers (ASHRAE) "ANSI/ASHRAE cabin air standard", the Federal Aviation Administration (FAA) operating standard 14CFR121.219, and the Russian Aviation Medicine agency standard, see Table 1 (WHO, 2021; FAA, 1965; ANSI-ASHRAE, 2018; Gilinskiy et al., 1963; SAE, 2018; NIOSH, 2007; ACGIH, 2021a, 2021b; US Environmental Protection Agency, 2000; ASHRAE, 2016; European Union, 2022). The FAA regulation was introduced in 1965, and allows a peak CO concentration of 50 ppm on aircraft in operation (FAA, 1965). In contrast the ANSI/ASHRAE is a recent standard, defining a trigger point to record and display CO data in the flight deck: an exceedance of either 10 min TWA at or above 9 ppm or a 60-second peak at or above 50 ppm (ANSI-ASHRAE, 2018). The Aviation Medicine agency in Russia stated that CO levels in pressurized passenger aircraft may not exceed 8.7 ppm, based on an old study of low concentrations of carbon monoxide-exposure of aircrew. This peak CO concentration of 8.7 ppm was recommended after in-flight tests of 347 air samples and observations of 185 aircrew and passengers in 30 flights (Gilinskiy et al., 1963). The Society of Automotive Engineers (SAE) stated in 2018 that a CO concentration above 2.3 ppm in cabin air could indicate an underlying source of either external or internal contamination (SAE, 2018). For chronic ambient exposure in ground-based environments, the World Health Organization (WHO) advocates an even stricter guideline, recommending that the TWA does not exceed 4–5 ppm over 24 h (WHO, 2021).

However, pilots operating a BAe 146 and monitoring CO during flight reported levels of 60 ppm at the top of climb (van Netten, 2005). And a 2021-review of 378 flights on various types of aircraft demonstrated that the maximum measured cabin CO levels were higher than the permissible levels for 15 min exposure (Chen et al., 2021). Emergency diversion of commercial airline jets, with symptomatic crew members (and passengers) because of CO intoxication has been well documented, and increased COHb levels are incidentally reported (Long and Flaherty, 2017; Michaelis et al., 2017). The toxicological assessment of fatal aircraft accidents that occurred in the United Kingdom in the eighties (commercial, private and military aircraft) found COHb concentrations above 10% in 90 of 439 (20%) fatalities evaluated. In more than half of these cases COHb concentrations even exceeded 20%, which could not be attributed to post-crash fires (Hill, 1986). Toxicological findings of aircrew in military aircraft showed that COHb levels may rise to 40% in extreme cases (Klette et al., 1992). CO concentrations in US army helicopters following firing certain weapons rose as high as 1000 ppm (Howlett and Shepard, 1973). High CO-levels in cabin-air were also measured during the waiting phase for take-off, with open cabin doors, due to intrusion of ground level emissions and high airport CO levels (UKHSA, 2022; Long and Flaherty, 2017). Measurements at Toronto International airport have shown CO concentrations as high as 150 ppm, representing an external source of CO, drawn into the cabin (Nagda et al., 1992).

Table 1
CO air quality standards.

Aviation-specific standards				
Institute/Organisation	ppm	mg/m^3	Time weighted average	References, year
US Federal Aviation Administration (FAA)	50	58.1	Operating standard for ventilation supply air on aircraft	FAA (1965) (14CFR121.219)
American National Standards Institute (ANSI)-ASHRAE standard 161-2018	9 9 50	10.5 10.5 58.1	CO concentration trigger point to record and display CO data in flight deck. 10 min twa 60 s peak	ANSI-ASHRAE, 2018, section 7.2
Aviation Medicine Agency, Russia	8.7	10.1	Peak CO limit	Gilinskiy et al. (1963)
Society of Automotive Engineers (SAE)	2.3	3.2	CO in bleed air above this concentration: indication of ext. or int. contamination	SAE Aerospace report (2018)
General ground-workplace/ environmental standards				
World Health Organisation (WHO)	85.8 51.5 30 9 4-5	100 60 35 10.5 4.6-5.8	For 15 min For 30 min For 1 h For 8 h For 24 h (chronic exposure)	WHO (2021)
National Institute for Occupational Safety and Health (NIOSH)	200 35	233 40.8	Peak value, not to be exceeded during a 15 min period. For 10 h	NIOSH (2007)
American Conference of Governmental Industrial Hygienists (ACGIH)	25	29.1	For 8 h	ACGIH (2021a, 2021b)
US Environmental Protection Agency (USEPA)	9	10.5	For ambient air	USEPA (2000)
American Society of Heating, Refrigerating and Air-conditioning Engineers (ASHRAE)	35 15 9	40.8 17.5 10.5	For outside air, 1 h twa For inside air For 8 h (building standard)	ASHRAE Standard, 62.1.2016
EU-OEL	20 100	23 117	For 8 h For 15 min	European Union (2022)

In this paper we review the available evidence that CO, as one of the components of the bleed air toxic cocktail, contributes to the AS. We review the identified publications measuring CO levels in cabin air of non-smoking flights. We discuss the relation between CO levels and altitude hypoxia, the effects of long-term, low dose CO exposure and the interrelationship between CO, PAN and OPs in cabin-air, since CO appears to impair OP detoxification, increasing the combined toxicity (Ramsden, 2021), and PAN may be additive to CO in causing hypoxia (Skold et al., 2011; WHO, 1998; Iolascon et al., 2021).

2. Methods

A literature search in MEDLINE via PubMed, and Science Direct was conducted to find the published in-flight measurement studies of cabin air quality or airborne pollutants (volatile and low-volatile organic compounds), that included measurements of carbon monoxide in

aircraft bleed air, published from 1990 to September 1, 2023. The 1990 limit was used because until that year most studies included only smoking flights.

As search terms were used: Carbon monoxide, cabin air, pilots, flight attendants, aircrew, cabin crew, bleed air, fume event, OPs, combustion, and aircraft. Studies (1990–2000) describing both smoking and non-smoking flights were only included if results of non-smoking flights were separately described. We only included large commercial passenger jet aircraft. We collected data on aircraft type, number of flights, method of measurement equipment and sampling design/location. We excluded recreational, military, and agricultural aircraft engaged in aerial application, and air medical transport aircraft. We also excluded experimental bleed-air simulation studies. We finally selected 22 studies, i.e., nine peer-reviewed papers, four health hazard evaluation reports from occupational safety and health organizations, three from the American Society of Heating, Refrigerating and Air-conditioning Engineers (ASHREA, 2016), one aviation accident report, one databank from the Global Cabin Air Quality Executive (GCAQE), two studies from the European Aviation Safety Agency (EASA) and the European Commission, and two abstracts. So, a considerable amount of data on cabin air quality are presented in technical reports of environmental forensic investigations, regulatory agencies, aviation authorities, aircraft manufacturers or occupational safety and health organizations (Balouet et al., 2023). We included these non-peer-reviewed data in our review; as a result, 13 of the reviewed 22 papers may contain methodological imperfections.

3. Results

The selected 22 studies included 888 flights, with 18 different aircraft types, see Table 2. Fume events were confirmed in 38 of 100 flights in one study (Crump et al., 2011). In another study a "smell event" was recorded (Rosenberger, 2018). Four studies were initialized after air quality incidents. This resulted in detection of leaks of seals in engine bearings in one study (van Netten, 1998). In addition, in three studies, aerosol sensors detected peaks in concentrations of nanoparticles, suggestive of oil leaks (Spengler et al., 2012; Schuchardt et al., 2017; Lordo et al., 2023). In the remaining studies, CO sampling has not been performed under fume event conditions. Measurement periods during flight varied from 5 min bleed air to whole-flight continuously. In one study ten sampling points were defined for each sector at various phases of flight (Crump et al., 2011). Sampling location was in the cabin, or both in cockpit and cabin. In two studies CO measurements were only performed above 3000 m, from 3000 m ascent to 3000 m descent (Spengler et al., 2012; Lordo et al., 2023). The lower detection limit of the CO electrochemical sensor in the reviewed studies varied from 0.1–2 ppm. Most of the reviewed studies were air quality studies.

To structure this review and based on health risk considerations we defined three categories of cabin/cockpit CO levels: 1) low (<5 ppm), without health implications, 2) moderate (5–10 ppm) with probably health implications in case of chronic exposure, and 3) high (> 10 ppm), with health effects in case of acute or chronic exposure. In 12 of 22 studies CO was detected at low levels (Schuchardt et al., 2017; Houtzager et al., 2021; Yu et al., 2021; O'Donnell et al., 1991; van Netten, 1998; Dumyahn et al., 2000; Honeywell, 2000; Spicer et al., 2004; MacGregor et al., 2008; Spengler et al., 2012; Rosenberger, 2018; Lordo et al., 2023). In another 6 studies moderate CO concentrations were measured (5.8–9.4 ppm), leading to health effects in case of chronic exposure (Crump et al., 2011; Pierce et al., 1999; Lee et al., 2000; Nagda et al., 2001; Waters et al., 2002; Ross et al., 2003). Four studies identified flights with high CO-levels (13–60 ppm) (Sussell et al., 1993; van Netten, 2005; GCAQE, 2006; NIOSH, 2006). On a total of 381 monitored flights in category 3, this concerned 129 flights (34%), in six aircraft types, mainly BAe. In total, toxic CO peak levels ranging between 13–60 ppm were identified in at least 129 of 888 (14.5%) flights. Five studies included a health questionnaire for passengers and aircrew. In one study, reported complaints were associated with max CO levels > 10 ppm, resulting in elevated HbCO levels in four flight attendants (Sussell et al., 1993). In the remaining four studies with health questionnaires, CO levels were low (Pierce et al., 1999; Lee et al., 2000; Spicer et al., 2004; Lordo et al., 2023).

Duration of peaks varied from 20–30 min in most studies (Crump et al., 2011; Ross et al., 2003; NIOSH, 2006), with "short-term peaks" in one study (Sussell et al., 1993). The four studies with high CO levels (cat. 3) were performed in the period 1993–2006. Although more recent studies show max CO levels < 5 ppm (Schuchardt et al., 2017; Houtzager et al., 2021; Yu et al., 2021; Rosenberger, 2018; Lordo et al., 2023), a 2017-survey still described four symptomatic cabin crew after a fume event, with COHb levels "at or above the high normal range" (Michaelis et al., 2017). Oil prices, fuel costs have driven investment in more efficient aircraft models, with low-emission combustors developed by manufacturers. These efforts have resulted in a steady decline of emission indexes over the years (Masiol and Harrison, 2014). However, there may be other reasons why these more recent studies do not show high CO levels: measurements were performed from 3000 m ascent to 3000 m descent, with no engine power setting changes in this period (Spengler et al., 2012; Lordo et al., 2023), sampling was performed during non-event conditions in the majority of studies, or CO levels were averaged over a sampling period, possibly concealing high level transient peaks (Waters et al., 2002). During ground operations CO in the exhaust gases of surrounding ground servicing vehicles or taxing aircraft may pollute the cabin air. However, CO-peaks in the waiting phase were < 6 ppm (Yu et al., 2021; Ross et al., 2003). During cruise, CO levels are low or very low in most studies. CO production varies greatly with aircraft thrust level, fuel consumption and engine temperature, factors influenced by speed and altitude. CO rate amounts to 8.8% of exhaust gases during takeoff, but falls to 3% when cruising (Howlett and Shepard, 1973). CO concentrations may build up to a (relatively) higher level after aircraft landed on the destination airports (Nagda et al., 1992; Yu et al., 2021; Ross et al., 2003]. The effect of aircraft engine age was studied in four studies [Schuchardt et al., 2017; Yu et al., 2021; Spicer et al., 2004; Rosenberger, 2018), with higher CO levels in older aircraft in one study (Yu et al., 2021). CO concentrations in bleedless B787 aircraft were lower than those of bleed air aircraft (Schuchardt et al., 2017).

4. Discussion

Leaks of engine oil or hydraulic fluid (and degradation products thereof) may lead to contaminated cabin air. More than three hundred toxic chemicals have been identified, of which more than hundred substances exhibit neurotoxicity (Balouet et al., 2023). Various recent aircraft cabin air quality studies attributed symptoms and neurotoxic hazards to other "key compounds" than CO: tributylphosphate (TBP), xylene or aldehydes (Gerber et al., 2023; Lou et al., 2022). It was suggested that process-generated nanoparticles may play a role as vector in the transport of low-volatile compounds (Michaelis et al., 2021; Hageman et al., 2023). Engine oil and hydraulic fluid can break down at very high temperatures, above 300 °C, and generate CO when in contact with hot metal surfaces. Pyrolysis studies of engine oil and hydraulic fluids show that at 525 °C jet engine oil generates CO, 5-fold more than hydraulic fluids (van Netten and Leung, 2001). In vitro characterization of bleed air contamination at stable temperatures of 350 °C (engine oil) and 200 °C (hydraulic fluid) showed that the mean concentration of CO in engine oil fumes is around 20 ppm, more than 25-fold higher than CO levels in fumes from hydraulic fluids (He et al., 2021). In four of 22 studies, in at least 129 flights, max CO levels may have been critical, higher than permissible levels. Comparing the CO levels in aviation (max 60 ppm) with urban street CO levels the CO exposure concentrations of aircrew are higher than pedestrians, cyclists and passengers of cars and buses (max 31 ppm) (Kaur et al., 2007).

Table 2
CO measurement studies.

Author, year	Aircraft type	Number of flights	Measurement technique	CO levels	Sampling location (s)	Remarks
O'Donnell et al. (1991)	7 identical aircraft, capacity 101 passengers; type NR	45 flights of 30-60 min (non-smoking); sampling frequency: every 5 min	Electrochemical cell monitor; detection limit: 1 ppm	Mean 1.6, range 1-4 ppm, max 4 ppm	Two sampling locations, in front of the first row and in front of the last row	
Sussell (NIOSH), 1993	MD-80 700	Part 1: 3 test flights, part 2: 10 flights, part 3: 2 flights (15 flights total) NIOSH investigation after complaints, reported by aircrew	Electrochemical dosimeter	1: 2-6 ppm, peak 5-10 ppm 2: 5 samples: 1-5 ppm 59 samples: 1-7 ppm, peak 25 ppm 3: peaks of 30-35 ppm	One sampling location in the cabin; In part 3: retest using paired dosimeters	Flight attendants experienced dizziness, headache, blurred vision, mental confusion. Four cases diagnosed as CO poisoning, with elevated COHb levels. Ambient CO level Seattle airport 9 ppm. "Short term CO peaks"
van Netten (1998)	BAe 146-200, Haviland Dash-100	1 BAe "problem aircraft" tested on the tarmac, 3 during flights (4 flights total)	Electrochemical dosimeter	Tarmac: 3 ppm Flights: no detectable CO	NR	In BAe leaks of seals found in engine bearings. COHb levels in 4 symptomatic aircrew: 0.7-2% (normal), suggesting that symptoms do not result from CO
Pierce et al. (1999)	Boeing 777	8 flights, 4 domestic, 4 international; measurements during boarding, ascent, descent and deplaning	CO sensor, detection limit 0.1 ppm	72% of the 5 min mean periods: CO below detection limit. Range < 0.1-7 ppm, max 7 ppm	Sampling location in 3 flights: in the rear section; in 5 flights in the forward section of coach class	Health and comfort questionnaire completed by 930 passengers and 27 flight attendants; Symptoms were more often related to flying by flight attendants than by passengers
Lee et al. (2000)	Boeing 747-400, Airbus 330,340	5 non-smoking flights of 3-14 h; sampling frequency: every 5 min	Electrochemical dosimeter, detection limit: 1 ppm	Range 1-6, max 6 ppm	One sampling location, business class area	Health survey questionnaire completed by 185 aircrew: high scores on irritation, neuro-behavioural and gastro-intestinal complaints
Dumyahn et al. (2000)	Variety of aircraft: 22 flights; B777: 6 flights	Total of 28 flights	Electrochemical dosimeter	Mean 0.7 ppm, max not reported	One location, cabin, not specified	CO levels were compared with buses and subway
Honeywell (2000)	BAe 146-200	1 flight (incident during domestic flight)	Colorimetric measurement technique	CO below detection limit	2 locations: in the aft section of the cabin, at ventilators on the flight deck	The Incident was not handled as a serious incident, but as an engine fault. Investigation four days later, after that corrective measures were performed
Nagda, (ASHRAE) (2001)	Boeing 767, 737, 747	10 flights; measurements during boarding, ascent, cruise and descent	Electrochemical dosimeter, detection limit 0.1 ppm	Max 9 ppm	CO-measurements of bleed air in cabin	Normal operation conditions; max during boarding
Waters et al. (2002)	Boeing 777	36 flights of 42-863 min	Electrochemical dosimeter, detection limit 0.2 ppm	5 min average conc. range: < 0.2-2.9 ppm, max 9.4 ppm	2 sampling locations, in front and rear coach.	No incidents reported in these 36 flights.
Ross (BRE) (2003)	BAe 146-100,200, 300: 8 flights Boeing 737-300: 6 flights	14 flights of 1-3 h	Electrochemical sensor, minimal detection limit 0.1 ppm	BAe 146: mean range 0.1-0.9, max 5.8 ppm Boeing 737: mean range 0.1-1.3, max 3.0 ppm	Sampling at seated head height in the cabin;	max values on the ground, high outside CO levels; peaks of 20-30 min
Spicer, (ASHRAE) (2004)	MD-80, Boeing 737-800 and Boeing 757-200	4 flights of 3-4 h; Short-term measurements in bleed air for a few min. during each flight, from boarding to deplaning.	Electrochemical sensor, detection limit 2 ppm	Most levels < 2 ppm (detection limit). Max 3.7 ppm	Sampling under seat, in front	Age of aircraft 4.5-6.5 years. CO peaks of 20-30 min. Health and comfort questionnaires: most reported symptoms: pressure in ears, throat/nose complaints, dry eyes, tiredness. No reported fume events.
van Netten (2005)	BAe 146	1 flight	Electrochemical dosimeter	Max 60 ppm	Pilots monitoring CO levels in the cockpit during flight	At the top of climb
GCAQE (2006)	BAe 146	350 flights	CO sensors	Mean CO 9.4 ppm; 37% of recordings > 10 ppm. Max: 60 ppm;	Cabin	CO detection in 81% of flights 66 of 350 (19%): CO below detection level
NIOSH (2006)	Avro RJ-85	10 flights of 3-4 h	Electrochemical CO monitor	Peaks of 10 flights: 1-13 ppm, max 13 ppm	Sampling at the aft cabin wall	Noise measurements for flight attendants above recommended limits Duration of peaks: 10-25 min
MacGregor et al. (2008)	MD 80, Boeing 737 and 757	4 flights of 3-4 h; continuous sampling from	CO sensor, detection limit 2 ppm	Range < 2-3.7 ppm, max 3.7 ppm	2 locations, in the middle seat of a three	Bleed air sampling after environmental control system was shut off for 5 min

(*continued on next page*)

Table 2 (*continued*)

Author, year	Aircraft type	Number of flights	Measurement technique	CO levels	Sampling location (s)	Remarks
		boarding to deplaning (cabin air)			seat row, bleed air: close to a gasper	
Crump et al. (2011)	Boeing 757 cargo and passenger, Airbus A 320, 319 and BAe 146	100 flights; ten sampling point were defined for each sector at various flight phases	Electrochemical cell, detection limit 0.1 ppm	Range < 1-7 ppm. In one flight max of 10 ppm, equipment malfunction?	Flight deck	Peak of 7 ppm during taxiing back after flight. Fume or smell events on 38 of 100 flights.
Spengler et al. (2012)	6 aircraft types: Airbus: 4 Boeing: 2	83 domestic and international flights of 1-16 h; 37% short-haul flights. Continuous measurements from 10000 ft ascent to 10000 ft descent	Electrochemical dosimeter, detection limit: 1 ppm	CO not detected (< 1 ppm)	Sampling in an aisle seat or middle seat in the economy class	Two flights with no food preparation on board had major "events", consistent with fume events
Schuchardt (EASA) (2017)	8 aircraft types: Boeing 747, 757, 767, 767BER and 787 (bleedless) Airbus 320,321,340	69 flights, whole flight sampling in 5 flight phases: taxi-out, take off-climb, cruise, descent-landing, taxi-in.	Electrochemical sensor, detection limit 0.5 ppm	Range: 0.5-4.8, max 4.8 ppm; max CO levels in bleedless B 787 aircraft (8 flights): 1.6 ppm	Jump seat in the cockpit	Airplane age ranging from 1.1-26.6 years. Peaks of nanoparticles, detected by aerosol sensors, suggestive of oil leaks
Rosenberger (2018)	Airbus 321	17 flights, 3 flight phases: taxi-take off-climb, cruise and descent-landing	Electrochemical sensor, detection limit 0.5 ppm	Range < 0.5-2.2 ppm. Mean 1 ppm. Max cockpit: 1.7 ppm Max cabin: 2.2 ppm	Two sampling locations: flight deck and cabin	Airplane age ranging from 7.5-17.5 years. One smell event recorded.
Houtzager et al. (2020)	Long range twin aisle aircraft	2 flights: 1 baseline and 1 test flight	Electrochemical sensor, detection limit 0.5 ppm	Range 0.7-3.3 ppm, max 3.3 ppm	Cabin and cockpit	Both laboratory (bleed air simulator) and in-flight measurements. Two contamination events recorded.
Yu et al. (2021)	Airbus 320	CO measurements in 2 domestic flights of 170-175 min	Q trak indoor air quality monitor; accuracy 3 ppm	Max 1.2 ppm	Sampling under the seat in the cabin.	Aircraft age 3.6 and 5.9 years. 10x higher mean levels in older aircraft. Highest CO levels in the waiting phase and after landing
Lordo et al. (2023)	6 aircraft types: Airbus 340, 380 Boeing 737, 747, 767, 777	CO measurements on 80 domestic and intern. flights; continuous measurements from 10000 ft ascent to 10000 ft descent	CO sensor, detection limit 2 ppm; Accuracy 3 ppm	Range 0-1.6 ppm (< 2 ppm)	Sampling location: seat in the middle of the cabin economy class.	6135 passengers and 1034 crew completed health and comfort surveys with data on 130 flights. Peaks of nanoparticles, detected by aerosol sensors, suggestive of oil leaks

NR=not reported, MD= MacDonnell Douglas, BAe= British Aerospace

4.1. Symptoms of chronic CO intoxication vs aerotoxic syndrome

The most common signs and symptoms of chronic CO intoxication are nonspecific and include headache, dizziness, lethargy, and confusion (Piantadosi, 2002). Other symptoms and signs are cognitive impairment, sleep, vision, sense of smell, as well as anxiety, fatigue, psychomotor dysfunction and balance problems (Townsend and Maynard, 2002). Abdominal pain, chest pain, cardiac arrhythmias and tachycardia can occur. Varying degrees of cognitive impairment have been reported (Prockop, 2005; Prockop and Chichkova, 2007). Students voluntary exposed to CO concentrations of 17–100 ppm, mean 61 ppm for 1.5 to 2.5 h scored significantly lower on tests of memory, learning, attention, concentration and visuomotor skills than controls (Amitai et al., 1998). The diagnosis of chronic CO intoxication may be difficult because the percentage COHb often is not noticeably elevated (Rutchik and Ratner, 2022). The amount of COHb formed depends on the duration of exposure to CO, the CO concentration in the inspired air and the alveolair ventilation. In acute CO poisoning, elevated COHb measurements correlate weakly with clinical symptoms (Hampson and Hauff, 2008). The half-life of COHb is 4–5 h. The delay between termination of CO exposure to the time blood is obtained, as well as intervening administration of oxygen allow the COHb level to fall (Hampson and Hauff, 2008). The best way to diagnose a chronic CO intoxication is to measure the CO concentration and the duration of exposure (Weaver, 2009; WHO, 2021). Since flight attendants board before the passengers and deplane after them, they are subject to higher potential (duration of) exposure.

In Table 3 we compare symptoms of chronic CO intoxication to symptoms of AS (Michaelis, 2010; MackenzieRoss, 2008; Townsend and Maynard, 2002; Weaver, 2009; Michaelis et al., 2017; Prockop and Chichkova, 2007). The reported chronic symptoms of AS, although often non-specific, appear to closely match those for chronic exposure to carbon monoxide. These symptoms of aircrew are considered to be the result of chronic exposure to pyrolytic products, including CO, PAN, volatile organic compounds, and the organophosphate constituents of the oils and fluids (Hageman et al., 2022; Burdon et al., 2023).

4.2. Temperature and carbonmonoxide

Bleed air temperature conditions of an aircraft engine vary during the various phases of flight. At maximal power take-off and top of climb the bleed air temperature ranges from 310–350 °C, and is lower during cruise and descent: from 185–250 °C. During ground operations, with compressor air from the APU, the temperature is about 170 °C (Houtzager et al., 2017; NRC, 2002). Incidentally high stage engine compressor temperatures are reached up to 650 °C at take-off power (Hildre and Jensen, 2015; Michaelis, 2011; Hunt et al., 1995). CO generation is dependent on the temperature to which oil and hydraulic fluid is heated

Table 3
Symptoms of long-term carbon monoxide intoxication and of Aerotoxic Syndrome.

Chronic CO intoxication	Aerotoxic syndrome
Neurological symptoms	
Headache, dizziness	Headache, dizziness
Balance problems	Balance problems
Resting and intention type of tremor, Parkinsonism	Paresthesias, numbness, tremor
Decreased level of consciousness	Sleep disorders, anxiety
Neuropsychological symptoms and impairments	
Confusion, disorientation, cognitive impairment	Slowed mental processing, impaired attention
Mood and personality changes	
Short term memory	Memory and concentration
Verbal fluency, learning	Working/verbal memory
Executive function	Executive function
Motor and visuospatial skills	Multi-tasking and Psychomotor speed
Respiratory symptoms	
Shortness of breath, chest pain	Shortness of breath, chest pain
Cardiovascular symptoms	
Tachycardia, arrhythmias	Increased heart rate, palpitations
Gastro-intestinal symptoms	
Nausea, vomiting, abdominal pain, diarrhea	Nausea, vomiting, abdominal pain, diarrhea
General symptoms	
Flu-like symptoms, general "weakness"	Fatigue, muscle pain, flu like symptoms

Adapted from Prockop and Chichkova (2007); Michaelis (2010); Michaelis et al. (2017); MackenzieRoss (2008); Hageman et al. (2022); Townsend and Maynard (2002); Rutchik and Ratner (2022); Weaver (2009).

(Houtzager et al., 2017). Engine oils and hydraulic fluids have a high thermal stability. In a toxicity study of thermal degradation products from petroleum-based aircraft engine oils and synthetic hydraulic fluids, the temperature was raised slowly to a max of 533 °C. Measurable CO formation did not occur until the temperature was raised above 300 °C, and CO evolution increased rapidly upon further heating (Crane et al., 1983). This pattern was also demonstrated in a bleed air simulation study (Houtzager et al., 2017). It may explain why in other cabin air quality studies, with lower bleed air temperatures, CO levels remain low (Jones, 2022).

4.3. CO levels, altitude hypoxia and CO exposure limits

A typical cruise altitude for modern civil aircraft is between 33,000 and 41,000 ft (10–12.5 km). As altitude increases, the pressure inside the cabin declines, although the concentration of oxygen is kept constant at about 20% (Winder and Balouet, 2002). With higher altitudes, the toxicity of CO increases: 1) CO-uptake into the bloodstream is exacerbated, 2) the bonding of CO to hemoglobin and thus the formation of COHb increases, and 3) as a consequence of the lower oxygen availability, combustion tends to produce more CO due to incomplete burning (Rathore and Rein, 2016). Moreover, decreased oxygen availability at altitude may lead to mild hyperventilation resulting in higher CO uptake in the lungs (Rathore and Rein, 2016). Thus, for the same concentration of CO, increasing altitude may result in higher COHb levels. Consequently, CO-toxicity at altitudes > 8000 ft (> 2.5 km), is 50% higher than at sea level (US air force, 1992; Winder and Balouet, 2002). This means that guidelines for CO-exposure limits established at sea level may not be suitable for aviation circumstances. The ACGIH states that its limits should not be applied to altitudes above 5000 ft (ACGIH, 2021a, 2021b). The aircraft cabin is a reduced pressure environment, with a corresponding reduction in the partial pressure of oxygen. Under these circumstances aircrew may have an advantage over the general population, as a result of altitude acclimatization with an increase of blood hemoglobin level, apart from some adaptation to chronic CO-exposure (Howlett and Shepard, 1973).

4.4. Mixtures of toxic compounds

It may well be that the chronic symptoms reported by aircrew cannot be attributed to one single chemical compound. The simultaneous exposure to organophosphates and CO in aircraft cabins has raised concern. Although the concentrations of each of these substances individually are often too low to pose a hazard (WHO, 2021), their interaction can be of clinical significance. The detoxification of organophosphates in the liver is regulated by cytochrome P450 (CYP) enzymes. CO not only binds to hemoglobin and myoglobin, but also to CYP, leading to impaired organophosphate detoxification, and thus increased toxicity of the mixture of toxic compounds in bleed air (ACGIH, 2021a, 2021b). In addition, exposure to phenyl-naphthylamine (PAN) induces the formation of methemoglobin, rendering hemoglobin incapable of oxygen transport. Therefore, simultaneous exposure to CO and PAN should be assessed assuming additive toxicity (Skold et al., 2011; WHO, 1998; Iolascon et al., 2021).

Hydraulic fuels and engine oils contain a large number of potentially toxic chemicals. A recent review on cabin air quality studies comprising 177 flights revealed approximately 100 compounds (Schuchardt et al., 2019). Over the last decade various air monitoring studies have been conducted to identify these chemical compounds released into the cabin following an engine oil leak (Hageman et al., 2022). Measurements include organophosphate compounds (tricresyl phosphate (TCP), triphenyl phosphate (TPhP), dibutyl phenyl phosphate (DBPP) and tri-n-butyl phosphate) and (semi-)volatile organic compounds (toluene, benzene, [form]aldehyde, acetic acid, acetone, ethanol) (Solbu et al., 2011; Winder and Balouet, 2002). Furthermore, most of the 22 reviewed measurement studies looked at CO, but also carbon dioxide, ozone, nitrogen dioxide and sulphur dioxide. Some studies also measured ultrafine particulate matter and black carbon (Crump et al., 2011; Houtzager et al., 2021; van Netten, 1998; Dumyahn et al., 2000). Cabin crew, exposed to fume events, may exhibit increased COHb levels and lowered butylcholinesterase levels, as a result of simultaneous CO and organophosphate exposure (Michaelis et al., 2017). In other studies, the simultaneous exposure to CO and volatile compounds or antioxidants (Chen et al., 2021; Winder et al., 2002; MacGregor et al., 2008; Lou et al., 2022; Murawski, 2011) is described. It is conceivable that risk assessments based upon acute and single substance exposure underestimate the chronic toxicity of a real-life mixture (Cattaneo et al., 2023). Exposure limits for individual compounds may not apply to complex mixtures with many components (ACGIH, 2021a, 2021b). The ACGIH explicitly states that its limits should not be applied to complex mixtures of chemicals, such as combustion products. Effects of exposure to contaminant mixtures have only received cursory attention (Hayes et al., 2021).

5. Limitations

There is a considerable amount of data on cabin air quality, but only a fraction is published in the scientific literature. Useful data are presented in technical reports of environmental forensic investigations, regulatory agencies or occupational safety and health organizations (Balouet et al., 2023). We included these non-peer-reviewed data in our review: reports and documents on cabin air quality, released by aviation authorities, aircraft manufacturers and national or international research groups. As a result, 13 of the reviewed 22 papers may contain methodological imperfections. Of the four studies with CO peak levels of 13–60 ppm, one study was peer-reviewed, two were NIOSH health hazard evaluation reports, and one was the Global Cabin Air Quality Executive (GCAQE) carbon monoxide database collated on 350 BAe 146 flights in the UK.

It is obvious that the most frequent signs and symptoms of chronic CO intoxication are nonspecific, as are the common signs and symptoms of AS. It is very unlikely that the AS can be attributed to one single toxic compound (Hageman et al., 2022; Burdon et al., 2023). Chronic

symptoms of aircrew are considered to be the result of chronic exposure to pyrolytic products, including CO, combined with volatile organic compounds, PAN, and the organophosphate constituents of the oils and fluids.

When we review the CO data collated by the Global Cabin Air Quality Executive, and collected on 350 BAe 146 flights, it appears that fume events with detectable CO levels were predominantly identified on the BAe 146 aircraft type; however, CO levels > 10 ppm were established on 5 other aircraft types too.

6. Conclusion, recommendations

The majority of studies presented here suggest that CO concentrations in aircraft cabin air are generally below those associated with health effects. Nevertheless, in six studies CO peaks may be associated with health risks at chronic exposure, and in four studies CO peak concentrations were high, associated with health risks both in acute and chronic exposure. At least in 129 of 888 flights (14,5%) evidently elevated CO levels have been described. There is a lack of cabin air quality studies, with medical investigation of symptomatic aircrew, including COHb measurements. It remains unclear whether CO is a contributory factor to the reported long-term intoxication effects, although there is no dispute that thermally degraded jet engine oils are a major source of CO in cabin air (Cheraghi et al., 2009; Chaturvedi, 2010; Ramsden, 2021). And that the symptoms of AS appear to closely match those for chronic exposure to CO.

The recommended safety limits for CO in the air vary widely, depending on the organization setting the limit and the population exposed. The limits set by NIOSH, OSHA and ACGIH are intended for ground-based workplace exposures of healthy adults. The ACGIH for instance recommended a ground-based workplace limit for CO at 25 ppm (ACGIH, 2021a, 2021b). The 50 ppm peak limit for CO in aviation specific standards seems to be too high (Table 1). In agreement with the WHO in circumstances of chronic exposure we plea for a more restrictive aviation OEL for CO of 5 ppm (8 hr TWA) (WHO, 2021). While the appropriate level for CO is positioned below the 8-hour guideline of 9 ppm, the WHO suggests the maximum CO level to be as low as 4–5 ppm to minimize health effects (WHO, 2021). There are several reasons for this recommendation: 1) Altitude increases the toxicity of CO, 2) CO binds to CYP enzymes, resulting in impaired organophosphate detoxification, what may lead to increased toxicity of a mixture of toxic compounds in bleed air, 3) PAN displaces oxygen from hemoglobin, forming methemoglobin, contributing to hypoxia, 4) intercontinental flights often last more than 8 h, and 5) the aspect of a prolonged, "life-time" exposure of aircrew to CO.

Carbon monoxide cannot be ignored as one of the components of the cocktail of toxic compounds, leading to Aerotoxic Syndrome. Therefore, pilots and cabin crew should be trained to recognize the early signs and symptoms of CO poisoning (ACGIH, 2021a, 2021b). And, CO detectors should be installed in the air supply ducts to the aircraft cabin, combined with sensors to detect oil fumes.

CRediT authorship contribution statement

Gerard Hageman: Conceptualization, writing original draft. Pieter van Broekhuizen: writing, review and editing. Jik Nihom: writing, review and editing.

Declaration of Competing 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.

Data Availability

No data was used for the research described in the article.

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